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Special Issue Reprint

Advances in the Diagnosis and Management of Vasculitis

Edited by
Alicia Rodriguez-Pla

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Guest Editor

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This is a reprint of the Special Issue, published open access by the journal *Diagnostics* (ISSN 2075-4418), freely accessible at: https://www.mdpi.com/journal/diagnostics/special_issues/MJE91FD2YN.

For citation purposes, cite each article independently as indicated on the article page online and as indicated below:

Lastname, A.A.; Lastname, B.B. Article Title. *Journal Name* **Year**, *Volume Number*, Page Range.

ISBN 978-3-7258-7500-9 (Hbk)
ISBN 978-3-7258-7501-6 (PDF)
https://doi.org/10.3390/books978-3-7258-7501-6

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About the Editor

Alicia Rodriguez-Pla

Alicia Rodriguez-Pla earned her medical degree from the University of Navarra in Spain and completed rheumatology training in Barcelona (Spain). She obtained her Ph.D. from the Universitat Autonoma de Barcelona while working on giant cell arteritis. Her interest in vasculitis led her to pursue post-doctoral training in the U.S. from 2003 to 2007, where she worked as a visiting post-doctoral research fellow at Johns Hopkins University. During her last two years at Johns Hopkins, she was funded through a Vasculitis Clinical Research Consortium (VCRC)/Vasculitis Foundation (VF) fellowship. She also received a Master's in Public Health (MPH) at The Johns Hopkins Bloomberg School of Public Health. In addition, she worked on lupus research at the Baylor Institute for Immunology Research in Dallas before completing a clinical fellowship in rheumatology at Boston University, where her interest in scleroderma increased. She completed her residency in internal medicine at Lahey Hospital and Medical Center in Burlington, MA. She worked as an Assistant Professor in the Rheumatology Division at the University of Arizona in Tucson and at Mayo Clinic Arizona before becoming the Rheumatology Division Chief at UCSF Fresno in September 2022, where she was also an Assistant Professor of Clinical Medicine. While at the University of Arizona, she was the Director of the Vasculitis Center and the Co-Director of the Scleroderma Program. At Mayo Clinic Arizona, she was the Director of the Vasculitis Program. In May 2023, she joined Sierra Pacific Arthritis and Rheumatology Centers. At the end of 2025, she established her own private practice, Premier Rheumatology, P. C., in Fresno, California. She is a physician-scientist, and her main interests are vasculitis, scleroderma, and IgG4-related disease. She is interested in translational and clinical research. She is board-certified in internal medicine and rheumatology by the American Board of Internal Medicine (ABIM).

Preface

It is with immense pleasure that we present this Reprint, a curated collection of eleven significant articles originally published in the Special Issue "Advances in the Diagnosis and Management of Vasculitis" for the journal *Diagnostics*.

This compilation reflects the dynamic and rapidly advancing nature of research in the field of systemic vasculitis, bringing together diverse perspectives from leading research groups across Spain, Poland, the USA, Germany, Romania, and Turkey.

The primary subject of this Reprint is the multifaceted nature of primary systemic vasculitides—a group of rare but potentially life-threatening diseases characterized by blood vessel inflammation. The scope of the works is intentionally broad, covering large-vessel vasculitis, such as giant cell arteritis and Takayasu arteritis, as well as small-vessel involvements like ANCA-associated vasculitis and IgA vasculitis. By including original research, case reports, and comprehensive reviews, this Reprint addresses the entire clinical trajectory, from the initial diagnostic hurdle to long-term therapeutic management and the prevention of relapses.

The aim and purpose of this collection are to provide a centralized resource that highlights the most recent breakthroughs in the field. In recent years, the management of vasculitis has undergone a paradigm shift. We have moved from a heavy reliance on high-dose glucocorticoids toward a more nuanced "steroid-sparing" approach powered by targeted biological therapies. This Reprint serves to document these advances, focusing on the search for reliable biomarkers and the implementation of innovative imaging techniques—such as PET-CT and advanced neurosonography—that allow for earlier intervention and more precise monitoring of disease activity.

The motivation for assembling this scientific work stems from the inherent diagnostic challenges these diseases pose. Vasculitis often mimics other conditions, leading to delays that can result in irreversible organ damage or vision loss. Our goal was to bridge the gap between bench research and clinical practice, providing evidence-based insights that can immediately impact patient outcomes.

This Reprint is addressed to a wide audience of healthcare professionals and scientists. It is intended for rheumatologists, internists, radiologists, and immunologists who seek to refine their diagnostic accuracy and therapeutic strategies. Furthermore, it provides a robust foundation for students and early-career researchers looking to understand the current landscape and future directions of vasculitis research. We hope that the insights shared in these pages inspire further collaboration and innovation, ultimately leading to a brighter future for patients living with these complex conditions.

Alicia Rodriguez-Pla
Guest Editor

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Editorial

Advances in Diagnosing and Managing Primary Systemic Vasculitides: A Transforming Landscape

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As we conclude this Special Issue of *Diagnostics*, "Advances in the Diagnosis and Management of Vasculitis," we reflect on a vibrant collection of eleven articles that span the globe from Spain and Poland to the USA, Germany, Romania, and Turkey. This international collaboration underscores a universal knowledge in rheumatology: while vasculitis remains a diagnostic "chameleon," our collective ability to understand it has never been stronger [1,2].

The primary systemic vasculitides occupy a unique space in medicine—rare enough to challenge timely recognition, and serious enough to demand urgent, evidence-based action. Despite the significant progress over the past two decades, the path from symptom onset to accurate diagnosis remains fraught with complexity, and therapeutic strategies continue to evolve at an unprecedented pace. The approval of avacopan for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) in 2021 [3], the Food and Drug Administration (FDA) approval of upadacitinib for giant cell arteritis (GCA) in April 2025 [4], and the accelerating integration of advanced imaging modalities into clinical workflows have collectively reshaped how we conceptualize and manage these diseases [5]. This Special Issue of *Diagnostics* was conceived to capture this momentum—bringing together original research, reviews, and case reports that address diagnostic challenges, emerging biomarkers, novel imaging approaches, treatment strategies, and patient outcomes across the vasculitis spectrum.

1. Diagnostic Complexity of Giant Cell Arteritis

GCA remains the most common systemic vasculitis in adults over 50 years of age, yet its heterogeneous presentation continues to pose significant diagnostic hurdles [6]. Updated classification criteria, advances in imaging technologies, the evolving biomarker landscape, and emerging therapeutic strategies including the role of targeted therapies are rapidly transforming the management paradigm [7–9]. Importantly, no single pathognomonic feature defines GCA and that a multimodal approach integrating clinical assessment, laboratory evaluation, and imaging is essential to reduce the risk of complications such as irreversible vision loss [10].

The urgency of rapid diagnosis is illustrated by Stańska et al., who present a case report of a 74-year-old patient in whom diagnostic delays led to bilateral vision loss. Their work supports ultrasound as the first-line imaging tool for suspected GCA, in alignment with the 2023 European League Against Rheumatism (EULAR) recommendations that position color duplex sonography (PCDS) above temporal artery biopsy (TAB) for its sensitivity, non-invasiveness, and wide availability, while acknowledging that operator expertise remains a key limiting factor, and TAB remains a valuable tool in many clinical situations [11].

2. The Expanding Role of Imaging

Imaging has emerged as a central pillar in vasculitis diagnosis and monitoring. The role of positron emission tomography/computed tomography (PET/CT) in GCA has been established, especially in specific clinical scenarios—including atypical presentations, suspicion of large vessel involvement, and diagnostic uncertainty in the setting of mimickers—in which this imaging modality can provide decisive information [12]. Color duplex ultrasound and magnetic resonance imaging have also been found to be helpful tools for diagnosing GCA [13].

3. Rare Presentations and Diagnostic Mimickers

The vasculitis spectrum extends beyond GCA and AAV. In the arena of monogenic vasculopathies, [14] contributed an important case report on hepatic vascular involvement in deficiency of adenosine deaminase 2 (DADA2), describing large regenerative nodules with a focal nodular hyperplasia (FNH)-like appearance not previously reported in this setting. Notably, etanercept therapy resulted in sustained clinical stabilization and the marked regression of liver lesions over nine years of follow-up, expanding our understanding of the hepatic manifestations and treatment responsiveness in this rare condition.

4. ANCA-Associated Vasculitis: From Pathogenesis to Prognosis

Significant advances in biomarker research in AAV is helping to change the treatment paradigm [15,16]. In the context of the expanding therapeutic armamentarium—including avacopan, which was found to be superior to prednisone in sustained remission at 52 weeks in the ADVOCATE trial —the ability to stratify patients by relapse risk has direct implications for treatment selection and monitoring intensity [17].

5. Nephritis in IgA Vasculitis: Outcomes Under Immunosuppression

Yıldırım et al. contributed a prospective observational study of 49 adults with IgA vasculitis nephritis (IgAVN), an area with a notable absence of specific management guidelines. Their findings challenge the prevailing perception of uniformly poor renal outcomes in adults, demonstrating that ESRD occurred in only one patient (2%) when effective immunosuppressive therapy was employed. The identification of nephrotic-range proteinuria as an independent risk factor for unfavorable outcomes (OR: 17.18) provides a practical prognostic marker. Importantly, the study also highlights the infection risk associated with immunosuppression, particularly in older adult patients—a reminder that therapeutic gains must be weighed against treatment-related morbidity [18].

6. A Transformative Era

Collectively, these 11 contributions illustrate that the field of vasculitis is undergoing a transformation driven by converging advances in imaging, immunopathogenesis, targeted therapeutics, and clinical phenotyping. The expanding application of US, PET/CT, and contrast-enhanced ultrasound (CEUS) across the vasculitis spectrum enables earlier diagnosis, more precise disease monitoring, and better-informed therapeutic decision-making [19,20]. The common thread among these diverse papers, ranging from prospective studies in Turkey to retrospective cohorts in Spain, is the urgent need to reduce treatment toxicity without compromising efficacy. The approval of complement inhibitors such as avacopan for AAV [21] and JAK inhibitors such as upadacitinib for GCA [4] mark a paradigm shift toward mechanism-based, steroid-sparing strategies to offer a roadmap for improving long-term outcomes and quality of life.

However, many unresolved questions persist. The optimal duration and intensity of immunosuppression, the role of imaging in treatment de-escalation, the identification of

https://doi.org/10.3390/diagnostics16050788

validated biomarkers for disease activity and relapse prediction, and the development of tailored approaches for rare vasculitis phenotypes all require continued investigation. The diversity of contributions in this Special Issue—spanning LVV, small-vessel vasculitis, IgA vasculitis, IgG4-RD, and monogenic vasculopathy—reflects the breadth of the challenges and the vitality of the research community dedicated to addressing them.

I am deeply grateful to all contributing authors for their rigorous work and to the reviewers whose constructive assessments strengthened each manuscript. I hope that this collection serves as both a practical resource for clinicians and a catalyst for future study, advancing us closer to the ultimate goals: timely diagnosis, personalized treatment, and improved outcomes and quality of life for all patients with vasculitis.

Funding: This research received no external funding.

Conflicts of Interest: The author declares the following financial interests/personal relationships that may be considered as potential competing interests: Alicia Rodriguez-Pla (ARP) is the owner and founder of Premier Rheumatology. ARP also reports serving as a member of an independent Data Monitoring Committee for Bristol Myers Squibb and has served as a member of a scientific advisory board for AstraZeneca. These roles occurred within the 36 months prior to this submission. The companies and entities had no role in the design of this study; in the collection, analyses, or interpretation of data; in the writing of this manuscript; or in the decision to publish the results. ARP also previously served as a Principal Investigator for clinical trials involving Systemic Lupus Erythematosus and IgG4-Related Disease sponsored by Zenas BioPharma. These roles concluded in 2025 and were outside the scope of the submitted work on vasculitis diagnostics.

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Review

Diagnostic Challenges and Modern Therapeutic Strategies in Giant Cell Arteritis

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Abstract

Giant cell arteritis (GCA) represents one of the most diagnostically challenging systemic vasculitides, characterized by its heterogeneous clinical presentation, lack of pathognomonic features, and potential for devastating complications, with a special concern for irreversible vision loss. This comprehensive review synthesizes current evidence regarding the multifaceted diagnostic challenges in GCA, incorporating recent advances in classification criteria, imaging technologies, biomarker research, and emerging therapeutic strategies.

Keywords: giant cell arteritis; temporal arteritis; vasculitis; diagnostic challenges; differential diagnosis; temporal artery biopsy

1. Introduction and Clinical Significance

GCA is an inflammatory disease of large and medium-sized vessels that predominantly affects individuals over 50 years of age, with peak incidence between 70 and 80 years [1], and it is specially concerning for visual loss [2]. The condition's clinical significance extends beyond its inflammatory nature, as delayed diagnosis can result in catastrophic complications, including permanent blindness, which occurs in 15–20% of untreated patients, stroke, aortic dissection, and aortic aneurysm formation [3–5].

The pathophysiology of GCA involves complex interactions between adaptive and innate immune systems, with granulomatous inflammation involving arterial walls and resulting in vessel occlusion and tissue ischemia [6]

The reason GCA is so difficult to manage is that different "pockets" of inflammation in the artery respond differently to therapy. The clinical manifestations of GCA are the direct result of a spatially organized inflammatory process within the temporal artery wall. Recent research using spatial transcriptomics has demonstrated that macrophages and T cells are not uniformly distributed; rather, they organize into three functionally distinct layers that dictate disease progression and treatment response [7,8]. The adventitia serves as the primary gateway for leukocyte entry and the epicenter of the systemic acute-phase response. Here, a cluster of differentiation (CD)64^+ macrophages and Th17 cells forms a potent proinflammatory circuit. This layer is characterized by the high production of interleukin (IL)-6, IL-1β, and IL-23. This "adventitial signature" correlates strongly with elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and constitutional symptoms such as fever and weight loss. Importantly, this pathway is highly sensitive to glucocorticoids and IL-6 receptor antagonists, e.g., tocilizumab, often resulting in a rapid normalization of systemic markers. Tissue injury is concentrated in the arterial media, where multinucleated giant cells and $CD206^+$ macrophages orchestrate the degradation of the internal elastic lamina. This destructive phenotype is driven by the secretion of

matrix metalloproteinase (MMP)-9, YKL-40/chitinase 3-like, and reactive oxygen species (ROS). Recent data highlight granulocyte macrophage colony-stimulating factor (GM-CSF) as the master regulator of this medial destruction, providing a rationale for the use of GM-CSF receptor blockers, e.g., mavrilimumab, to prevent permanent structural damage to the vessel wall. The most clinically catastrophic feature of GCA, luminal occlusion, occurs in the intima. This layer is dominated by $CD163^+$ and folate receptor (FR)-β+ macrophages, which drive a "response-to-injury" program. These cells secrete vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), triggering neoangiogenesis and the migration of myofibroblasts. Unlike the adventitial inflammatory markers, this intimal remodeling program is notably resistant to glucocorticoids. This explains the "vascular-systemic dissociation" frequently observed in GCA, where patients may develop ischemic complications, e.g., vision loss, despite having a normal CRP and an apparently suppressed systemic inflammatory response (Figure 1) [7–12].

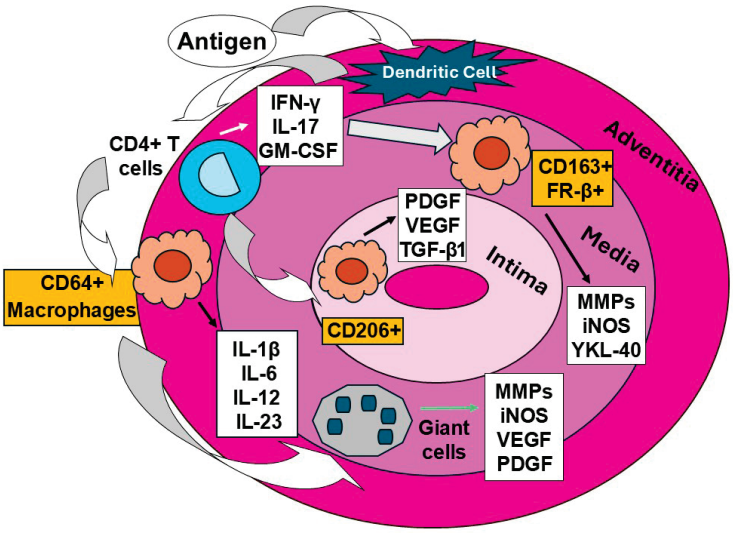

Figure 1. Compartmentalized macrophage and T cell effector functions in GCA: layer-specific immunopathology and steroid resistance mechanisms. The inflammatory landscape of GCA exhibits a functionally distinct "division of labor" across the arterial wall, with each compartment contributing to specific pathogenic outcomes. (A) Adventitia, systemic signaling hub: $CD64^+$ macrophages and $CD4^+$ Th17 cells orchestrate systemic inflammation through production of IL-6, IL-1β, and IL-23, which drive hepatic acute-phase protein synthesis, with elevated CRP and serum amyloid A (SAA), and constitutional symptoms like fever and malaise. This axis is highly glucocorticoid-responsive. (B) Media, zone of vascular wall destruction: multinucleated giant cells derived from macrophage fusion and $CD206^+$ alternatively activate macrophages localize to the internal elastic lamina (IEL), where they secrete MMP-9, MMP-2, and the chitinase 3-like protein YKL-40. These proteases, combined with reactive oxygen species (ROS) by activated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, mediate degradation of elastin and collagen, resulting in focal wall thinning, medial necrosis, and aneurysmal dilatation. (C) Intima, zone of occlusive remodeling: $CD163^+$/FR-β^+ alternatively activate macrophages, and resident myofibroblasts secrete platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), promoting neoangiogenesis, intimal smooth muscle cell hyperplasia, and progressive luminal narrowing, leading to tissue ischemia. While the adventitial IL-6/Th17 axis responds dramatically to glucocorticoids, the medial giant-cell-driven matrix destruction and $CD163^+$-mediated intimal remodeling exhibit relative steroid resistance, perpetuating subclinical inflammation and late-stage ischemic complications even after initial clinical remission. Abbreviations: CD, cluster of differentiation; iNOS, inducible nitric oxide synthase; MMP: matrix metalloproteinases; PDGF, platelet-derived growth factor; IL: interleukin; GM-CSF: granulocyte macrophage colony-stimulating factor; TGF-β1, transforming growth factor-β1; IFN, interferon; FR, folate receptor.

https://doi.org/10.3390/diagnostics16030470

Despite significant advances in understanding pathogenic mechanisms, the etiology remains unknown, and diagnostic approaches continue to rely on combinations of clinical assessment, laboratory findings, imaging, and histopathological examination [13].

The diagnostic challenges of GCA can be divided into two major categories: (1) failure to diagnose the disease correctly and in a timely manner, which may be complicated due to its unspecific symptoms; (2) diagnosing GCA in patients who do not have the disease but a mimicker.

2. Material and Methods

This narrative review summarizes current evidence on diagnostic challenges, including evolving classification criteria and therapeutic strategies in GCA. We conducted a comprehensive literature search of PubMed/MEDLINE, Web of Science, and Scopus databases for articles published through December 2025. Search terms included combinations of MeSH terms and keywords: "giant cell arteritis", "temporal arteritis", "large vessel vasculitis", "diagnosis", "classification criteria", "imaging", "ultrasound", "temporal artery biopsy", "biomarkers", "treatment", "glucocorticoids", and "biologics".

We prioritized peer-reviewed original research articles, systematic reviews and meta-analyses, randomized controlled trials, large observational cohort studies, and evidence-based clinical guidelines. We primarily focused on publications from the last 10 years while including seminal earlier works that established foundational concepts. We focused on clinically relevant studies addressing diagnostic accuracy, classification criteria performance, imaging modality comparisons, biomarker validation, and therapeutic efficacy.

We emphasize that this is narrative and not a systematic review. Therefore, we did not conduct formal systematic quality assessments or meta-analysis, but we critically evaluated the strength and consistency of evidence throughout our synthesis. By "prioritization", we mean that when multiple sources addressed the same topic, we preferentially cited peer-reviewed original research, systematic reviews, meta-analyses, and randomized controlled trials over case reports, editorials, or lower-quality evidence. This is a narrative synthesis based on expert clinical judgment rather than a systematic review with predefined inclusion criteria and quality scoring. Throughout the manuscript, we explicitly note areas of conflicting evidence, methodological limitations of studies, and gaps in the current literature to provide appropriate critical appraisal while maintaining the narrative review format.

3. Risk Factors and Epidemiological Consideration

3.1. Genetic Factors

GCA is not considered a purely hereditary disease that is directly inherited. Research indicates that a genetic predisposition plays a role in increasing an individual's susceptibility to GCA. However, although certain genetic factors may raise the risk, they do not guarantee the development of the disease.

Genetic predisposition is suggested through familial clustering and association with specific human leukocyte antigen (HLA) alleles, though the specific genetic factors remain unidentified. The HLA-DRB1*04 alleles, especially HLA-DRB10*401 and HLA-DRB10*404, have been identified as significant genetic risk factors, particularly in Caucasian populations. The HLA-DRB1 molecules are involved in antigen presentation to CD4+ T cells, suggesting that specific HLA variants may present antigens that trigger pathogenic immune responses in genetically predisposed individuals. While there is a higher incidence of GCA in families with a history of the condition, familial cases are relatively rare, accounting for about 1% of all patients. This complex genetic landscape underscores that while genetics contribute to risk, there are other factors also at play [14,15].

3.2. Geographic and Demographic Patterns

The incidence of GCA varies significantly worldwide, with North American estimates ranging from 15 to 30 cases per 100,000 individuals aged 50 and older [16]. Scandinavian countries report the highest incidence rates, suggesting that genetic, environmental, and/or geographic factors may play important roles in disease susceptibility [17]. A recent meta-analysis examining nine studies found an overall pooled prevalence of 51.74 cases per 100,000 people over 50 years, with prevalence remaining stable across publication years using linear fit modeling [18].

The female predominance is consistent across populations, with women affected 2–4 times more frequently than men [16]. This gender disparity likely reflects hormonal influences on immune system function, though the specific mechanisms remain incompletely understood [19]. Age represents the most significant risk factor, with the disease rarely occurring before age 50 and demonstrating an exponential increase in incidence with advancing age [1,20].

Some studies reported a seasonal variation with increased diagnostic frequency during fall and winter months, suggesting possible infectious triggers or environmental precipitants [21], although none of them has been yet demonstrated.

3.3. Pathophysiological Risk Factors

Several age-related biological processes contribute to GCA susceptibility. Immunosenescence, characterized by declining naïve T and regulatory T cell populations, accumulation of CD28-null T cells with enhanced cytotoxic potential, decreased thymic output reducing T cell receptor diversity, and increased proinflammatory cytokine production, including IL6-IL1β, and antitumor necrosis factor (TNF)α, which creates a proinflammatory state termed "inflammaging", and shifts in CD4/CD8 cell distributions, creates a proinflammatory milieu conducive to vasculitis development [10,22,23].

Concurrent vascular aging, marked by loss of arterial elasticity and increased wall stiffness, provides the structural substrate for inflammatory targeting. Age-related loss of adventitial *vasa vasorum* may create hypoxic conditions in the arterial wall, while accumulation of oxidative damage and advanced glycation end products in the elastic lamina may generate neoantigens that trigger autoimmune responses [24,25].

4. Clinical Presentation and Diagnostic Complexity

4.1. Cranial Manifestations

The classic cranial presentation of GCA encompasses a constellation of symptoms that, while characteristic, are not pathognomonic. New-onset headaches are often described as severe and different from previous headache patterns [26–28]. Temporal artery abnormalities, including tenderness, thickening, or reduced pulsation, provide important physical examination findings and are present in 40–60% of cases, making them one of the more common physical signs in GCA [13,29].

Jaw claudication due to ischemia of masticatory muscles during chewing demonstrates high specificity for GCA, approximately 90%, and occurs in 35–50% of patients [30–32]. While jaw claudication is less common than temporal artery abnormalities, its high specificity makes it a particularly valuable diagnostic clue when present [13,33,34]. The "chewing gum test", while not superior to clinical history alone, may provide additional diagnostic utility when pain onset occurs within two minutes of chewing [35].

Visual complications are also part of the cranial manifestations, but we will discuss them separately given their potentially devastating clinical consequences.

4.2. Visual Complications

Visual manifestations represent the most feared complications of GCA, occurring in 15–20% of patients and potentially progressing to irreversible blindness [36–38]. Arteritic anterior ischemic optic neuropathy (AAION) constitutes the most common mechanism, characterized by acute monocular vision loss with "chalk-white" optic disc edema, often accompanied by retinal whitening or cotton wool spots [39,40].

The spectrum of visual involvement includes transient visual disturbances, diplopia from cranial nerve palsies, and various patterns of visual field defects [41,42]. Central retinal artery occlusion occurs in approximately 10% of cases [43,44], while posterior ischemic optic neuropathy and choroidal infarction represent less common but serious manifestations [45–48]. The irreversible nature of most visual complications underscores the critical importance of rapid diagnosis and treatment initiation [49,50].

4.3. Systemic and Constitutional Symptoms

Constitutional symptoms, including fatigue, fever, anorexia, and unintentional weight loss, occur in 40–60% of GCA patients [51–53]. These non-specific symptoms often precede more characteristic manifestations and may lead to diagnostic delays, particularly in patients presenting with isolated systemic features [53,54].

Polymyalgia rheumatica (PMR) coexists with GCA in approximately 40–50% of cases, manifesting as bilateral shoulder and pelvic girdle pain, weakness, and stiffness [55]. The relationship between PMR and GCA remains complex, with some experts considering them manifestations of the same disease spectrum [56]. PMR symptoms may precede, accompany, or follow GCA diagnosis, and their presence should prompt careful evaluation for underlying vasculitis [57].

4.4. Extracranial Large Vessel Disease

Recognition of extracranial large vessel involvement has expanded significantly with advanced imaging capabilities. Large vessel GCA (LV-GCA) affects the aorta and its major branches in 50–80% of patients, depending on imaging modality sensitivity [58]. This phenotype may be present without classic cranial symptoms, leading to diagnostic challenges and potential delays [59–61]. Patients with isolated extracranial disease often present with non-specific constitutional symptoms, refractory PMR, fever of unknown origin, or limb claudication. Specific presentations may include limb claudication, upper extremities more commonly than lower, blood pressure discrepancies > 10 mmHg between arms in cases of subclavian involvement, carotid or subclavian bruits, or absent pulses, especially radial pulses. Some patients report unexplained fever, night sweats, or refractory PMR that fails to respond adequately to moderate-dose glucocorticoids.

Characteristic imaging findings in LV-GCA include concentric mural thickening with fluorodeoxyglucose (FDG) uptake or contrast enhancement in a "macaroni sign" pattern, typically involving subclavian arteries (75–80%), thoracic aorta (40–60%), and abdominal aorta (30–40%). The axillary arteries show bilateral involvement in a majority of cases, which is highly specific for GCA versus atherosclerotic disease [62].

The absence of temporal artery abnormalities in these patients necessitates high clinical suspicion and appropriate imaging to establish diagnosis. Recognition of isolated LV-GCA is critical as these patients often do not meet traditional diagnostic criteria focused on cranial symptoms, potentially leading to diagnostic delay. The 2022 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria partially address this gap by incorporating imaging of large vessels and assigning points for bilateral axillary involvement [63,64].

Patients with extensive large vessel involvement may require longer duration of glucocorticoid therapy and have higher relapse rates during tapering. Some evidence suggests that these patients may benefit from earlier introduction of steroid-sparing agents, though this remains an area requiring further study [65].

5. Laboratory Findings and Biomarkers

5.1. Traditional Inflammatory Markers

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remain cornerstone laboratory tests in GCA evaluation, though their limitations are well recognized. ESR elevation (>50 mm/h using the Westergren method) occurs in approximately 76–84% of GCA patients, while CRP demonstrates slightly higher sensitivity, at 86–98%, depending on the study population [66–70]. However, normal inflammatory markers occur in approximately 4–20% of biopsy-proven cases (with most studies reporting 7–10%), representing a population enriched for atypical presentations such as early disease course, predominantly large vessel involvement without cranial manifestations, or concurrent use of medications that suppress inflammatory markers such as tocilizumab or glucocorticoids [59,71,72].

The combination of ESR and CRP provide enhanced diagnostic utility, with concordant elevation yielding 99% sensitivity for positive temporal artery biopsy. Conversely, both normal ESR and CRP confer high negative predictive value, though this cannot definitively exclude diagnosis in patients with high clinical suspicion [70].

5.2. Platelet Count and Hematological Parameter

Thrombocytosis (>400 $\times$ $10^3/\mu L$) occurs in 50–70% of GCA patients (range from multiple studies) and demonstrates comparable diagnostic performance to traditional inflammatory markers [73]. Platelet counts >400 $\times$ $10^3/\mu L$ show specificity of 80–90% (95% confidence interval (CI): 75–92%) for positive temporal artery biopsy, though sensitivity remains moderate at 50–60% [74]. The combination of elevated CRP and platelet count may provide optimal diagnostic utility, with both positive tests yielding 77% positive predictive value [75].

Normochromic normocytic anemia affects approximately 60–80% of patients, with mean hemoglobin levels around 11.7 $\pm$ 1.6 g/dL [76]. Leukocytosis occurs less consistently but may accompany active disease phases [77].

5.3. Emerging Biomarkers

Research into novel biomarkers has identified several promising candidates that could potentially enhance diagnostic accuracy and disease monitoring. However, while numerous candidate biomarkers have been identified, most have been evaluated in single-center studies with limited sample sizes and lack independent validation in diverse populations. Furthermore, few studies have demonstrated that these biomarkers provide diagnostic or prognostic information beyond that available from ESR, CRP, and platelet count.

Among emerging biomarkers, SAA shows the most clinical potential because it strongly correlates with disease activity, it demonstrates elevation in GCA patients compared to healthy controls, and it demonstrates superior sensitivity to ESR for detecting active vasculitis (85–90% vs. 76–84%). SAA may decline more rapidly with effective treatment, potentially enabling earlier detection of inadequate response [78–80]. SAA assays are already available in many clinical laboratories, facilitating rapid translation. However, SAA lacks specificity for GCA vs. other inflammatory conditions, as in the case of ESR and CRP [78].

Cytokine profiling reveals elevated levels of interleukin-6 (IL-6), IL-23, and various chemokines in GCA patients [81–84]. IL-6 levels correlate with disease activity and form

the rationale for tocilizumab therapy [81]. B-cell activating factor (BAFF) and chitinase 3-like protein (YKL-40) show promise as inflammatory markers with potential roles in disease pathogenesis [85,86].

Vascular remodeling biomarkers including matrix metalloproteinases (MMPs), especially MMP-2, MMP-9, and MMP12; vascular endothelial growth factor (VEGF); and angiopoietins may provide insights into vessel wall damage and repair processes [11,12,15,87]. These reflect vascular remodeling processes but are not GCA-specific, and require specialized assays not widely available. These may have greater utility as research tools for understanding pathogenesis than as clinical biomarkers.

The most promising future approach may be composite biomarker panels combining traditional markers (ESR, CRP, platelets) with selected novel markers (e.g., SAA, IL-6) and clinical parameters, potentially enhanced by machine learning algorithms. Such algorithms could improve diagnostic accuracy and predict relapse risk but require rigorous validation in prospective multicenter cohorts before clinical implementation. It is important to take into account that none of these novel biomarkers have achieved clinical implementation yet, and further validation studies are required.

6. Imaging Advances and Diagnostic Modalities

6.1. Ultrasound as First-Line Imaging

Color Doppler ultrasound (CDUS) has emerged as the preferred initial imaging modality for suspected GCA with cranial involvement, as supported by 2018 EULAR recommendations [88]. The pathognomonic "halo sign", representing hypoechoic vessel wall thickening, demonstrates sensitivity of 43–77% and specificity of 89–100% when compared to ACR 1990 criteria [89]. However, while the 2018 EULAR recommendations support CDUS as first-line imaging for suspected cranial GCA, implementation varies globally due to limited availability of trained operators experienced in vascular ultrasound, particularly in resource-limited settings, rural areas, and healthcare systems without dedicated rheumatology-based ultrasound programs [90]. Ultrasound advantages include non-invasiveness, immediate availability when integrated into rheumatology practice, cost-effectiveness, and ability to examine multiple vessel territories [91,92]. The technique allows assessment of both cranial arteries (temporal, occipital, facial) and extracranial vessels (axillary, subclavian, carotid) [93]. Bilateral halo signs increase diagnostic specificity to 100%, though sensitivity decreases with glucocorticoid treatment duration [94].

Technical considerations for optimal ultrasound performance include the use of high-frequency transducers (>15 MHz), experienced sonographers, and standardized examination protocols [95]. The addition of extracranial vessel assessment increases sensitivity from 70% to 89% while maintaining specificity at around 91% [89,92].

6.2. Advanced Cross-Sectional Imaging

Magnetic resonance imaging (MRI) with vessel wall imaging has demonstrated excellent diagnostic performance, with sensitivity of 94% and specificity of 85% for GCA diagnosis. High-resolution MRI can detect mural inflammation in temporal arteries, with grading systems distinguishing physiologic from pathologic enhancement. The technique shows utility in extracranial vessel assessment and may obviate need for temporal artery biopsy when clearly normal [96,97].

Computed tomography angiography (CTA) provides complementary structural information regarding vessel stenosis, occlusion, and aneurysm formation [98–100]. While less sensitive than MRI for early inflammatory changes, CTA offers superior assessment of calcification and luminal abnormalities [100].

6.3. Nuclear Medicine Imaging

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computerized tomography (CT) demonstrates sensitivity of 80% and specificity of 91% for large vessel vasculitis diagnosis [101]. The technique excels in detecting aortic and major branch vessel involvement, with particular utility in extracranial disease phenotypes [102]. FDG uptake typically affects subclavian arteries (75%), thoracic and abdominal aorta (50%), and axillary arteries (40%) [103].

PET/CT limitations include reduced sensitivity in cranial vessels due to spatial resolution constraints and decreased uptake following glucocorticoid treatment initiation [104]. The technique requires careful timing, with optimal diagnostic yield within three days of treatment and declining sensitivity after 10 days [105].

6.4. Multimodal Imaging Approaches

Integration of multiple imaging modalities provides comprehensive vascular assessment and may optimize diagnostic accuracy [106]. Proposed algorithms suggest initiating with ultrasound for cranial assessment, followed by FDG-PET/CT or MRI for extracranial evaluation in appropriate clinical contexts. This approach maximizes detection of both cranial and large vessel involvement while maintaining cost-effectiveness [107,108].

6.5. Fast-Track Diagnostic Pathways

Fast-track clinics dedicated to rapid evaluation of suspected GCA have demonstrated significant improvements in patient outcomes. These pathways typically incorporate same-day or next-day assessment combining clinical evaluation, inflammatory marker testing, and vascular ultrasound, with treatment initiation based on this integrated assessment.

Evidence from multiple centers demonstrates that fast-track pathways reduce time to diagnosis from weeks to days (median 0–2 days vs. 9–24 days in traditional pathways), decrease rates of irreversible vision loss (0–5% vs. 13–20%), and reduce unnecessary temporal artery biopsies and prolonged glucocorticoid courses in patients without GCA [109,110]. Cost-effectiveness analyses suggest that these pathways are economically favorable due to prevention of vision loss and reduced diagnostic testing.

Critical elements of successful fast-track clinics include dedicated access for urgent referrals, availability of experienced vascular ultrasonographers, integrated rheumatology–ophthalmology care pathways for patients with visual symptoms, and standardized protocols for treatment initiation and follow-up. Implementation challenges include resource allocation, staff training, and establishing referral networks, but outcomes support wider adoption of this model.

6.6. Integration of 2023 EULAR Imaging Recommendations

The 2023 EULAR recommendations for imaging in large vessel vasculitis provide updated guidance emphasizing multimodal imaging approaches. Key recommendations include the following: (1) CDUS as first-line imaging for suspected cranial GCA when expertise is available; (2) FDG-PET/CT, MRA, or CTA for assessment of extracranial large vessel involvement; (3) systematic evaluation of both cranial and extracranial vessels in all GCA patients when feasible; (4) recognition that negative imaging does not exclude GCA in patients with high clinical suspicion; and (5) consideration of repeat imaging in patients with disease relapse or atypical features. These recommendations emphasize that imaging should complement, rather than replace, clinical judgment and that the choice of modality should consider local expertise, availability, and individual patient factors [107].

7. Temporal Artery Biopsy: Evolving Role

7.1. Current Diagnostic Performance

The temporal artery biopsy (TAB) remains important as a diagnostic tool despite imaging advances, with specificity approaching 100% and sensitivity of 61–77% [111]. The Society for Cardiovascular Pathology guidelines emphasize standardized processing and interpretation protocols to optimize diagnostic yield [112] (Figure 2).

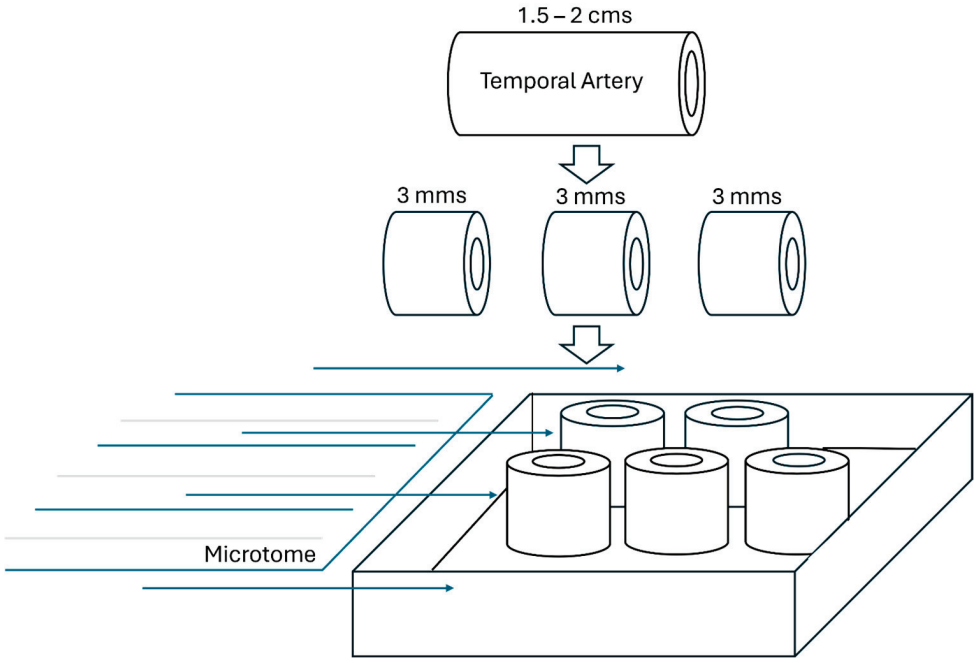

Figure 2. Schematic representation of pathological processing of temporal artery specimens. To minimize the high rate of false-negative results due to "skip lesions" (areas of inflammation interspersed with normal artery) or inadequate sampling, the guidelines standardize the handling of the specimen. (1) Optimal specimen length: the consensus recommends an adequate length (often cited as 1.5–2 cm to maximize the chance of capturing a skip lesion. (2) Complete submission: The entire segment of the biopsied artery should be submitted for processing. (3) Serial sectioning: Instead of only examining a few cuts, the specimen should be evaluated by serial sectioning at multiple levels. This means cutting the entire artery segment into numerous thin sections (e.g., in a specific interval) to examine the vessel at many different points along its length, drastically improving the chance of finding a focal lesion.

Factors affecting TAB sensitivity include specimen length (optimal >2 cm), number of examined sections, timing relative to glucocorticoid initiation, and disease segmental nature [113]. Bilateral biopsy may improve diagnostic yield in cases of high clinical suspicion with negative unilateral results [111].

7.2. Histopathological Considerations

Characteristic histopathological features include granulomatous inflammation with multinucleated giant cells, IEL destruction, and arterial wall thickening [112] (Figure 3). However, giant cells are present in only 50–60% of positive biopsies, and their absence does not exclude diagnosis [113]. Alternative inflammatory patterns, including lymphocytic infiltration without giant cells, may represent valid diagnostic findings [113,114].

The distinction between "healed arteritis" and age-related arteriosclerosis affecting the temporal artery remains challenging and lacks definitive criteria [115]. Recent guidelines recommend caution in diagnosing healed arteritis based solely on intimal thickening or medial fibrosis without clear inflammatory markers [112].

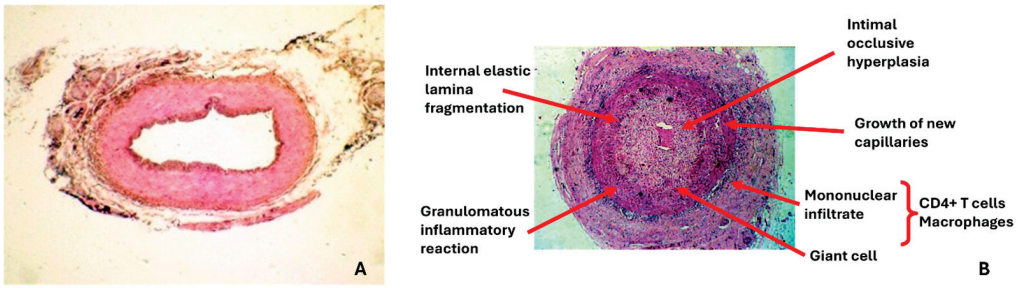

Figure 3. (**A**) **Image of a normal temporal artery biopsy without signs of inflammation/vasculitis.** Hematoxylin and eosin (H&E) stain, original magnification ×25. (**B**) **This image demonstrates findings consistent with vasculitis in a temporal artery biopsy, a common finding in GCA.** Key features shown include the following. (1) Panarteritis: A dense inflammatory infiltrate of mononuclear cells is visible throughout all layers of the vessel wall (tunica adventitia, media, and intima). (2) Intimal thickening and lumen occlusion: The inner layer (tunica intima) is markedly thickened and proliferative, leading to severe luminal stenosis and near-occlusion of the artery's central channel. (3) Thrombus formation: Fibrinoid material and inflammatory cells are seen within the center of the narrowed lumen. Hematoxylin and eosin (H&E) stain, original magnification ×25 (same magnification as panel A for direct comparison). Temporal artery biopsy specimens are from the personal collection of Dr. Rodriguez-Pla.

7.3. Integration with Clinical Assessment

TAB should be considered within comprehensive clinical context rather than as a standalone diagnostic test [116]. The procedure remains valuable when imaging results are inconclusive or contraindicated, and in research settings requiring histopathological confirmation [13,117]. Fast-track clinical pathways often initiate treatment based on clinical and imaging findings while awaiting biopsy results [109].

8. Classification Criteria Evolution

8.1. 1990 American College of Rheumatology (ACR) Criteria Limitations

The 1990 ACR classification criteria require three of five features: age > 50 years, new headache, temporal artery abnormality, ESR > 50 mm/h, and abnormal arterial biopsy [118]. These criteria demonstrate 93.5% sensitivity and 91.2% specificity when distinguishing GCA from other forms of vasculitis in patients already diagnosed with vasculitis (original ACR validation study [118]), but show significantly lower sensitivity (53–80%) when applied in broader clinical settings where the differential diagnosis included non-vasculitic conditions. These criteria show limitations in contemporary practice.

Recognized shortcomings include underrepresentation of patients with isolated ocular manifestations, lack of incorporation of imaging findings, absence of large vessel involvement criteria, and potential for missing cases with normal inflammatory markers [119]. The criteria were designed for classification purposes to include patients in clinical trials and not for diagnosis, limiting their clinical applicability [118].

8.2. 2022 ACR/EULAR Classification Criteria

The updated 2022 classification criteria address many limitations of previous versions while incorporating modern diagnostic modalities [64]. The new criteria require age $\geq$ 50 years as absolute requirement plus cumulative score $\geq$ 6 points from weighted clinical, laboratory, and imaging features [64].

Key innovations include incorporation of imaging findings (positive temporal artery biopsy or halo sign +5 points), recognition of large vessel involvement (bilateral axillary involvement +2 points, FDG-PET activity throughout aorta +2 points), and expanded

clinical features, including morning stiffness and scalp tenderness [64]. Validation studies demonstrate an area under the curve of 0.91 with 87% sensitivity and 95% specificity [64].

Despite significant advances, the 2022 ACR/EULAR criteria have important limitations that affect clinical implementation. The criteria's incorporation of imaging findings, while improving sensitivity for large vessel disease, creates dependency on imaging availability and expertise that varies globally. In settings without access to vascular ultrasound or FDG-PET/CT, the criteria may perform less optimally than in resource-rich environments where they were primarily validated.

The weighted point-based system, while statistically more sophisticated than the simple 3-of-5 approach of the 1990 criteria, introduces practical challenges. Clinicians must calculate cumulative scores incorporating diverse elements with different point values, which may be cumbersome in busy clinical settings compared to dichotomous criteria. Furthermore, the requirement for age $\geq$ 50 years as an absolute inclusion criterion means that the criteria cannot classify younger patients with GCA-like presentations, though such cases, while rare, do occur.

An additional limitation is that classification criteria are designed to create homogeneous populations for clinical trials rather than to diagnose individual patients. The 2022 criteria were validated against final clinical diagnosis, but "gold standard" diagnostic criteria for GCA do not exist, potentially leading to circular reasoning. Patients with atypical presentations or early disease may not fulfill classification criteria, but, nonetheless, require treatment. This highlights the importance of not using them for diagnosis.

Finally, the criteria assign equal weight to halo sign and positive temporal artery biopsy (+5 points each), yet these tests have different performance characteristics depending on timing relative to glucocorticoid initiation, clinical phenotype, and technical quality. This simplified approach may not reflect the nuanced diagnostic reasoning required in complex cases.

8.3. Side-By Side Comparison of the 1990 ACR and the 2022 ACR/EULAR Classification Criteria for GCA

The 2022 ACR/EULAR classification criteria represent a major update to the 1990 criteria, primarily by integrating imaging studies and moving to a weighted point-based system. The new 2022 criteria aim to improve sensitivity and more accurately classify patients, particularly those with large vessel-GCA (LV-GCA) that do not involve the temporal arteries (Table 1).

The 1990 ACR criteria were validated against other forms of vasculitis, not against non-inflammatory conditions, which partially explains the performance differences in real-world clinical settings where the differential diagnosis is broader.

The new criteria were developed to address the limitations of the 1990 criteria, which had low sensitivity, especially for patients who primarily had large vessel involvement without typical cranial symptoms.

The key changes are listed below:

1. **Inclusion of imaging:** The most significant change is the incorporation of imaging—specifically ultrasound (halo sign) and FDG-PET/CT—allowing for the classification of patients based on objective non-invasive evidence.
2. **Increased weight for key findings:** Highly specific findings like a positive biopsy/halo sign (+5 points) and sudden visual loss (+3 points) are weighted more heavily, reflecting their high diagnostic value.
3. **Expanded clinical criteria:** Symptoms like PMR (morning stiffness) and scalp tenderness are formally included as weighted criteria, improving classification in the early or non-classic stages of the disease.

Table 1. Comparison of 1990 ACR and 2022 ACR/EULAR criteria.

Criteria	1990 ACR Criteria	2022 ACR/EULAR Criteria
Number of items	5 items.	10 items.
Classification rule	$\geq$3 of 5 (equal weighting).	Score $\geq$ 6 points (weighted items).
Age requirement	One of 5 items.	Mandatory requirement.
New additions	N/A.	Morning stiffness, sudden vision loss, jaw claudication, CRP, temporal artery ultrasound, bilateral axillary involvement, FDG-PET.
Sensitivity	93.5% (vs. other vasculitides, original validation study); 53–80% (vs. non-vasculitic conditions, subsequent validation studies) *.	87%.
Specificity	80–91%.	95%.
Strengths	Simple, straightforward.	Better discrimination, incorporates imaging, improved large vessel detection.
Limitations	Poor for LV- GCA, no imaging criteria, outdated.	More complex, requires more investigations.
Imaging modalities	None (biopsy only).	Temporal artery ultrasound, FDG-PET.
Best application	Cranial GCA with systemic symptoms.	All GCA phenotypes (cranial, large vessel, constitutional).

* The original Hunder et al. 1990 [118] ACR validation study tested giant cell arteritis against other vasculitides only. The 53–80% specificity against non-vasculitic conditions is derived from subsequent validation studies [119, 120].

9. Differential Diagnostic Challenges

9.1. Mimicking Conditions

Different conditions share clinical features with GCA, and we call them mimickers. Most mimickers are infections, malignancies, atherosclerosis, and other vasculitides. Some of them can be easily distinguished through specific diagnostic tests, e.g., infectious etiologies identifiable through cultures or serology, or some malignancies that can be diagnosed by pathology, imaging, and/or laboratory testing. On occasions, the distinction is more challenging and requires a more comprehensive evaluation. A differential diagnosis should thoroughly rule out all the possible mimickers before diagnosing and treating GCA, especially in those patients without pathological confirmation.

The TAB, despite its limitations discussed in Section 7, maintains importance as a diagnostic tool, particularly when imaging results are inconclusive [120]. From my point of view, the importance of having a positive temporal artery biopsy lies in the confirmation of GCA avoiding the need for further evaluation. If the patient does not repond or relapses during treatment, we should pursue other treatment modalities for GCA or investigate the treatment compliance. In contrast, if the patient has had no biopsy done or if it has been negative, in case of lack of response to treatment, it may be necessary to perform additional testing to rule out other possible alternative diagnosis.

Infectious causes, including bacterial endocarditis, septicemia with mycotic aneurysms, syphilis, mycobacterial infections, and even viral infections, require exclusion through appropriate microbiological testing [121–123].

Malignancies may manifest with constitutional symptoms, elevated inflammatory markers, and vascular involvement, as in patients with GCA. Therefore, cases of suspected GCA necessitate comprehensive evaluation, including age-appropriate cancer screening [121,122].

Primary central nervous system vasculitis can mimic GCA with headache and neurological symptoms but typically affects younger patients and involves smaller intracranial vessels [124,125]. Other systemic vasculitides, including antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis [126], Takayasu arteritis [127], and secondary vasculitis associated with connective tissue diseases [128] or infections [123], require differentiation through specific serological testing, imaging patterns, demographic characteristics, additional clinical manifestations, and biopsy findings [129]. In addition, complicating the picture even more, GCA may coexist with other types of systemic vasculitis [130]. Atherosclerotic disease with secondary inflammation may simulate large vessel involvement but typically demonstrates different distribution patterns and risk factor profiles [59,129].

Misdiagnosing GCA may have severe consequences [131]. It is important to remember that diagnostic criteria do not exist, and the classification criteria have been developed to decide inclusion of the patients in clinical trials; they often fail to differentiate mimics from true GCA [64,118,119]. Clinician vigilance and expertise, biopsy for pathology confirmation whenever possible, and fast improving imaging tools are critical for ruling out or confirming GCA and should be used widely used in the setting of careful clinical judgement and consideration of all possible alternative diagnosis. Diagnostic delays may result in severe outcomes, and patients who are misdiagnosed with GCA are at serious risk of suffering severe adverse effects from high doses of prolonged glucocorticoids therapy. Reducing diagnostic delay is essential for improving patient survival in severe mimic cases [131].

A systematic approach to excluding mimickers includes the following. (1) Comprehensive infectious workup in patients with fever or atypical features (blood cultures, HIV, syphilis, tuberculosis screening, viral serologies based on exposure history, coccidiosis, histoplasmosis, or Lyme disease depending on geographical location). (2) ANCA serology and urinalysis in all suspected GCA cases. (3) Age-appropriate cancer screening and consideration of PET/CT (which can identify both GCA and malignancy). (4) Assessment for features atypical for GCA that should prompt consideration of alternative diagnoses (age < 50 years, lack of cranial symptoms with isolated systemic features, neurological deficits, renal involvement, pulmonary infiltrates). (5) Temporal artery biopsy in diagnostically uncertain cases, or biopsy of other affected organs, as specific histopathological patterns (infectious organisms, malignant cells) can identify mimickers (Table 2).

Table 2. Distinguishing features of major GCA mimickers.

Mimicker	Shared Features with GCA	Distinguishing Features
Infectious endocarditis	Fever, elevated inflammatory markers, headache, anemia.	Blood cultures positive, heart murmur, cardiac imaging abnormalities, absence of temporal artery or large vessel inflammation on imaging.
ANCA-associated vasculitis	Constitutional symptoms, elevated inflammatory markers, vascular involvement.	Positive ANCA serology (anti-PR3 or anti-MPO), smaller vessel involvement (glomerulonephritis, pulmonary hemorrhage), different demographic (younger patients), nasal/sinus involvement common.
Primary CNS vasculitis	Headache, neurological symptoms, elevated inflammatory markers.	Neurological deficits, abnormal brain MRI with multiple lesions, CSF pleocytosis, angiographic abnormalities of intracranial vessels, negative temporal artery biopsy and extracranial imaging.
Metastatic cancer	Constitutional symptoms, elevated inflammatory markers, anemia, weight loss.	Identification of primary tumor or metastases on imaging, abnormal tumor markers, absence of arterial inflammation, lymphadenopathy.
Atherosclerosis	Large vessel involvement on imaging, vascular stenosis, old age.	Calcified plaques, eccentric rather than concentric vessel wall thickening, traditional cardiovascular risk factors, lower inflammatory marker elevations.

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CNS, central nervous system; CSF, cerebrospinal fluid; GCA, giant cell arteritis; MRI, magnetic resonance imaging; MPO, myeloperoxidase; PR3, proteinase 3.

9.2. Age-Related Diagnostic Considerations

The elderly population affected by GCA frequently presents diagnostic challenges due to multiple comorbidities and frequent atypical presentations [132]. Age-related changes, including presbyopia, cataracts, and chronic pain conditions, may mask or mimic GCA symptoms [133,134]. Polypharmacy and medication interactions may complicate laboratory interpretation and treatment decisions [135].

Cognitive impairment in elderly patients may limit symptom reporting accuracy and adherence to diagnostic procedures [136]. Healthcare providers must maintain a high index of suspicion while carefully evaluating competing diagnoses in this vulnerable population [137].

10. Treatment Implications and Monitoring

10.1. Glucocorticoid Therapy

High-dose glucocorticoids remain the cornerstone of GCA treatment. Optimal initial glucocorticoid dosing remains debated. Traditional regimens used prednisolone 40–60 mg daily for uncomplicated cranial disease, but recent evidence suggests that lower initial doses (30–40 mg daily) may provide equivalent efficacy with reduced toxicity in selected patients [138]. Patients with visual involvement require higher doses, with most guidelines recommending intravenous methylprednisolone 500–1000 mg daily for 3 days followed by high-dose oral therapy [139]. Treatment should be initiated immediately upon clinical suspicion without waiting for confirmatory testing, as delays beyond 48 h may result in irreversible complications, especially permanent visual loss [140].

Tapering strategies significantly impact outcomes. Rapid tapering (reaching 10 mg daily by 3 months) increases relapse risk compared to more gradual approaches. The GCA Actemra (GiACTA) trial's 26-week taper (from 40 mg to zero) demonstrated feasibility in tocilizumab-treated patients but resulted in high relapse rates (86%) in placebo-treated patients [141]. The optimal tapering schedule remains debated, with EULAR recommendations suggesting reduction to 15–20 mg daily within 2–3 months and <5 mg daily by one year [142,143]. Current evidence supports individualized tapering based on symptoms, inflammatory markers, and imaging findings, with slower tapers (maintaining 10–15 mg daily for 6–12 months) in high-risk patients, including those with large vessel involvement, cranial ischemic complications, or relapsing disease [144,145]. However, relapse rates of 40–75% during tapering necessitate careful monitoring and individualized approaches [146]. Prolonged glucocorticoid exposure results in significant toxicity in >80% of patients, including posterior subcapsular cataracts (41%), bone fractures (38%), infections (31%), and hypertension (22%), among others [147].

10.2. Steroid-Sparing Agents

Tocilizumab represents the first Food and Drug Administration (FDA)-approved steroid-sparing agent for GCA, demonstrating significant efficacy in the GiACTA trial with sustained remission rates of 56% (weekly dosing) and 53% (every other week) compared to 14–18% with placebo at 52 weeks [141]. The drug provides substantial glucocorticoid-sparing effects and improved health-related quality of life [141].

Long-term tocilizumab studies reveal relapse rates of approximately 50% following discontinuation, suggesting a potential need for extended treatment in selected patients [148]. Cost considerations, side effects such as liver damage, worsening hyperlipidemia or increased infection risks, and the lack of universal patient response limit widespread accessibility, highlighting need for additional therapeutic options [149].

Upadacitinib was FDA-approved for the treatment of GCA in November 2024 based on the results of the SELECT-GCA clinical trial. The trial demonstrated that 15 mg daily of

upadacitinib in combination with a glucocorticoid taper achieved a sustained remission rate of 46% compared to 29% in the placebo group, with a safety profile consistent with other approved indications [150].

Meta-analysis of individual patient data suggests that methotrexate 15–25 mg weekly provides modest reduction in relapse risk (RR 0.65–0.85) and cumulative glucocorticoid exposure (mean reduction 842 mg over first year), though these benefits are substantially smaller than those seen with tocilizumab or upadacitinib [151–154].

Practical considerations for methotrexate use include dosing typically 15–20 mg weekly (oral or subcutaneous), mandatory folic acid supplementation, baseline assessment and monitoring of liver and renal function and blood counts, and awareness that beneficial effects may not become apparent until 12–16 weeks of therapy. The modest benefit–risk profile suggests that methotrexate may be most appropriate for patients unable to access or tolerate biologics, or as adjunctive therapy in refractory cases.

Leflunomide shows promise in recent studies, with relapse reduction in over 75% of patients and favorable safety profile [155].

Critical Appraisal of Biologic Evidence

Tocilizumab's efficacy is supported by the high-quality GiACTA trial (n = 251, randomized, double-blind) which demonstrated sustained remission in 56% (weekly dosing) vs. 14% (placebo) at 52 weeks. However, critical analysis reveals important limitations: (1) after tocilizumab discontinuation at 52 weeks, approximately 50% of patients relapsed within the subsequent year, raising questions about optimal treatment duration; (2) the trial excluded patients with recent visual loss, limiting generalizability to high-risk patients; (3) cost (approximately $30,000–40,000 USD annually) limits accessibility; and (4) while glucocorticoid-sparing effects are substantial, patients still received significant cumulative glucocorticoid exposure (1862 mg in weekly tocilizumab arm vs. 3296 mg in placebo arm) [141,156].

Upadacitinib approval is based on the SELECT-GCA trial (n = 428), which showed sustained remission in 46% vs. 29% (placebo) with similar safety to other indications [150]. Critical considerations include the following: (1) shorter follow-up (52 weeks) than available for tocilizumab (multiyear data available); (2) the 17-percentage-point difference, while statistically significant, represents modest absolute benefit; (3) the trial used a shorter glucocorticoid taper (26 weeks) compared to typical clinical practice; (4) as an oral medication, upadacitinib may offer convenience advantages over subcutaneous tocilizumab, but requires consideration of JAK-inhibitor class warnings (infections, malignancy, cardiovascular events) established in other diseases. While upadacitinib demonstrated a statistically significant benefit (46% vs. 29%, absolute difference 17 percentage points), this is notably more modest than tocilizumab's performance in GiACTA (56% vs. 14%, absolute difference 42 percentage points), suggesting that tocilizumab remains the preferred biologic agent when glucocorticoid-sparing therapy is indicated.

Head-to-head trials comparing tocilizumab and upadacitinib are lacking, and biomarkers to guide selection between these agents are not available. Treatment selection currently relies on factors including patient preference for administration route, comorbidities, cost/insurance coverage, and physician experience.

10.3. Emerging Therapeutic Targets

Multiple novel therapeutic approaches are under investigation, reflecting improved understanding of GCA pathophysiology [114,157] (Figure 4).

IL-17 inhibition with secukinumab demonstrated encouraging results in Phase II trials, with sustained remission rates of 59.3% compared to 8.0% with placebo [158]. However,

The Phase III GCAptAIN study (NCT04930094), which evaluated secukinumab in adults with newly diagnosed or relapsing GCA did not meet its primary endpoint of sustained remission at week 52 according to results announced by Novartis in 2024 (full peer-reviewed results pending publication). The failure of the Phase III trial to confirm Phase II results suggests that the Phase II findings may represent a false positive, and IL-17 inhibition does not appear to be an effective therapeutic target for GCA based on current evidence. Publication of the complete Phase III dataset will be important for understanding why the promising Phase II results were not reproduced.

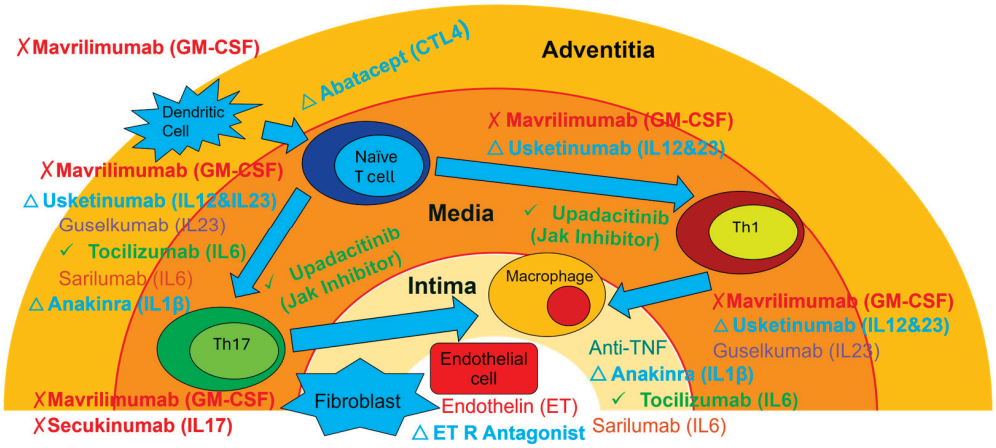

Figure 4. Therapeutic targets in GCA according to pathogenesis. This schematic illustrates the inflammatory cascade across the three layers of the arterial wall, the adventitia, media, and intima, and identifies the specific points of intervention for current and emerging biologic therapies. **In the adventitia,** the process is initiated by DCs which activate naïve T cells. This costimulation is targeted by abatacept (cytotoxic T-lymphocyte associated protein 4 [CTLA4]-Ig). **In the media,** activated T cells differentiate into Th1 and Th17 subsets. GM-CSF (targeted by mavrilimumab) and IL-12/23 (targeted by ustekinumab) drive this differentiation. JAK inhibitors act intracellularly to block these signaling pathways. **In the intima,** effector cells like macrophages and fibroblasts accumulate, leading to IL-6 production (targeted by tocilizumab/sarilumab) and TNF release. Endothelial cells release endothelin (ET), which promotes vascular remodeling and narrowing, countered by ET receptor antagonists. Agents are color-coded by regulatory/development status: green checkmark (✓)—FDA-approved agents (tocilizumab, upadacitinib); red X (✗)—Phase III failed (secukinumab) or development-terminated agents (mavrilimumab); blue triangle (△)—investigational agents (abatacept, ustekinumab, anakinra, endothelin receptor antagonists). **Abbreviations:** CTL4, Cytotoxic T-Lymphocyte Associated Protein 4; ET/ET R, endothelin/endothelin receptor, GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; IL, interleukin; JAK, Janus Kinase; Th1, T Helper Type 1 cell; Th17, T Helper Type 17 cell; TNF, tumor necrosis factor.

GM-CSF receptor blockade with mavrilimumab targets multiple pathogenic pathways and showed significant flare reduction in Phase II studies [9]. In early 2024, Kiniksa terminated its licensing agreement for mavrilimumab and discontinued its development for GCA to pivot to a cardiovascular-focused pipeline, effectively halting the planned Phase III trial. This termination prevented definitive evaluation of the GM-CSF pathway in GCA and raises questions about the clinical translational potential of this mechanism in GCA management.

As some of these are recently completed trials, we note where information is derived from company announcements pending full peer-reviewed publication.

Additional investigational agents include IL-1 receptor antagonists (anakinra), IL-23 inhibitors (guselkumab), and T cell costimulation blockers (abatacept) [114]. These diverse mechanisms reflect the complex pathophysiology of GCA and potential for personalized therapeutic approaches based on individual disease phenotypes [159].

10.4. Long-Term Disease Management

Treatment duration varies considerably among patients, with meta-analysis revealing that 89.7% remain on glucocorticoids at one year, 75.2% at two years, and 44.3% at five years. Mean glucocorticoid doses at these timepoints are 9.1 mg/day and 7.8 mg/day, respectively [160].

10.5. Predictors of Disease Relapse

Disease relapse occurs in 30–50% of patients during treatment tapering, with higher rates in younger patients, females, and those with large vessel involvement [161].

Identifying patients at high relapse risk could enable personalized monitoring and treatment strategies. Established predictors of increased relapse risk include the following:

1. Clinical factors:
    - Large vessel involvement at diagnosis.
    - Younger age at diagnosis (<60–65 years).
    - Female sex (modest association.
    - PMR symptoms at diagnosis.
    - History of prior relapse.
    - Prolonged disease duration and treatment.
2. Laboratory/imaging markers:
    - Persistently elevated or slow-to-normalize inflammatory markers during initial treatment.
    - Persistent vascular inflammation on FDG-PET or ultrasound despite clinical remission.
    - Thrombocytosis at diagnosis or during follow-up.
3. Treatment-related factors:
    - Rapid glucocorticoid tapering (reduction >10 mg/month).
    - Glucocorticoid dose <10–15 mg daily at time of relapse consideration.
    - Non-adherence to treatment.

Machine learning algorithms incorporating multiple clinical and laboratory parameters have demonstrated 71–76% accuracy in predicting relapse, superior to individual risk factors, though these require prospective validation before clinical implementation. The development and validation of composite risk scores could enable stratified approaches with intensive monitoring and preemptive treatment adjustments for high-risk patients [161].

11. Prognosis and Long-Term Outcomes

11.1. Visual Outcomes

Visual recovery following GCA-related vision loss remains disappointingly limited, with only 15% of patients showing improvement in visual acuity within the first month, and 5% demonstrating corresponding visual field improvement [162]. Visual deterioration occurs in approximately 27% of eyes within the first week despite high-dose intravenous glucocorticoids, with greatest risk in the first six days [163].

The irreversible nature of most visual complications emphasizes the critical importance of prevention through early recognition and treatment [164]. Recent studies suggest that 13.7% of GCA patients experience vision loss, which rarely recovers and is statistically more likely with advancing age [36].

11.2. Cardiovascular and Aortic Complications

GCA patients demonstrate significantly increased risk of aortic aneurysm development, with five-year risk of 3.6% compared to 1.8% in controls. Thoracic aortic aneurysms occur in 2.2% versus 1.0% of controls, while abdominal aortic aneurysms affect 1.8% versus 0.8% [4]. These complications may develop years after initial diagnosis and require long-term surveillance [165].

Aortic dissection represents a rare but life-threatening complication, occurring in approximately 1% of patients [166]. Symptomatic aortitis at diagnosis, characterized by chest or abdominal pain, identifies patients at particularly high risk for subsequent aortic complications with hazard ratio of 6.64 [167,168]. However, overall survival may not differ significantly from age-matched populations, particularly beyond the first five years following diagnosis [169].

11.3. Prevention and Mitigation of GCA-Related and Treatment-Related Complications

Given that >80% of GCA patients experience glucocorticoid-related toxicity, proactive prevention strategies are essential.

All patients initiating glucocorticoid therapy should undergo baseline bone density assessment and receive calcium (1200–1500 mg daily) and vitamin D (800–1000 IU daily) supplementation, with bisphosphonate therapy for those with osteoporosis or high fracture risk [170–172].

Baseline screening and regular monitoring for diabetes and hypertension are critical, with early intervention when indicated.

Vaccinations should be updated before initiating immunosuppression (pneumococcal, influenza, zoster), and *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis considered in patients receiving >20 mg prednisone daily for >1 month [173,174].

Annual ophthalmologic examination for cataracts and glaucoma is recommended. Given the 5-year aortic aneurysm risk of 3.6% (nearly double that of controls), systematic vascular surveillance is warranted. Baseline chest imaging to assess the thoracic aorta and consideration of periodic imaging (every 2–3 years) with CTA, MRA, or ultrasound for aortic assessment is recommended [175–177]. More frequent monitoring (annually) should be considered in patients with symptomatic aortitis at diagnosis, extensive large vessel involvement, or persistent vascular inflammation on imaging [175–177].

Emergency treatment protocols should be established for any new visual symptoms, with patient education regarding warning signs (amaurosis fugax, diplopia, visual field defects) [178,179].

Aspirin therapy (81–100 mg daily) may reduce cranial ischemic event risk, though evidence is not definitive [178,179].

Regular assessment of quality of life, physical therapy to maintain function, early introduction of steroid-sparing agents in high-risk patients, and screening for depression (affecting 20–30% of GCA patients) optimize long-term outcomes [180,181].

These preventive strategies require systematic implementation through structured care pathways [182].

12. Future Directions and Emerging Technologies

12.1. Artificial Intelligence (AI) and Machine Learning

AI applications in GCA diagnosis and management represent rapidly evolving areas with significant potential [161,183,184]. Machine learning algorithms demonstrate effectiveness in predicting GCA diagnosis and relapse risk, with random forest models achieving 71–76% accuracy using clinical and laboratory data [185–187].

https://doi.org/10.3390/diagnostics16030470

Deep learning approaches for ultrasound image analysis show promise for automated halo sign detection and diagnostic support [183,184]. Convolutional neural networks applied to temporal artery biopsy specimens may enhance histopathological interpretation and reduce inter-observer variability [188].

Point-of-care ultrasound (POCUS) combined with AI-driven diagnostics could revolutionize GCA diagnosis, particularly in emergency and primary care settings [189]. Such systems could provide rapid, on-the-spot diagnosis and potentially prevent up to 500,000 cases of visual impairment projected by 2050 [190].

12.2. Advanced Imaging Technologies

Novel imaging techniques continue to expand diagnostic capabilities and disease understanding [191]. Contrast-enhanced ultrasound, shear wave elastography, and ultrasound biomicroscopy offer enhanced tissue characterization and may improve diagnostic accuracy [192].

PET-MRI integration combines the inflammatory detection capabilities of PET with superior anatomical resolution of MRI. Novel PET tracers beyond FDG may provide more specific inflammatory targeting and reduced background uptake [193].

Black blood MRI techniques and orbital MRI show particular promise for detecting cranial vessel involvement and ophthalmic complications. These advances may enable earlier detection of subclinical disease and better monitoring of treatment response [194].

12.3. Personalized Medicine Approaches

The recognition of distinct GCA phenotypes suggests potential for personalized diagnostic and therapeutic strategies. Evidence increasingly supports phenotype-based treatment stratification: (1) cranial-predominant GCA may be optimally managed with shorter treatment courses (18–24 months); (2) large vessel-predominant GCA likely requires longer treatment duration (>2–3 years) with routine imaging surveillance given higher relapse rates; and (3) PMR-overlap phenotype requires clarification regarding optimal management intensity [175,195].

Emerging evidence suggests that biomarker-guided therapeutic selection may improve outcomes. High IL-6 levels at diagnosis predict better tocilizumab response in some studies [196]. However, despite IL-6 having been detected in temporal arteritis, and the efficacy of IL-6-inbition treatments, the diagnostic value of serum IL-6 for GCA is limited. Although IL-6 measurement is increasingly available in many laboratories, it is likely to have similar limitations to the analysis of ESR and CRP despite much higher costs, which limits its use in clinical practice [197]. Imaging-detected persistent vascular inflammation during clinical remission identifies high relapse risk patients who may benefit from treatment intensification [198]. Pharmacogenomic applications show promise: polymorphisms in glucocorticoid receptor genes (NR3C1, HSD11B1, ABCB1) influence efficacy and toxicity [199], while variants in IL-6 pathway genes may predict tocilizumab response and [200,201].

Integration of clinical, laboratory, and imaging data into composite risk scores could enable precision medicine, including diagnostic risk scores, relapse risk scores, and complication risk scores [202]. Machine learning algorithms have demonstrated 71–76% accuracy in predicting relapse [187], though prospective validation is required before clinical implementation.

Translating personalized medicine to clinical reality requires validation of phenotype classifications in large multicenter cohorts, prospective biomarker validation studies with predefined treatment algorithms, clinical trials testing phenotype-specific protocols versus standard care, development of point-of-care assays, integration of prediction algorithms into electronic health records, and cost-effectiveness analyses [203,204].

https://doi.org/10.3390/diagnostics16030470

13. Conclusions

Giant cell arteritis exemplifies the challenges of diagnosing and managing heterogeneous systemic vasculitis in an aging population. Three key developments have transformed the GCA landscape, and they define the path forward.

First, the diagnostic paradigm has shifted from biopsy-centric, criteria-based classification toward multimodal, probabilistic assessment. The integration of vascular imaging with clinical evaluation enables earlier diagnosis, particularly of large-vessel-predominant disease. The 2022 ACR/EULAR classification criteria formalize this approach, though accessibility challenges and the classification-versus-diagnosis distinction remain important limitations.

Second, therapeutic advances, particularly tocilizumab and upadacitinib approval, provide evidence-based alternatives to prolonged glucocorticoid monotherapy, yet important questions remain. The modest absolute benefits (46–56% sustained remission versus 14–29% with placebo) highlight the need for more effective therapies and biomarkers to guide therapeutic selection, optimal treatment duration, and strategies for preventing late complications.

Third, the evolution toward personalized medicine, supported by phenotypic classification, imaging-based risk stratification, and emerging predictive algorithms, offers potential to match treatment intensity to individual patient risk, though this requires prospective validation.

Key priorities for advancing GCA care include development of composite biomarker panels, comparative effectiveness trials of biologics and combination strategies, standardized implementation of fast-track diagnostic pathways, systematic aortic surveillance protocols, integration of AI-assisted diagnostic tools, and investigation of treatment de-escalation strategies.

Important limitations remain in the GCA literature, including heterogeneity in diagnostic criteria across studies, limited head-to-head imaging comparisons, predominantly Caucasian study populations limiting generalizability, and paucity of data on optimal treatment duration and safe discontinuation predictors.

GCA management has evolved from diagnostic uncertainty and treatment limited to glucocorticoids to an era of sophisticated imaging, mechanistically targeted therapeutics, and emerging precision medicine approaches. The ultimate goal, i.e., preventing irreversible complications while minimizing treatment toxicity through early, accurate diagnosis and personalized management, is increasingly achievable but requires sustained research investment and systematic quality improvement efforts.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: Alicia Rodriguez-Pla (ARP) is the owner and founder of Premier Rheumatology, P. C. ARP also reports serving as a member of an independent Data Monitoring Committee for Bristol Myers Squibb and has served as a member of a scientific advisory board for AstraZeneca. These roles occurred within the 36 months prior to this submission. The companies and entities had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. ARP also formerly served as a Principal Investigator for clinical trialsinvolving systemic lupus erythematosus and IgG4-related

diseasesponsored by Zenas BioPharma. Her involvement in those trials concludedin 2025. These past roles are outside the scope of the current review onvasculitis.

Abbreviations

The following abbreviations are used in this manuscript:

AAION	Arteritic anterior ischemic optic neuropathy
ACR	American College of Rheumatology
AI	Artificial intelligence
BAFF	B-cell activating factor
CD	Cluster of differentiation
CDUS	Color Doppler ultrasound
CTL4	Cytotoxic T-lymphocyte associated protein 4
CRP	C-reactive protein
CT	Computed tomography
CTA	Computed tomography angiography
DC	Dendritic Cell
ESR	Erythrocyte sedimentation rate
ET/ET R	Endothelin/Endothelin receptor
EULAR	European League Against Rheumatism
FDG	Fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose positron emission tomography
FR	Folate receptor
GiACTA	Giant cell arteritis Actemra trial
GM-CSF	Granulocyte macrophage colony-stimulating factor
HLA	Human leukocyte antigen
IL	Interleukin
i NOS	inducible nitric oxide synth2ase
JAK	Janus Kinase
IEL	Internal elastic lamina
IFN-γ	Interferon-γ
iNOS	inducible nitric oxide synthase
LV-GCA	Large vessel giant cell arteritis
MMP	Matrix metalloproteinase
MPO	Myeloperoxidase
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PDGF	Platelet-derived growth factor
PET	Positron emission tomography
PMR	Polymyalgia rheumatica
POCUS	Point-of-care ultrasound
PR-3	Proteinase-3
SAA	Serum amyloid A
TAB	Temporal artery biopsy
TGF-β1	Transforming growth factor-β1
Th1	T Helper Type 1 cell
Th17	T Helper Type 17 cell
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

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Interesting Images

Central Retinal Artery Occlusion Associated with Takayasu Arteritis

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Abstract: Takayasu arteritis is a chronic inflammatory vasculitis with granulomatous panarteritis particularly impacting large vessels including the aorta and its branches, especially the subclavian arteries, with clinical manifestation dependent on the involved artery. Sequelae of the active disease vary, including stenosis, occlusions, or aneurysmal dilatations of the large vessels. The prevalence of Takayasu arteritis is higher in the Asian population and in Japan, but quite low in the United States, varying from 0.9–8.4 per million people. Ocular manifestations are rare and lead to a delay in diagnosis and appropriate treatment. Ocular manifestations include Takayasu retinopathy, anterior ischemic optic neuropathy (AION), retinal artery occlusion (RAO) and retinal vein occlusion (RVO). We present two cases in which central retinal artery occlusion (CRAO) was associated with Takayasu arteritis. CRAO is an ophthalmic emergency with an incidence of 1.9 per 100,000 person years in the United States; only 5% of cases are arteritic, which can be observed with inflammatory vasculitides secondary to the formation of immune deposits.

Keywords: Takayasu arteritis; retinal artery occlusion; large-vessel vasculitis

A 35-year-old woman with a prior history of left central retinal artery occlusion and bilateral sensorineural hearing loss, initially concerning with respect to neurosarcoidosis (never histologically proven), presented for clinical follow-up. She had a complicated disease course dating back many years, involving different specialists, and including fluctuating hearing loss partially responsive to corticosteroids necessitating cochlear implants and developed central retinal occlusion of the left eye (Figures 1 and 2). This was concerning with respect to possible underlying inflammatory conditions such as neurosarcoidosis or Susac syndrome (MRI atypical sans corpus lesion), and she received IV immunoglobulin treatment. When she returned for follow-up, she had complaints of episodes of confusion, but quiescent symptoms without visual change, status post adalimumab and methotrexate addition. She sought emergency care for new transient arm numbness and confusion, and a neck CTA revealed carotid bulb circumferential thickening suggestive of vasculitis. A rind of soft tissue thickening involving the distal half of the common carotid artery, carotid bifurcation and the proximal internal and external carotid arteries was visualized. There was smooth narrowing of the encased carotid artery lumen, producing roughly 50% diameter stenosis of the distal common carotid artery. A small ulceration was noted on the left carotid bulb (Figures 3–5). The patient was initiated on infliximab with IV methylprednisolone and close follow-up with neurology and vascular medicine for management of Takayasu arteritis.

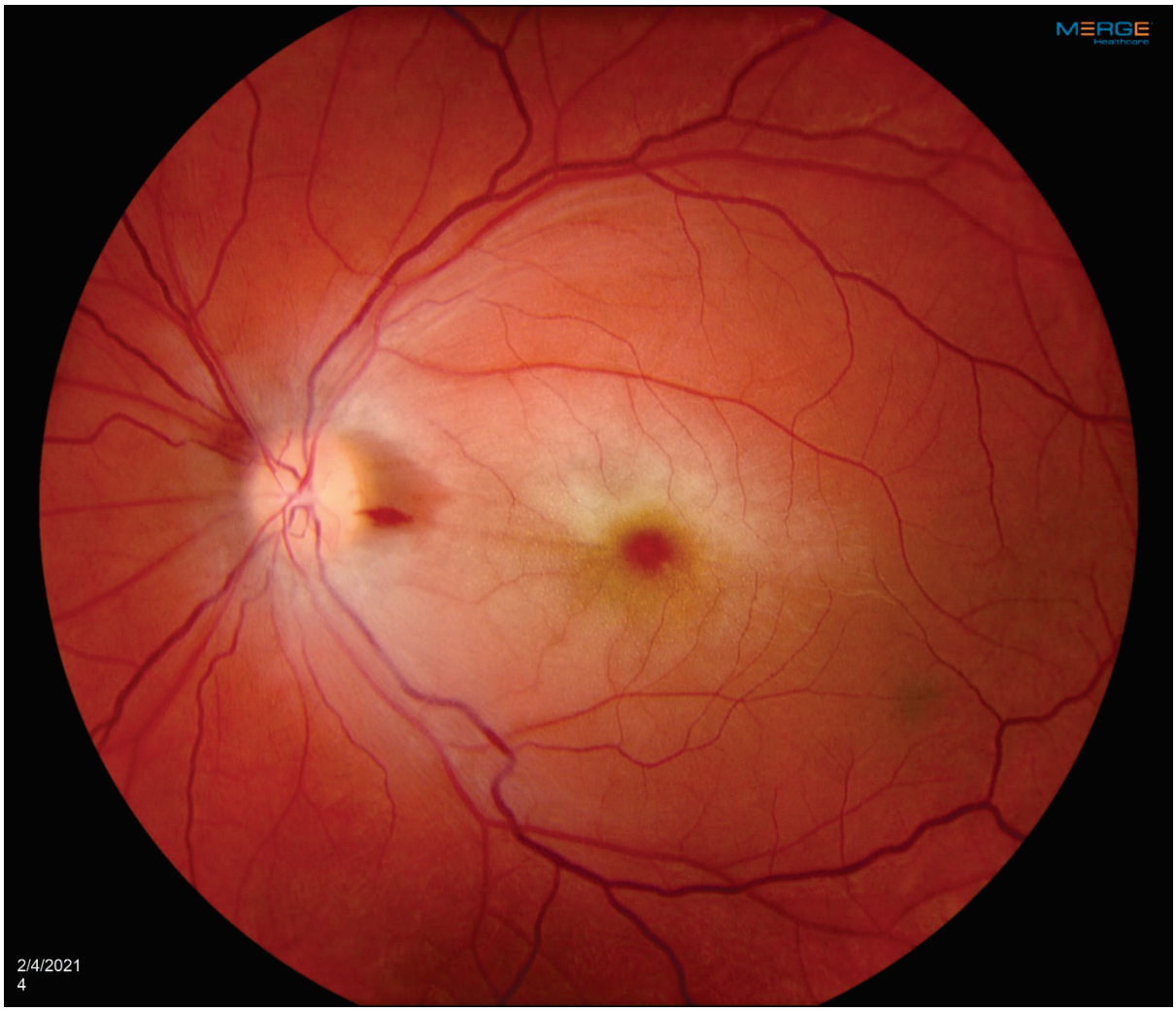

Figure 1. OS fundus photograph showing central retinal artery occlusion with characteristic cherry red spot and attenuated blood vessels. Patient developed left central retinal artery occlusion years prior to vasculitis diagnosis with loss of vision at a young age.

A 56-year-old woman was diagnosed with Takayasu arteritis in 1991, and initially treated with glucocorticoids for several years. Initial symptoms included constitutional symptoms and left-sided carotidynia. She had markedly elevated inflammatory markers and anemia at disease onset, and later developed erythema nodosum. Imaging studies in the early phase of her illness revealed moderate stenosis of the right subclavian artery and marked thickening of the left common carotid. She was subsequently treated with methotrexate and cyclosporine, and eventually her disease went into remission. In 2014, an MR angiogram of the chest showed radiographic evidence of vessel wall edema in the aorta, and at that time, the patient was started on mycophenolate mofetil. In November 2017, the patient developed blurry vision and there was leakage on her fluorescein angiogram, which was felt to be nonspecific. She was taken off mycophenolate due to no evidence of active vasculitis in clinical or laboratory findings. She was in remission; however, she required ascending aorta hemiarch repair and aortic valve replacement (and was subsequently on warfarin) for a dilated aortic root of 61 mm with histopathology showing healed arteritis. Two years later, she developed a paracentral scotoma in the left eye and was diagnosed by outside Ophthalmology as having branch retinal artery occlusion by retinal imaging, with suspected embolic disease in the context of subtherapeutic anticoagulation.

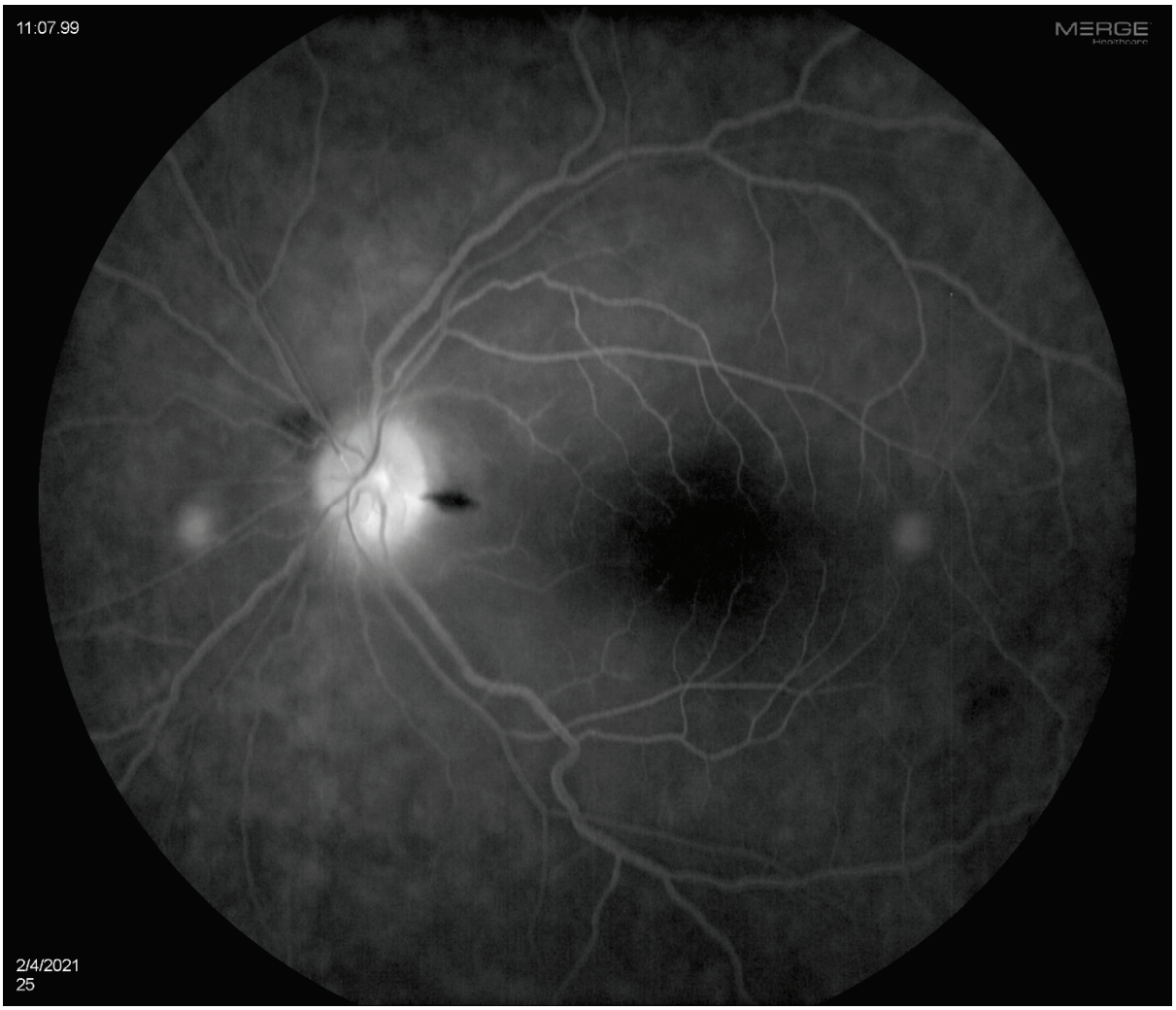

Figure 2. OS fluorescein angiogram showing arterial narrowing with some stain of vessels on the superior optic disc.

Clinical characteristics of patients with ocular manifestations and Takayasu's arteritis have been reported to be similar to those of patients without ocular manifestations with a mean age in the third decade of life and a majority of Asian origin. Ocular manifestations of Takayasu arteritis can be seen in a wide range (8.1–68%) of patients [1]. Apart from two case-based systematic reviews, the current literature is lacking in describing the extent of ocular involvement in Takayasu arteritis [1,2]. The current classification of Takayasu arteritis does not include visual changes, and consequently no ophthalmological examination is recommended, even after diagnosis, and ocular manifestations can go unnoticed.

A study by Pasko et al. noted ocular manifestations presenting prior to diagnosis of Takayasu arteritis in 74.6% of cases [3]. This may be explained by cases in which initial manifestations included constitutional symptoms that were non-specific. Limitation of flow in the carotid artery results in chronic ischemia and hypoperfusion retinopathy, and ocular ischemic syndrome may be of consequence [4]. It remains imperative to distinguish and categorize this ocular disorder and pursue retinal angiograms.

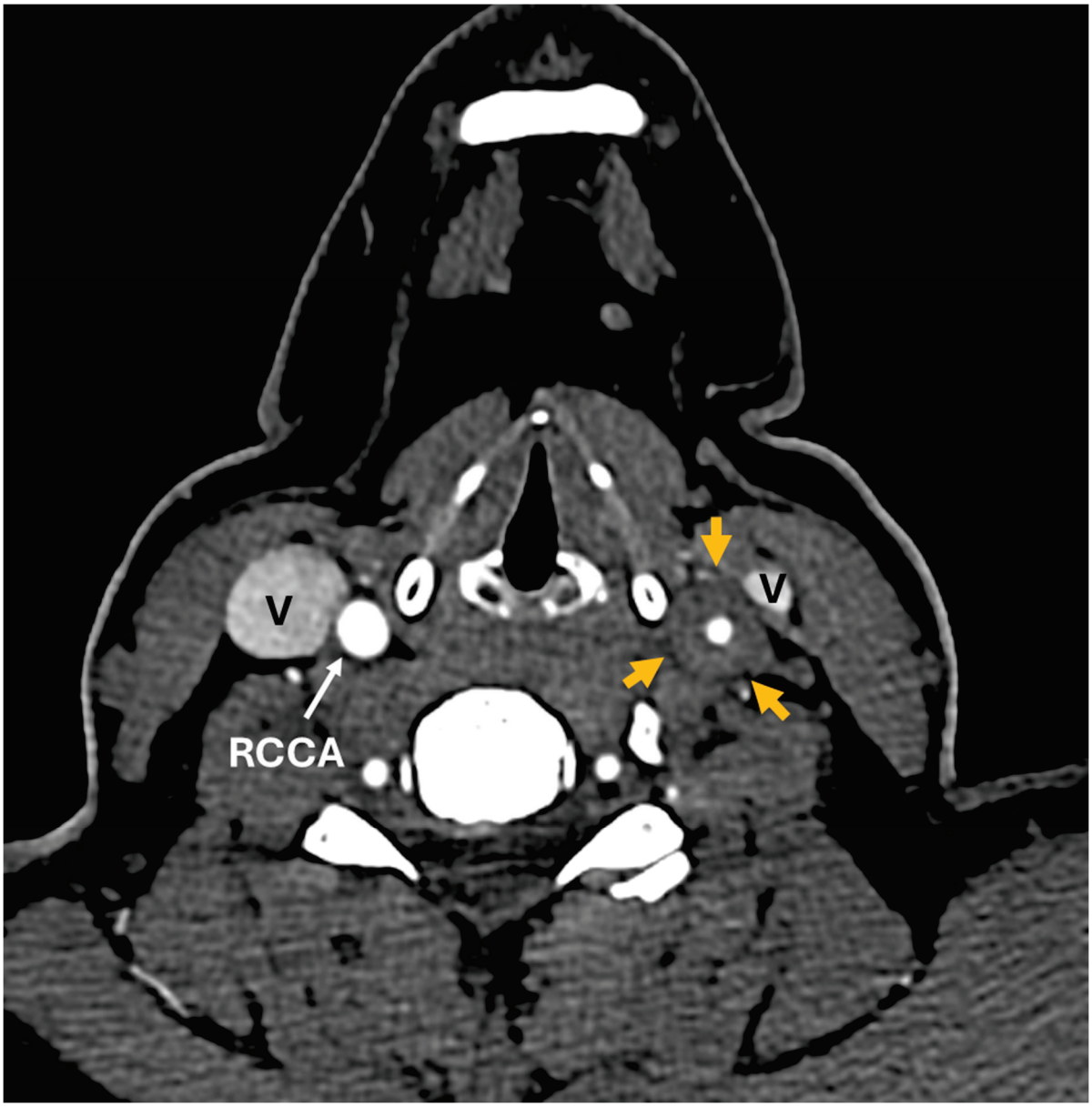

Figure 3. CT angiogram. Axial images below the level of carotid bifurcation show diffuse circumferential thickening of common carotid artery (CCA) and internal carotid artery (ICA) walls on the left side (orange arrows).

A study from 1994 pointed to the presence of Takayasu's retinopathy as a statistically significant poor prognostic factor [5]. Mirouse et al. associated Takayasu retinopathy independently with mortality and complication-free survival [6]. Reportedly, 64% of CRAO patients develop new vascular risk factors after a retinal occlusive event, implying this population of patients is prone to a secondary ischemic event and needs risk factor assessment [7]. Although medical management is the recommended initial management for Takayasu arteritis, patients who have vascular complications may require surgical interventions and endovascular procedures [8]. Medical management includes ocular massage, hyperbaric oxygen therapy, and intravenous tissue-type plasminogen activator; however, these are associated with risks, including mobilization of the embolus and exacerbating macular edema. Endovascular treatments, including intra-arterial thrombolysis, have shown promising results; however, they require exceptional skill to perform [9].

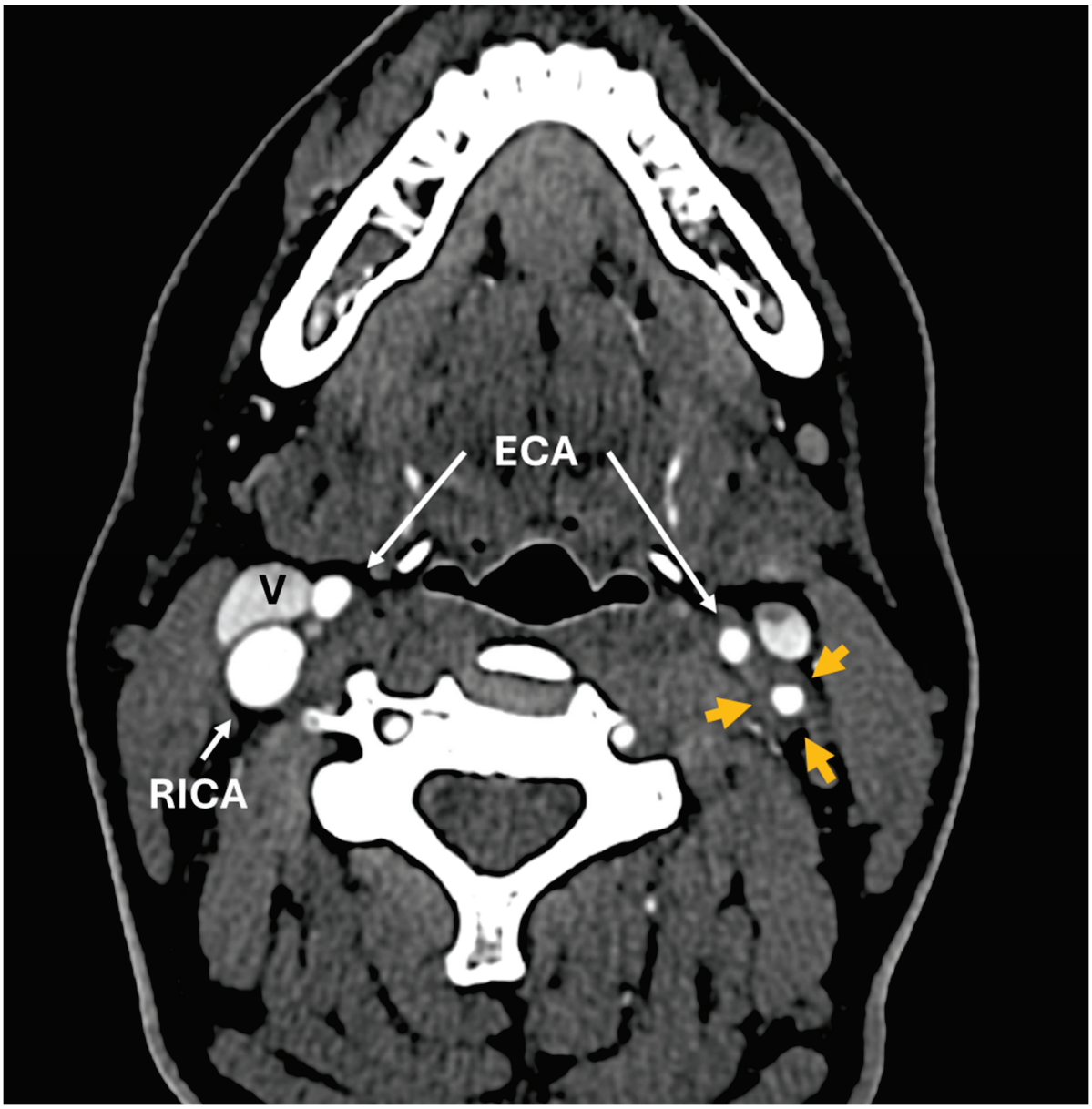

Figure 4. CT angiogram. Axial images above the level of carotid bifurcation show diffuse circumferential thickening of common carotid artery (CCA) and internal carotid artery (ICA) walls on the left side (orange arrows). Compare this to the normal wall thickness of the right carotid artery. White arrows point to the right common carotid artery (RCCA), right internal carotid artery (RICA) and bilateral external carotid arteries (ECAs). Internal jugular veins: (V). A repeat CT neck angiogram with contrast revealed a left-sided diffuse circumferential rim of soft tissue thickening involving the left carotid artery, which was concerning with respect to large-vessel vasculitis. It is unclear how long the carotid bulb thickening had been present.

Although information on ocular ischemia surgical management for Takayasu arteritis patients is limited, case series and case reports have demonstrated favorable results of balloon angioplasty and endovascular stenting in Takayasu retinopathy patients [1]. Adopting routine fundus fluorescein angiography for surveillance in patients with Takayasu arteritis may be beneficial. Newer diagnostic techniques, especially optical coherence tomography (OCT) angiography (OCTA), and novel diagnostics to assess retina perfusion must be investigated [1].

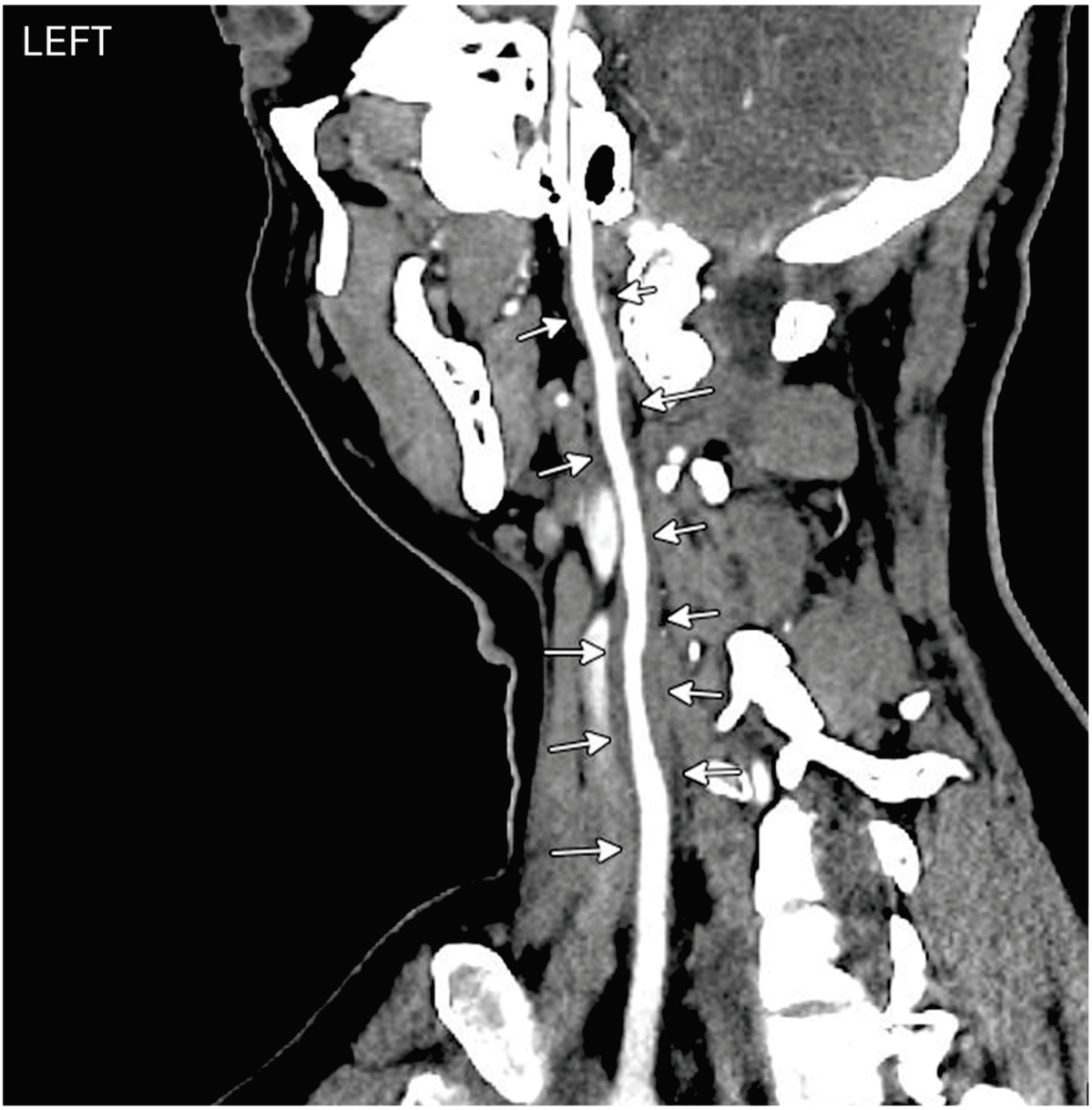

Figure 5. CT angiogram. Left carotid artery centerline reconstructions show diffuse arterial wall thickening (white arrows).

In young patients with visual loss and deficits, it is imperative to recall Takayasu arteritis as a potential suspect, even though such cases are rare, because it can translate into a meaningful difference in outcomes with proper management. Raising ophthalmological awareness of this association and increasing education regarding pursuing comprehensive diagnostic testing is crucial. Further investigation of arteritic CRAO in Takayasu arteritis patients is needed for the development and implementation of enhanced therapeutic techniques.

Author Contributions: Conceptualization, S.M., C.W. and A.A.; investigation, C.W. and S.M.; writing—original draft preparation, S.M. and C.W.; writing—review and editing, S.M. and C.W.; visualization, S.M., C.W., P.V., E.R.E. and A.A.; supervision, A.A. and F.B.; project administration, A.A. and F.B. All authors have read and agreed to the published version of the manuscript.

Funding: This study received no external funding.

Institutional Review Board Statement: This study was deemed exempt by the IRB at Mayo Clinic 1/31/24. IRB number 24-000157.

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: Written informed consent has been obtained from the patient to publish this paper.

Conflicts of Interest: The authors declare no conflicts of interest.

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Interesting Images

Giant Cell Arteritis: Can Simple Ultrasound Examination Prevent Complex Consequences?

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Abstract: Giant cell arteritis (GCA) is a rare disease of the arteries, occurring mainly in the elderly. Although the involvement of temporal arteries can be mostly symptomatic, the occlusion of ophthalmic arteries has severe consequences. GCA affecting temporal arteries is an emergency requiring quick commencement of treatment with glucocorticoids due to the serious consequences of neglect—blindness. According to the new guidelines released by EULAR, ultrasound is the tool of choice in support of the clinical diagnosis of giant cell arteritis, replacing temporal artery biopsy (TAB), as it is a sensitive and non-invasive method that is widely available. The main limitation is that the reliability of this imaging is based on the technical expertise of ultrasonographers. However, performing imaging should not delay commencing the treatment. In this work, we present ultrasound images from a case report of a 74-year-old female patient where difficulties in establishing a diagnosis led to vision loss in both eyes. In this example, we describe the ultrasound findings in giant cell arteritis, emphasizing its usefulness in supporting a diagnosis of GCA.

Keywords: GCA; vision loss; headache; ultrasonography; EULAR; OMERACT

Giant cell arteritis (GCA) is a rare disease of the arteries, affecting large and medium vessels, with cranial arteries—branches of carotid arteries—the most frequently involved. The condition occurs mainly in the elderly population, predominantly over 50 [1]. As the pathophysiology of GCA involves myointimal proliferation, it inevitably leads to ischemic events due to vessel occlusion [1]. Because of the involvement of cranial arteries in most cases, the signs and symptoms mainly include headaches of new onset in the temples and jaw claudication. Scalp tenderness and, importantly, visual disturbances are not uncommon [2]. That is why new-onset headaches, especially in the elderly population, should alert healthcare professionals. However, there are also general non-specific symptoms, such as weight loss, fatigue, and fever, with elevated inflammatory markers [3].

On physical examination, tender and thickened temporal arteries can be found. Giant cell arteritis, if left untreated, leads to blindness in 30% to 50% of patients, and vision loss is irreversible if the steroid treatment is not administered within a few hours [4]. The awareness of the doctors who consult the patient first is crucial as the patient requires rheumatology consultation immediately to shorten the diagnostic path and implement treatment without delay [1].

A 74-year-old female patient was consulted by a family medicine doctor several times because of neck pain radiating to the temporal areas of the head. The patient had a history of hypertension and was treated with lisinopril and hydrochlorothiazide (10 + 12.5 mg/day). The pain did not respond to a short course of dexibuprofen, and the painful sensation gradually increased. Moreover, she began having headaches, night sweats, edema of the submandibular area, and trismus also occurred. The condition was treated as a common cold with amoxicillin with clavulanic acid. However, the patient started experiencing light flashes two days after administering the antibiotic. The vision symptoms persisted,

and additionally, nine days later, the patient's vision deteriorated in the right eye. The day after that, the patient reported difficulties with color vision. Eventually, the day after, blindness occurred.

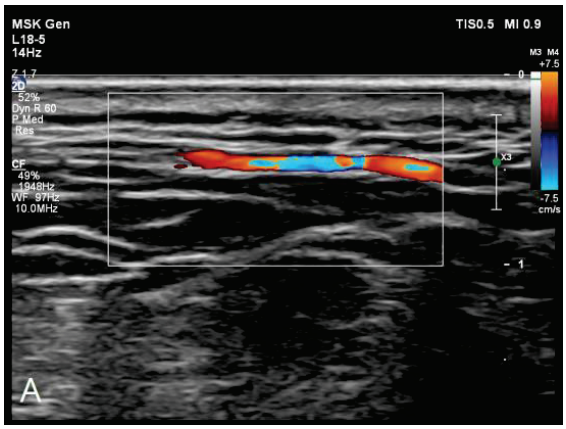
Thus, the patient was urgently admitted to the local Ophthalmology Department. The patient presented with anisocoria (L > P), the pupillary light response was medium, and she denied having any sense of light. No pursuit movements of the eyes were observed. Eventually, fundus examination revealed papilledema of the left eye and right optic nerve atrophy.

In the Ophthalmology Department, imaging was performed, including CT of the face, MRI of the orbits, and head MRI. None of them showed any significant abnormalities. Laboratory blood tests revealed an elevated CRP level of 109.8 mg/L. Upon the findings mentioned above, giant cell arteritis was suspected.

Three intravenous pulses of 1000 mg of methylprednisolone were administered on three consecutive days, then switched to oral dexamethasone at a dose of 16 mg/day. As an adjuvant therapy, vinpocetine i.v. was added. Regardless of the treatment, the vision did not improve.

Therefore, the patient was referred to the Clinical Rheumatology Department to continue the evaluations and modify the treatment. On admission, she presented with vision loss in both eyes and swelling of both temporal arteries. The erythrocyte sedimentation rate (ESR) and CRP were back to normal after initial therapy in the Ophthalmology Department, with values of 11 mm/h and 1 mg/L, respectively. There were also no significant abnormalities in other laboratory tests at that point.

In the rheumatology ward, CT angiography was carried out, and it showed a lack of contrast filling in the ophthalmic arteries. An ultrasound examination showed thickened walls of the temporal and carotid arteries with a halo sign (Figure 1B–D) and positive compression sign (Figure 2). Upon analyzing the whole clinical picture and imaging studies, the primary diagnosis of giant cell arteritis was confirmed. Therapy with glucocorticoids was continued with a daily dose tapered to 45 mg of prednisone on the day of discharge. Methotrexate at an initial dose of 20 mg per week in subcutaneous injections was added, with a planned rapid escalation to a dose of 25 mg/week. As a standard approach in methotrexate therapy, the patient was advised to take folic acid once weekly at a dose of 15 mg. The patient was also consulted by an ophthalmologist once more. The eye specialist recommended a referral to rehabilitation, aiming to improve the quality of life with blindness and enable the patient to adapt to functioning in new conditions. The patient was discharged from the hospital in a general good condition and was further evaluated in an ambulatory mode.



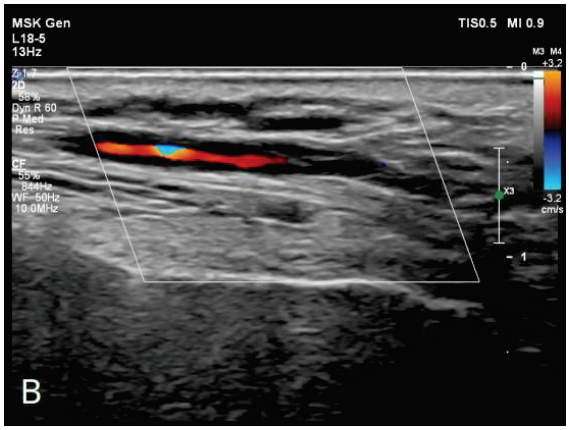


Figure 1. *Cont.*

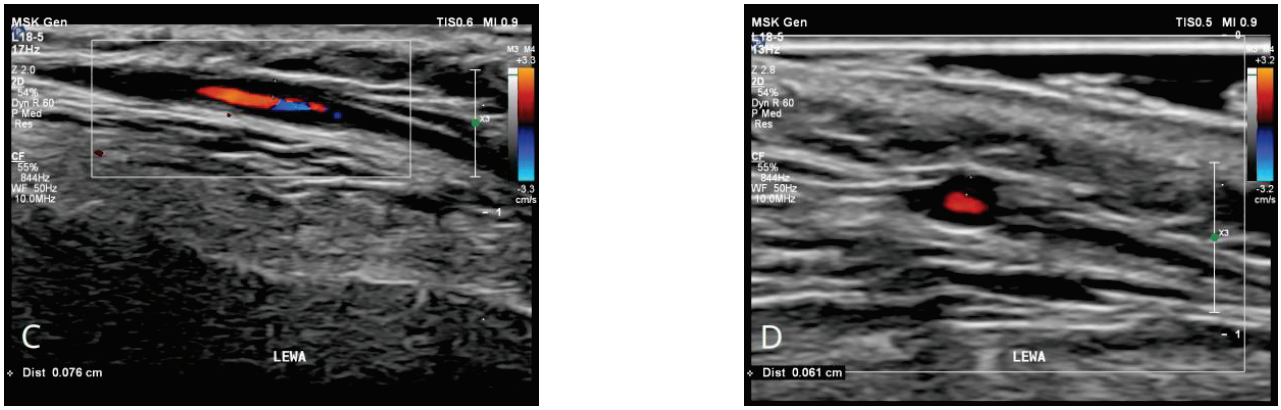


Figure 1. Ultrasonographic imaging of the temporal artery. Comparison of ultrasound images of an unchanged temporal artery (**A**) and inflammation of the temporal artery in giant cell arteritis (**B**). Both longitudinal (**C**) and transverse (**D**) views of the inflamed artery reveal the narrowing of the arterial lumen and homogenous, hypoechoic wall thickening (white markers), well delineated towards the luminal side, known as the "halo sign" [5].

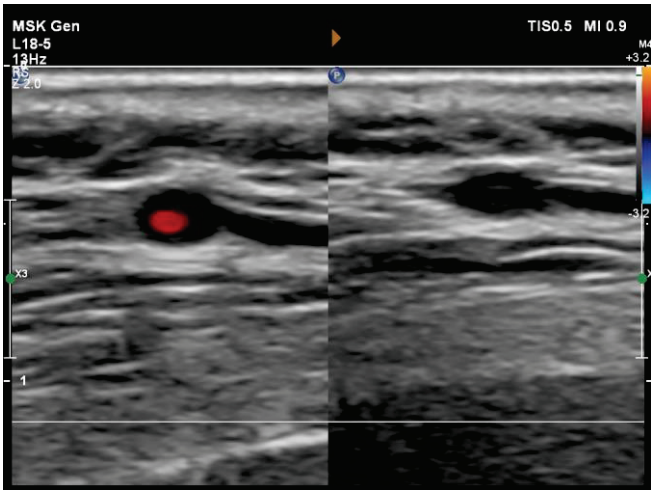


Figure 2. Detection of arterial inflammation by "compression sign". Pressure applied with an ultrasound probe collapses the artery. The resulting restriction of blood flow is confirmed by the absence or limitation of a Doppler signal in the arterial lumen. However, the thickened inflamed arterial wall remains visible as a hypoechoic area contrasting with the mid-echogenic to hyperechoic surrounding tissue [5].

The diagnostic process of GCA is challenging as some patients may present non-specific symptoms, mimicking other, less urgent conditions. Moreover, when a patient's clinical picture suggests GCA, it requires clinical experience and expertise to establish a prompt diagnosis, as a delay leads inevitably to serious consequences such as blindness [1]. Vision deterioration is often one of the first signs of GCA, as happened in the case of our patient. Recent registrations of patients with GCA showed the possible risk factors that are associated with visual involvement, which are older age and jaw claudication, while polymyalgia rheumatica, fever, a longer duration of symptoms, and a higher ESR lowered the risk of visual symptoms [6].

Imaging is recommended for every patient suspected of GCA. The "golden standard" for diagnosing giant cell arteritis has been performing temporal artery biopsy or conventional angiography for decades. However, according to the 2023 update of the EULAR [7] recommendations, ultrasound can be the first-line imaging test to be performed in cases of the suspicion of giant cell arteritis, thanks to its high diagnostic value (pooled sensitivity

from studies with low RoB of 88% and a specificity of 96%). The imaging studies aim to investigate the mural inflammatory changes in the affected arteries [7].

Due to the overlap of intra- and extra-cranial phenotypes of giant cell arteritis, according to the guidelines, axillary arteries should also be included in the ultrasound examination. It broadens the diagnostic yield and provides higher sensitivities than checking temporal arteries only [8]. In cases where neither temporal nor axillary artery scans are diagnostic, additional vessels can be included in the examination, such as facial, occipital, carotid, vertebral, subclavian, and femoral arteries, as well as the aorta [7].

According to European guidelines, TAB is still an adequate option, especially when there is no access to imaging or the sonographer's expertise is insufficient [7]. The preponderance of any of these diagnostic tools is still contentious, as seen in discrepancies between European and American guidelines for giant cell arteritis [8,9]. While the EULAR guidelines are raising the predominance of ultrasound over temporal artery biopsy, the American College of Rheumatology and Vasculitis Foundation are still reserved towards comprehensive utilization of ultrasound [9]. TAB is put conditionally in the first place as an optimal diagnostic approach, with ultrasound imaging only as a complementary tool in centers with appropriate training and expertise. Such hesitancy towards ultrasound is explained by the lesser experience of rheumatologists and radiologists in the US in using ultrasound to diagnose the involvement of temporal arteries in GCA [8].

It is worth emphasizing that even though imaging is recommended as a support to establish a diagnosis, it should not delay commencing the treatment because of the severe consequences—permanent vision loss and other ischemic complications of GCA [7]. Treatment consisting of steroids should be implemented as soon as possible. It was shown that the delay in introducing steroids when visual disturbances/visual loss are already present is the strongest risk factor for permanent blindness [1]. It was shown that performing an ultrasound examination after introducing glucocorticoid treatment gives as reliable results as performing it before starting the treatment. Therefore, it is recommended that an ultrasound, if it cannot be performed before introducing treatment, should be carried out within 72 h of pharmacotherapy [7].

Ultrasound is a readily available non-invasive method for quickly diagnosing giant cell arteritis. This is compared to angio-CT, which has several drawbacks, such as it requires an imaging center in a hospital, the procedure takes more time, radiation exposure occurs, and the patient may exhibit contraindications for administering a contrast agent. Moreover, the waiting time for a CT scan may be too long for patients with conditions requiring rapid action, such as giant cell arteritis [7]. Regardless of the undisputable advantage of ultrasound over other imaging methods, it has some limitations. It requires trained and well-qualified practitioners whose experience in ultrasonography of head and neck vessels can diagnose the pathologies with confidence and a low risk of error [7].

All patients presenting typical signs and symptoms of GCA and raised inflammatory markers (C-reactive protein, Erythrocyte Sedimentation Rate) should be promptly sent to a specialistic center with state-of-the-art imaging and TAB for a work-up of a multidisciplinary team consisting of a rheumatologist, radiologist, ophthalmologist, and/or neurologist [1,7–9]. It is essential that the diagnostic process is prompt and without any unnecessary delay so the patient can receive the proper treatment on time by the appropriate team of healthcare professionals. Prolonged diagnosis, and thereby delayed treatment, results in irreversible consequences [1]. That is why the awareness and proper training of doctors who consult the patient first—at a low level of the healthcare ladder—is important, so they can refer patients to fast-track clinics that are properly prepared for such emergencies [1,7–9].

Due to the non-specific nature of the symptoms, the diagnosis of GCA is difficult. That is why this pathology is considered to be underdiagnosed, because of the low degree of clinical suspicion [9]. Moreover, as patients with GCA are referred to the hospital from Primary Care or out-of-hospital emergencies, it implies the need for comprehensive protocols that enable bidirectional communication channels guaranteeing referrals between

specialists and the continuity of the care between the facilities. This could coordinate the services involved in the diagnostic and treatment process [9]. Another solution for improving the quality of care of patients with GCA is developing training sessions to continue the clinical education for healthcare professionals, at all levels of care involved in the process of the management of GCA [9].

The diagnosis of GCA is established upon the clinical picture and high inflammatory markers, supported by imaging or temporal artery biopsy. Giant cell arteritis with affected temporal arteries is an emergency, requiring immediate intervention and prompt administration of high doses of glucocorticosteroids. In these cases, the prognosis depends on the healthcare professionals, as a quick response and proper management can save many lives every year [1].

Author Contributions: Conceptualization, W.S. and R.K.; investigation, W.S., R.K. and A.J.; resources, R.K. and A.J.; writing—original draft preparation, W.S.; writing—review and editing, W.S. and R.K.; visualization, W.S.; supervision, R.K., A.B. and W.T.; funding acquisition, R.K., A.B. and W.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Due to the patient's vision loss, we could not obtain written informed consent. However, the patient verbally provided consent.

Data Availability Statement: No new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Long-Term Follow-Up in Patients with Large-Vessel Vasculitis Applying Extracranial and Transcranial Duplex Sonography

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Abstract

Background: Although large-vessel vasculitis (LVV) can affect both the anterior and posterior intracranial circulation, routine neurosonographic follow-up, including transcranial duplex sonography, has not been established. We aimed to characterize patients with giant cell arteritis (GCA) and Takayasu arteritis (TAK) regarding the detection of progressive or new-onset inflammatory vessel changes by using neurosonography, and to assess the impact on medical or interventional treatment strategies. **Methods:** We retrospectively identified all patients with LVV treated at our neurological department between January 2015 and October 2025 with at least one neurosonographic follow-up examination. Baseline and follow-up sonographic data, clinical characteristics, medical therapy, and interventional treatments were analyzed. **Results:** In total, 21 LVV patients (GCA, n = 16; TAK, n = 5) underwent sonographic follow-up (GCA: median 28 (2–106) months, 4.5 (2–33) sonographic assessments; TAK: 75 (33–255) months, 14 (4–60) sonographic assessments). Isolated or combined, progressive or new-onset intra- and extracranial arterial disease was detected in seven of the 16 GCA patients (43.8%), of whom three (18.8%) presented with ischemic stroke. Medical treatment was adapted in four progressive cases. In two patients, additional interventional treatment was performed. Among TAK, two of five (40%) patients showed progressive sonographic changes, with one patient experiencing an ischemic stroke requiring endovascular treatment for progressive common carotid artery stenosis and one patient showing asymptomatic intracranial ICA involvement. **Conclusions:** Progressive and symptomatic involvement of intracranial carotid and vertebral arteries is a frequent finding in patients with LVV. These changes can be effectively detected through comprehensive neurosonographic follow-up, including transcranial ultrasound assessment.

Keywords: giant cell arteritis; Takayasu arteritis; duplex sonography follow-up

1. Introduction

In addition to its diagnostic value, vascular ultrasound is increasingly used to monitor disease activity and the treatment response in large-vessel vasculitis (LVV) [1–6]. For giant cell arteritis (GCA), ultrasound examination of the extracranial arteries is routinely considered to monitor treatment and to detect disease relapses since IL-6 antibody therapy obscures laboratory markers of inflammation. The Outcome Measures in Rheumatology (OMERACT) Large Vessel Vasculitis Ultrasound Working Group recently developed a standardized ultrasound score (OGUS) for GCA, designed to quantify disease activity and enable longitudinal monitoring [7]. The OGUS includes intima-media thickness (IMT)

quotient measurements of the main branch of the superficial temporal artery, its frontal and parietal branches, and the axillary arteries, normalized to established reference values. Higher OGUS values may reflect greater inflammatory activity, potentially hold prognostic relevance, and indicate treatment failure [8]. Most current sonographic follow-up protocols for GCA rely on the OGUS or related IMT-based assessments, while only a few studies have additionally evaluated the extracranial carotid and vertebral arteries [1–3,9–11], and none have evaluated sonographic measurements of intracranial arteries. More recently, transorbital sonography measuring peak systolic velocity (PSV) of the central retinal artery has been applied, which may complement ophthalmologic evaluation and aid in the detection of ischemic complications in GCA [12,13].

Similarly, for Takayasu disease, the sonographic follow-up of brachiocephalic artery changes, with a focus on IMT measurements, neovascularization, and assessment of echogenicity, has proven valuable for long-term follow-up and monitoring of inflammatory vascular changes [14–19].

Neurosonographic follow-up examinations of intracranial arteries have not been systematically implemented in current monitoring protocols for either TAK or GCA. This gap persists despite intracranial arterial involvement being a recognized manifestation in both GCA and TAK. Intracranial vasculitis has been reported in approximately 7% of TAK patients. The cumulative risk of embolic or hemodynamic ischemic stroke in TAK with extra- and intracranial artery involvement is reported as 15–20% of patients [20–23]. In GCA, ischemic stroke occurs in about 3–7%, with emerging evidence suggesting that intracranial artery involvement may be more common than previously assumed: high-resolution black-blood magnetic resonance imaging (MRI) identified intracranial vessel wall alterations in 14.5% of GCA patients [24], and a recent systematic literature review of 102 studies summarized a total of 340 patients with reported intracranial vasculitis [25].

Currently, data on the frequency, temporal evolution, and potential therapeutic implications of intracranial vascular involvement as assessed by transcranial sonography remain scarce. Therefore, we conducted a retrospective analysis of patients with large-vessel vasculitis and serial sonographic follow-up at our comprehensive stroke center to evaluate the prevalence of neurosonographic changes and their impact on therapeutic decision-making in LVV.

2. Materials and Methods

2.1. Data Source, Patient Selection, and Cohort Development

In a retrospective approach, we identified all patients who were treated at our neurological department for giant cell arteritis or Takayasu arteritis and underwent at least one clinical and sonographic follow-up examination after baseline assessment between January 2015 and October 2025. All diagnoses were made in accordance with the ACR/EULAR criteria and confirmed by expert neurologists [26,27]. Sonographic follow-up was scheduled as indicated by clinical assessment. Clinical and sonographic data were retrieved from medical records.

2.2. Demographic, Clinical, and Sonographic Characteristics

Patient demographic and clinical characteristics included age at diagnosis and sex. We assessed the follow-up period and the number of sonographic examinations performed. Sonographic results were characterized at baseline by the presence of a halo sign in the temporal arteries (TA) and inflammatory involvement of the vertebral artery (VA), the subclavian artery (SA), the common carotid artery (CCA), the extracranial internal carotid artery (ICA), and intracranial arteries. New-onset inflammatory changes at follow-up sonography were assessed according to the anatomic site and time course of the disease. Medication

https://doi.org/10.3390/diagnostics16030455

and changes in treatment strategies, including medical and interventional procedures, were analyzed in patients with new-onset or progressive inflammatory vessel changes.

2.3. Sonographic Outcome Definitions

New-onset inflammatory artery disease was defined as the diagnosis of any newly detected vascular involvement during sonographic follow-up that was not reported at baseline sonographic assessment.

Progressive inflammatory arterial disease was defined as any significant deterioration of a previously documented vascular abnormality identified at baseline sonographic assessment, as demonstrated by increased severity at follow-up, such as progression of arterial stenosis.

2.4. Statistical Analysis

All statistical analyses were performed using "R" (version 1.4.1717; R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were presented as frequencies with percentages for categorical variables, as means with standard deviations for normally distributed continuous variables, and as medians with ranges for ordinal or non-normally distributed variables as appropriate.

3. Results

3.1. Patient Cohort

Overall, 43 patients were treated in our neurological department for GCA or TAK between January 2015 and October 2025. Twenty-two patients did not present for sonographic follow-up evaluation and were therefore excluded from the study. In total, we identified 21 patients who met the above-defined criteria. Of these, 16 patients were diagnosed with GCA and five patients with TAK. The follow-up period was a median of 28 (2–106) months, with a median of 4.5 (2–33) sonographic assessments for GCA and 75 (33–255) months with 14 (4–60) sonographic assessments for TAK. At the baseline sonographic assessment, three patients with GCA (18.8%) and two patients with TAK (40%) had intracranial involvement of vasculitis. The study flow chart is depicted in Figure 1. A comparison of baseline characteristics (age, sex, diagnosis) between the 22 patients excluded from the final analysis due to loss to follow-up and the 21 patients included in the final analysis is depicted in Supplementary Table S1.

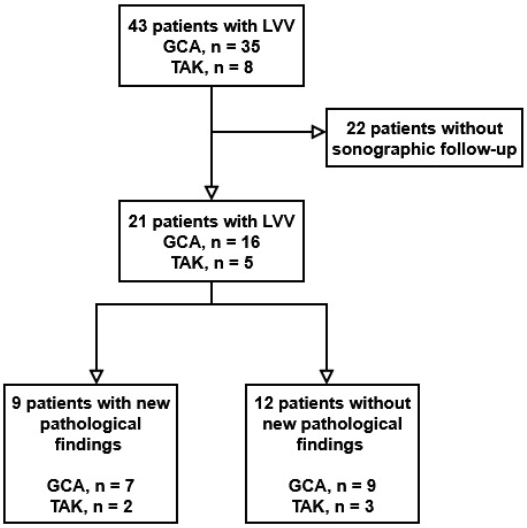

Figure 1. Study flow chart.

3.2. Patients with New-Onset or Progressive Inflammatory Artery Disease in GCA

In total, we detected new-onset or progressive inflammatory artery disease in seven of the 16 (43.8%) GCA patients. Patient characteristics are depicted in Tables 1 and 2. Three patients (18.8%) presented with progressive halo sign in the TA; however, only one of these was symptomatic with headaches, and medical treatment was hence adjusted. We further observed one case of symptomatic new-onset intracranial anterior circulation disease, and two cases of combined symptomatic intracranial anterior and posterior artery disease, with one of these having combined extra- and intracranial VA involvement. All patients with new-onset or progressive intracranial inflammatory artery disease suffered ischemic complications and required adjustment of medical therapy. In two patients, additional interventional treatment of the anterior intracranial circulation was performed (stent angioplasty of the intracranial ICA, balloon dilatation of the intracranial ICA). Lastly, we observed one case of asymptomatic progressive extracranial VA involvement, which slightly regressed over a total follow-up of four months. Figure 2 illustrates the case of a 72-year-old GCA patient with intracranial VA involvement 4 months after the first diagnosis and bilateral cerebellar infarctions in the MRI scan. Figure 3 shows the case of a 64-year-old GCA patient with progression of bilateral, distal ICA stenosis.

Table 1. Baseline demographic, clinical, and sonographic characteristics. SD = standard deviation, n = number of patients, IA = intracranial arteries, VA = vertebral artery, CCA = common carotid artery, ICA = internal carotid artery, SA = subclavian artery.

Patient Characteristics			
		GCA	TAK
Patients	Number of patients included	16	5
	Age (years), mean (±SD)	72.8 ± 7.4	37.6 ± 8.4
	Gender		
	Female *n* (%)	9 (56.3%)	3 (60%)
	Male *n* (%)	7 (43.8%)	2 (40%)
	Follow-up period (months), median (range)	28 (2–106)	75 (33–255)
	Number of sonographic assessments during follow-up, median (range)	4.5 (2–33)	14 (4–60)
Baseline sonography	Halo sign TA, *n* (%)	13 (81.3%)	-
	Involvement of VA, *n* (%)	8 (50.0%)	2 (40%)
	Involvement of SA, *n* (%)	-	5 (100%)
	Involvement of CCA, *n* (%)	-	2 (40%)
	Involvement of extracranial ICA, *n* (%)	-	2 (40%)
	Involvement of anterior circulation IA, *n* (%)	3 (18.8%)	2 (40%)
New or progressive artery involvement detected in follow-up sonography	Total, *n* (%)	7 (43.8%)	2 (40%)
	Symptomatic progress, *n* (%)	4 (25.0%)	1 (20%)
	Progress or new-onset involvement of VA, *n* (%)	3 (18.8%)	-
	Progress or new-onset involvement of anterior circulation IA, *n* (%)	3 (18.8%)	1 (20%)
	Progress or new-onset involvement of CCA, *n* (%)	-	1 (20%)
	Change of medical treatment following progress, *n* (%)	4 (25.0%)	-
	Interventional treatment following progress, *n* (%)	2 (12.5%)	1 (20%)

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Table 2. Clinical and sonographical findings in patients with progressive inflammatory artery disease and their medical impact. GCA = giant cell arteritis, TAK = Takayasu arteritis, f = female, m = male, TA = temporal artery, VA = vertebral artery, ICA = internal carotid artery, CCA = common carotid artery, SA = subclavian artery, MTX = methotrexate, CYC = cyclophosphamide, TOC = tocilizumab, MPS = methylprednisolone.

Clinical and Sonographic Findings in Patients with Progressive Inflammatory Artery Involvement in LVV and Their Therapeutic Impact										
Clinical Information						**Progressive Inflammatory Artery Disease During Sonographic Follow-Up**			**Medical and Interventional Treatment Following Progress**	
	Age	**Sex**	**Follow-up Period (Months)**	**Number of Sonographic Examinations**	**Baseline Pathology**	**Time from First Diagnosis (Months)**	**Symptomatic Progress**	**Sonographic Findings**	**Baseline**	**Change**	**Interventional Treatment**
GCA	68	m	105	20	Halo TA Extracranial VA stenosis	36	-	Progressive halo sign TA	Prednisolone + MTX	-	-
GCA	67	f	55	19	Occlusion intracranial right VA	3	Recurrent left-hemispheric strokes	High-grade stenosis of both ICAs (petrous segment) Stenosis MCA left	Prednisolone	MPS pulse (1000 mg for 5 days), MTX	Stent angioplasty of the left intracranial ICA
GCA	64	m	30	33	Halo TA Intracranial right VA stenosis Intracranial, bilateral ICA stenosis	1	Recurrent bihemispheric strokes	Progressive stenosis ICA and MCA left Progressive stenosis VA right extracranial and both intracranial VA	Prednisolone	MTX, TOC, CYC	Balloon dilatation of both ICAs
GCA	83	m	60	3	Halo TA	41	-	Progressive halo TA	Prednisolone + TOC	-	-
GCA	80	f	4	4	Halo TA Extracranial VA stenosis	1	-	Progressive extracranial, right-side VA stenosis	Prednisolone + MTX	-	-
GCA	72	m	23	6	Halo TA Intracranial VA stenosis	4	Recurrent vertebro-basilar strokes	Intracranial, bilateral VA occlusion Intracranial, bilateral ICA stenosis	Prednisolone + TOC	MPS pulse (1000 mg for 5 days), CYC, MTX	-
GCA	80	m	12	2	Halo TA	5	Headache	Progressive halo TA	Prednisolone + TOC	Prednisolone dose increase	-
TAK	26	f	75	14	VA, SA, CCA, ICA (extracranial)	57	-	Intracranial left-side ICA stenosis	Prednisolone + Certolizumab	-	-
TAK	33	f	254	60	SA, ACC	95	Right-hemispheric stroke	Progressive right-side CCA stenosis	Prednisolone + MTX	-	Stent angioplasty right CCA

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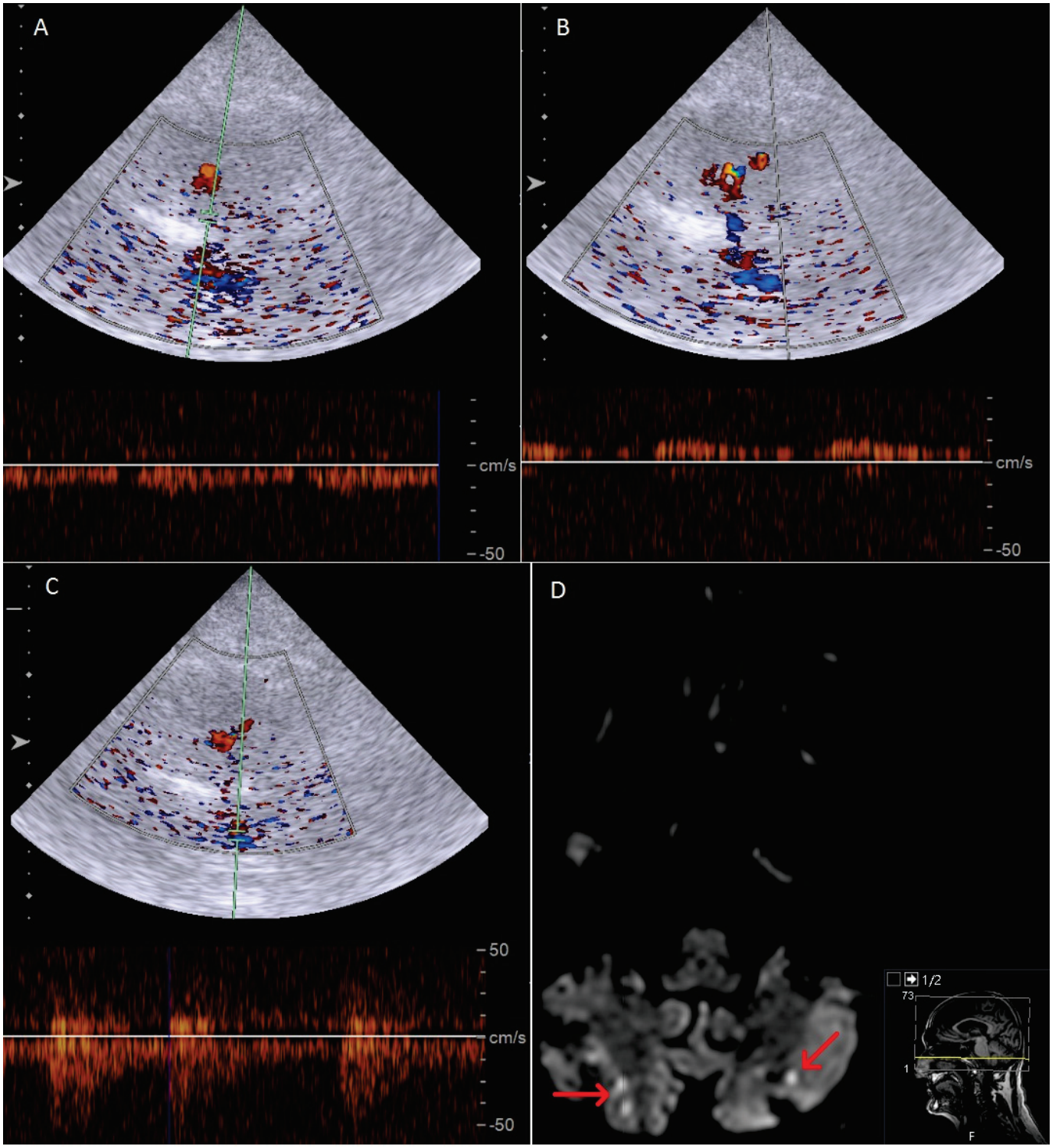

Figure 2. Exemplary case of a 72−year-old patient with GCA and images of a follow-up examination 4 months after the first diagnosis showing bilateral vertebral involvement. (**A**) Transnuchal duplex sonography showing highly reduced pulsatility of the right distal VA. (**B**) Retrograde perfused left distal VA. (**C**) Decreased blood flow in the basilar artery. (**D**) MRI scan (Diffusion Weighted Imaging sequence) showing new bilateral cerebellar infarctions (red arrows).

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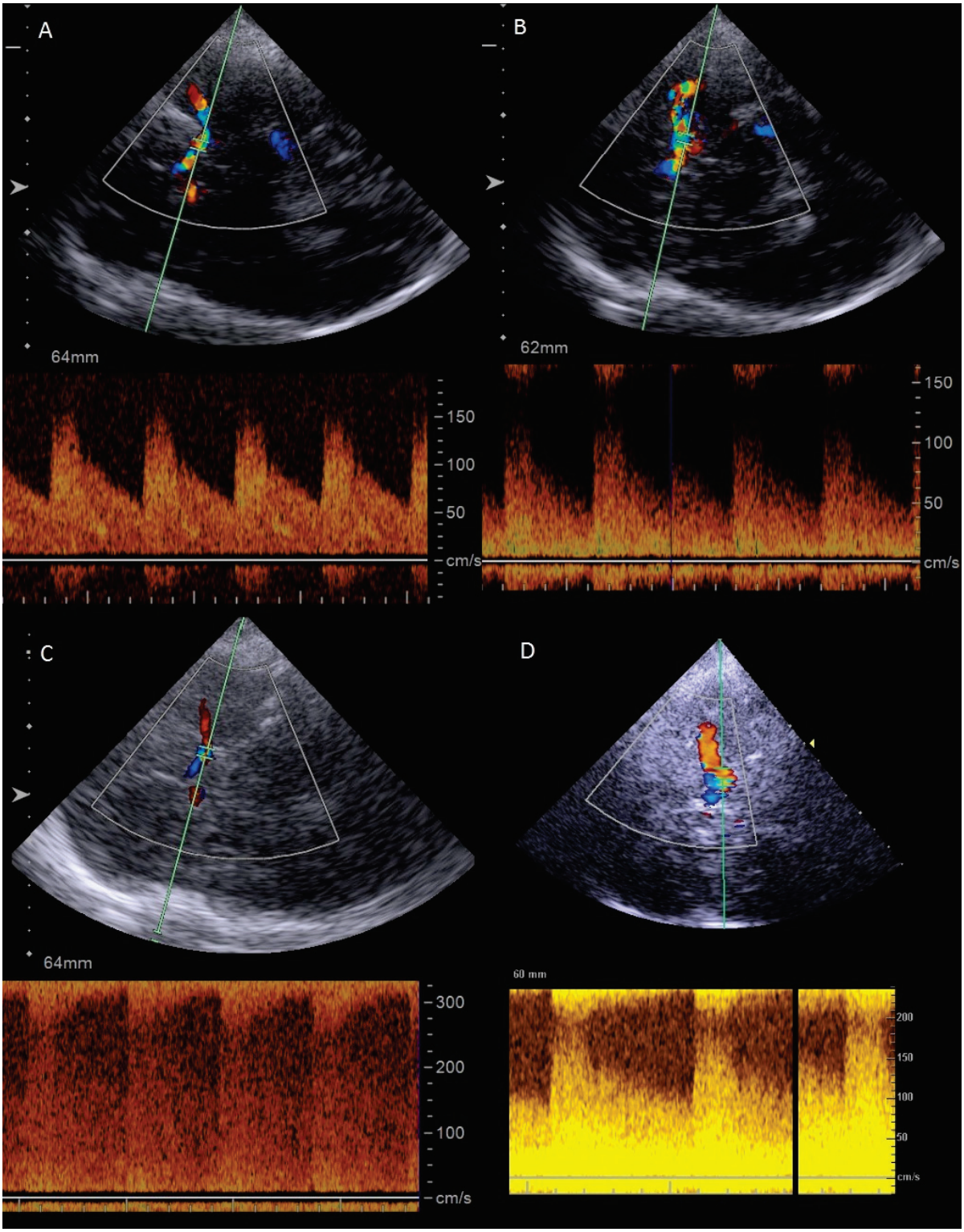

Figure 3. Exemplary case of a 64-year-old patient with GCA and transcranial sonographic images showing bilateral, distal ICA stenosis. (**A**,**B**) Baseline duplex sonography showing mildly increased blood flow velocity of the left (**A**) distal ICA and of the right (**B**) distal ICA. (**C**,**D**) Follow-up duplex sonography one month after baseline assessment showing highly increased blood flow velocity of the left (**C**) distal ICA and of the right (**D**) distal ICA.

3.3. Patients with New-Onset or Progressive Inflammatory Artery Disease in TAK

In total, we detected new-onset or progressive inflammatory artery disease in two of five TAK patients. Patient characteristics are depicted in Tables 1 and 2. One patient

presented with asymptomatic intracranial involvement of the ICA, but we refrained from adjusting medical therapy. The sonographic and MR images of this patient are depicted in Figure 4. One patient presented with ischemic stroke due to progressive CCA involvement, and stent angioplasty of the CCA was performed.

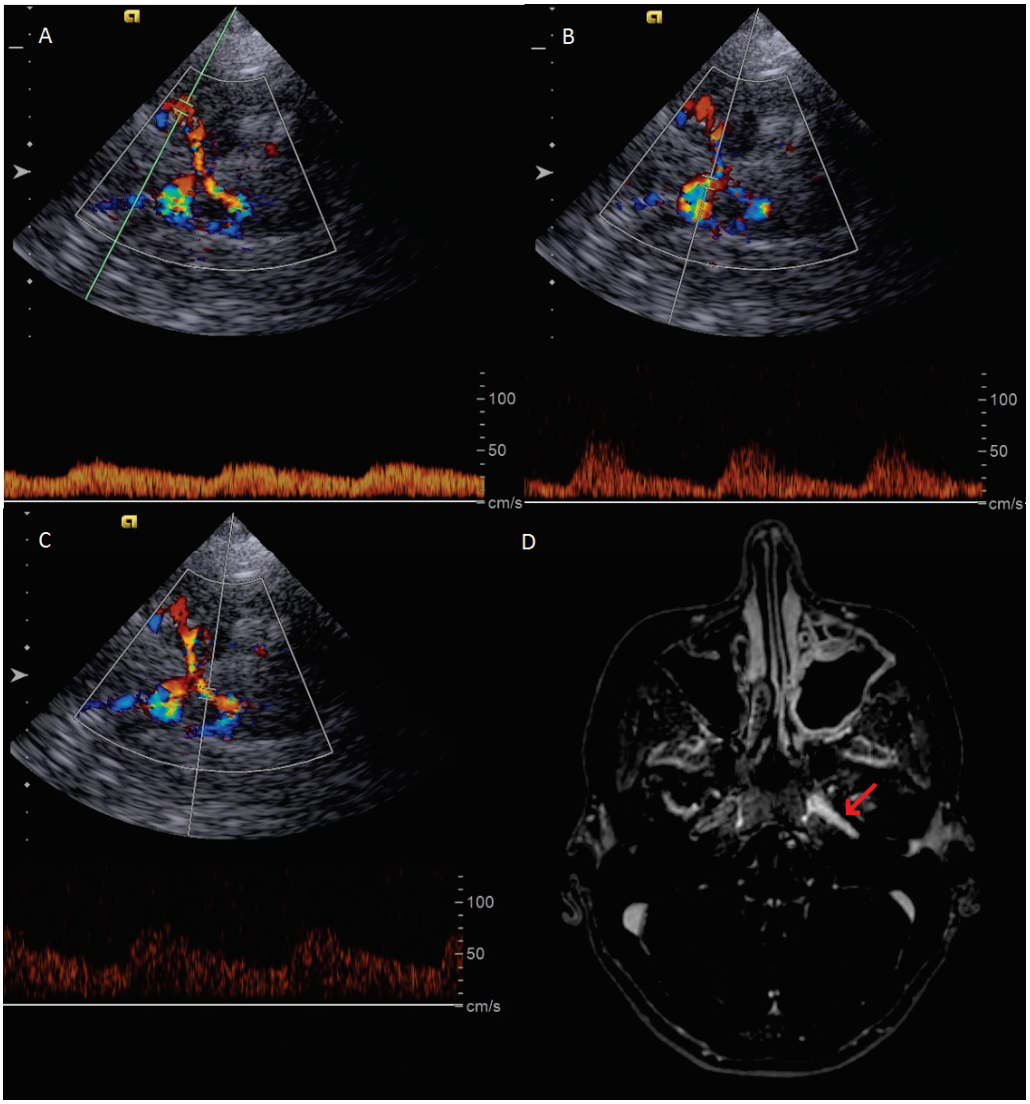

Figure 4. Exemplary case of a patient with TAK and images of a follow-up examination 5 years after the first diagnosis showing signs of high-grade stenosis of the left distal ICA. (**A**) Transcranial duplex sonography showing reduced pulsatility of the left distal MCA. (**B**) Retrograde perfused left ACA. (**C**) Cross-flow circulation from the left PCA to the left MCA through the posterior communicating artery (**D**) MRI scan (subtraction T1-weighted 3D TRA sequence) confirming high-grade stenosis and vascular inflammation of the left distal ICA (red arrow).

4. Discussion

We present the first study to demonstrate the value of transcranial neurosonography for detecting new-onset or progressive intracranial inflammatory vessel involvement during routine baseline and follow-up visits for LVV. To date, a comprehensive neurosonographic approach, including both transcranial and transnuchal sonography, has not been integrated into proposed study designs for sonographic follow-up or disease monitoring in GCA or TAK.

In GCA, current sonographic follow-up protocols primarily emphasize the measurement of IMT of the temporal and axillary arteries, as captured by composite scoring

systems such as the OGUS, the halo count, the halo score, and the Southend halo score [2,3]. The clinical utility of these standardized ultrasound-based scoring systems in follow-up sonographic assessment has been supported by several studies. Inter alia, Kirby et al. demonstrated that the use of the OGUS, halo score, and halo count facilitated reproducible and standardized disease monitoring in clinical practice [9]. Ponte et al. reported that sonographic changes in the temporal and axillary arteries—particularly regression of the halo sign and a reduction in IMT—can occur rapidly in response to effective glucocorticoid therapy [28].

The assessment of further supraaortic branches—including the VA, SA, brachial artery, CCA, and ICA—has been incorporated into sonographic follow-up protocols, in addition to the scoring systems described above. Thus far, the examined arteries and their reported treatment responses vary between study protocols. For example, Seitz et al. reported a decline in the IMT of the SA, in addition to reductions in the axillary arteries and TA, after treatment induction with methylprednisolone pulse therapy followed by tocilizumab [29]. The treatment effect of tocilizumab, as assessed by sonographic IMT measurements, appeared later in the axillary and subclavian arteries than in the temporal artery. Hansen et al., in a prospective study of 48 therapy-naïve GCA patients, noted a rapid decrease in IMT in the temporal and axillary arteries within ten days of glucocorticoid initiation, in contrast to the slower changes in other supraaortic arteries, including the CCA and brachial arteries [10]. Similarly, Ford et al. demonstrated a rapid regression of inflammatory changes in the TA, whereas involvement of the SA and axillary arteries tended to persist on sonographic follow-up in a retrospective evaluation of 42 patients with a median follow-up of 5.1 months [30]. Haaversen et al. prospectively evaluated 132 GCA patients for halo signs in the temporal and facial arteries as well as for IMT changes in supraaortic vessels, including the CCA, VA, and SA, and reported moderate sensitivity and specificity for detecting clinical relapse as defined by the EULAR definitions of key symptoms and clinical findings suggestive of active disease [11]. Nielsen et al. performed a prospective clinical and sonographic follow-up of 47 patients at 8 weeks, 24 weeks, and 15 months, demonstrating that IMT measurements of the TA—particularly those included in the OGUS score—showed a moderate-to-strong correlation with disease activity. In contrast, large-vessel involvement, as assessed by IMT of the CCA, was associated with a poor treatment response [31]. Aschwanden et al. conducted a 24-month longitudinal follow-up of 42 patients, with a median of two sonographic examinations per patient. They found that regression of IMT in large arteries—specifically the CCA, ICA, external carotid artery, VA, SA, axillary artery, popliteal artery, and superficial femoral artery—was substantially less common than IMT reduction in the TA [32]. Schäfer et al. confirmed significant decreases in the total number of affected arteries, i.e., the CCA and VA, and in OGUS values, in 36 newly diagnosed patients who completed a 12-month follow-up period with regular sonographic assessments after treatment initiation [1]. In contrast to some of the previously described studies, in these patients, the mean IMT of the axillary artery normalized before the common TA.

For TAK, sonographic follow-up protocols mostly include IMT measurement of the CCA, SA, and VA, with an additional focus on vessel wall echogenicity. It has been reported that hypoechogenic vessel walls are commonly more prevalent in acute or new-onset inflammatory diseases, with possible long-term progression to hyperechogenic vessel wall changes accompanied by fibrotic stripes [14,18,33,34]. Thus far, various scores, including the above-mentioned parameters, have been proposed for differentiating active disease. Firstly, combining echogenicity and IMT measurements of the CCA, SA, and axillary artery, the Takayasu Ultrasound Index has been validated in the follow-up assessment of TAK [18]. Similarly, the ultrasonographic activity score (ULTRAS) has recently been

https://doi.org/10.3390/diagnostics16030455

proposed, which includes wall thickness and semi-quantitative echogenicity scores in patients with CCA involvement. Additionally, neovascularization, as detected by contrast-enhanced ultrasound and the presence of intramural arteries, has been described, indicating secondary inflammatory changes in TAK, which may be sonographically detectable in follow-up assessments [15,16,18]. Nevertheless, sonography has not been established for routine diagnostic follow-up in TAK [17,19]. If performed, the frequency of imaging follow-up in TAK has not been specified. A recent retrospective multicenter study favors patient-specific and individualized periods, as radiological progress was unlikely in the absence of clinical activity, but in the case of its detection, seemed highly relevant for medical treatment [19].

Collectively, these findings highlight the potential value of sonographic parameters as biomarkers of disease activity and treatment response in LVV. Since the pattern of vessels is highly variable, we propose adding transcranial sonography to the standard LVV work-up. Although inflammatory involvement of intracranial arteries has been described in both TAK and GCA [20–25], transcranial sonography has not been implemented in sonographic protocols thus far. In our patient population, baseline as well as new-onset or progressive intracranial artery involvement was relatively common in both GCA and TAK, and was well detected by a complete sonographic examination. Hence, we argue that the expansion of sonographic protocols, incorporating transcranial and transnuchal approaches in addition to a complete assessment of VA, CCA, and ICA, provides a more comprehensive evaluation of vascular inflammation in both baseline and follow-up assessments, and may identify patients at risk of ischemic complications.

Recent evidence suggests that transorbital sonography, with measurement of the peak systolic velocity (PSV) of the central retinal artery, may provide a tool for the assessment of intracranial vascular involvement in GCA [12,13]. Since the PSV of the central retinal artery can be directly affected by intracranial ICA pathology, this finding highlights the clinical relevance and frequency of intracranial artery involvement in GCA, and thereby the importance of additionally performing a comprehensive neurosonographic work-up that includes a complete transcranial assessment.

Data on the prevalence of extra- and intracranial involvement of the VA in GCA remain heterogeneous. Reported frequencies vary considerably depending on the characteristics of the studied cohort, particularly in patients presenting with GCA-associated stroke, and on the imaging modality employed [19–21]. For example, Penet et al. identified VA involvement in 2.4% of patients when assessed by sonography, whereas positron emission tomography (PET) revealed involvement in 22% [22]. Intracranial VA involvement has been reported in 83.9% of patients with intracranial GCA and GCA-related stroke, predominantly affecting the V3 and V4 segments before the origin of the posterior inferior cerebellar artery (PICA), and typically exhibiting the characteristic “slope sign” [19]. At baseline, we detected extra- or intracranial involvement of the VA in 50% of patients within our neurological cohort.

In our study, intracranial ICA involvement at baseline was identified in 18.8% of GCA patients. More recent evidence suggests that intracranial large-vessel anterior arteritis may be more common than previously recognized, predominantly detected by high-resolution MR imaging. Guggenberger et al. reported intracranial ICA involvement in 10.9% of patients using MR imaging with black-blood sequences and MR angiography [24]. Other MR-based studies have demonstrated intracranial ICA involvement in up to 50% of patients with GCA [35]. While vessel wall imaging is not feasible in transcranial ultrasound, the resulting hemodynamic ICA stenoses can be reliably identified, which may thus serve as a practical modality for longitudinal follow-up.

The incidence of GCA-related stroke remains controversial, with reported rates ranging from 1.5% to 16%. Strokes have been reported to predominantly affect the vertebrobasilar circulation and are more frequently observed in male patients [36–39]. In our cohort, GCA-related stroke occurred in 18.8% of patients, all of whom exhibited sonographically detected new-onset or progressive inflammatory involvement of intracranial arteries and presented with intracranial VA stenosis at baseline as a possible risk factor for GCA-related stroke [39]. Of note, and contrary to the previously discussed literature, there was, even though limited by the restricted patient numbers, no evident increase in the occurrence of vertebro-basilar ischemic stroke in our patient cohort.

The finding of a progressive halo sign without clinical relevance in two GCA patients strengthens the importance of a standardized assessment using the proposed OGUS score, which was not routinely assessed during the study period [1,7,8].

The key limitation of our study is the relatively small sample size, which restricts the extent to which the findings can be generalized. However, our findings provide valuable clinical insights into a rare disease for which data are overall scarce, helping to expand the limited evidence base and create a potential blueprint for future prospective multicenter studies. Secondly, the retrospective design of the study represents another important limitation, as our analyses depend on clinical data from medical records that were not primarily collected for research purposes. For GCA, the above-described therapeutic uncertainties regarding both the localization and duration of inflammatory vessel wall changes following treatment initiation have thus far prevented sonography from being included in international EULAR recommendations on the clinical follow-up of patients without suspected disease relapse [5]. This lack of consensus on a standardized sonographic follow-up may account for the high rate of patients without sonographic follow-up, resulting in the discussed restricted numbers of included patients and possible selection and attrition bias. In our study, approximately half of the patients did not return for sonographic follow-up, representing a relatively high dropout rate. Due to the retrospective design, the reasons for non-attendance are unknown, and the resulting attrition bias limits the interpretation of the true prevalence of newly identified pathologies. One possible explanation for non-attendance at follow-up could be that some patients were clinically stable and asymptomatic, and therefore did not perceive a need for further evaluation. Thus, the pathological findings observed in the remaining cohort may appear more pronounced, giving a misleading impression of the true prevalence of pathological findings in sonographic follow-up of LVV patients.

Overall, this study demonstrates the feasibility and potential diagnostic yield of transcranial sonographic monitoring. However, it is not suitable to define a standardized monitoring protocol, mainly owing to its retrospective design and limited sample size. Notably, this is the first study to highlight these considerations, delineating the primary motivation for a prospective, multicenter trial with clear, protocol-defined time points and parameters for clinical and sonographic assessments. A large prospective trial would enable systematic evaluation of disease progression and the utility of sonographic monitoring, while minimizing bias and enhancing generalizability.

5. Conclusions

In conclusion, this study highlights the potential medical implications of comprehensive neurosonographic assessment in the follow-up of patients with GCA and TAK. The addition of transcranial and transnuchal sonography to the established protocols may help to detect progressive or new-onset inflammatory artery disease in known LVV, thereby influencing medical and interventional decision-making. Incorporating these modalities into routine follow-up examinations of patients with LVV could facilitate earlier recognition

https://doi.org/10.3390/diagnostics16030455

of clinically silent progression and hence identify patients at risk for ischemic complications. The central innovative aspect of this study lies in the inclusion of transcranial sonography, representing, to the best of our knowledge, the first systematic evaluation of this modality in patients with large-vessel vasculitis. By extending ultrasound assessment beyond extracranial vessels, this approach supports a more comprehensive, non-invasive diagnostic strategy that may contribute to future updates and refinements of EULAR recommendations for the imaging-based diagnosis and monitoring of LVV. Further prospective studies are warranted to validate these observations and to clarify their impact on patient outcomes.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics16030455/s1, Table S1: Comparison of baseline characteristics of patients with GCA and TAK included and excluded from final analysis.

Author Contributions: Conceptualization: J.H. and E.B.; methodology: J.H. and E.B.; validation: S.W. and A.B.; formal analysis: J.H. and E.B.; investigation: J.H. and E.B.; data curation: J.H., E.B., S.L. and F.H.; writing—original draft preparation: J.H. and E.B.; writing—review and editing: J.H., E.B., S.L., F.H., A.B. and S.W.; visualization: J.H. and E.B.; supervision: S.W. and A.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of the Technical University of Munich, ID: 2025-647-S-SF, approval date: 3 December 2025.

Informed Consent Statement: Patient consent was waived due to the retrospective study design and data anonymization.

Data Availability Statement: The data that support the findings of this study are available upon reasonable request from the corresponding author.

Acknowledgments: We thank Beate Eckenweber, Maria Kassil, Christina Leonhard, and Rebecca Husel for their work at the local sonography laboratory and data acquisition.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACA	anterior cerebral artery
BA	basilar artery
CCA	common carotid artery
GCA	giant cell arteritis
ICA	internal carotid artery
IMT	intima-media thickness
LVV	large-vessel vasculitis
MCA	middle cerebral artery
MRI	magnetic resonance imaging
OGUS	giant cell arteritis ultrasonography score
PCA	posterior cerebral artery
PSV	peak systolic velocity
SA	subclavian artery
TA	temporal artery
TAK	Takayasu arteritis
TCD	transcranial duplex sonography
VA	vertebral artery

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diagnostics

MDPI

Review

Positron Emission Tomography/Computed Tomography in Polymyalgia Rheumatica: When and for What—A Critical Review

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Abstract: Polymyalgia rheumatica (PMR) is an inflammatory disease common in people aged 50 years and older. This condition is characterized by the presence of pain and stiffness involving mainly the shoulder and pelvic girdle. Besides the frequent association with giant cell arteritis (GCA), several conditions may mimic PMR or present with PMR features. Since the diagnosis is basically clinical, an adequate diagnosis of this condition is usually required. Positron emission tomography/computed tomography (PET-CT) has proved to be a useful tool for the diagnosis of PMR. The use of 18F-FDG-PET imaging appears promising as it provides detailed information on inflammatory activity that may not be evident with traditional methods. However, since PET-CT is not strictly necessary for the diagnosis of PMR, clinicians should consider several situations in which this imaging technique can be used in patients with suspected PMR.

Keywords: FDG uptake; polymyalgia rheumatica; giant cell arteritis; positron emission tomography/computed tomography (PET-CT) with 18F-fluorodeoxyglucose (FDG)

1. Introduction

Polymyalgia rheumatica (PMR) is a common condition in individuals over 50 years in Western countries. PMR predominantly affects people aged 50 years and older, with an average age of onset of around 70 years [1–3]. It is rare in people under 50 years of age. PMR is more common in women than men, with a female/male ratio of approximately 2:1 [1–3].

The incidence of PMR varies geographically. In northern Europe and North America, the incidence is higher than in the other parts of the world. In this regard, in Sweden, the incidence of PMR ranges from 34 to 50 per 100,000 people aged 50 years and older per year [4,5]. In Norway, the annual incidence of PMR among residents aged 50 years and older was 112.6 per 100,000, with 137.7 per 100,000 in women and 83.2 per 100,000 in men [6]. In Olmsted County, Minnesota (USA), where the population is predominantly of Scandinavian descent, the incidence has been reported at 63.9 per 100,000 per year, with a prevalence of 701 per 100,000 [7,8]. A lower incidence was reported in southern Europe and other regions. In this regard, in Northern Spain, the incidence was 18.67 cases per 100,000 people aged 50 years and older per year between January 1987 and December 1996 [9]. In Reggio-Emilia (Italy), the average annual incidence rate of PMR was 12.8 per 100,000 population aged 50 years or older [10].

A genetic predisposition contributes to the development of PMR [11]. Certain types of human leukocyte antigens have been linked to an increased risk [12]. Moreover, an

association with gene polymorphisms located outside the HLA region has also been described [13,14].

Environmental triggers, such as infections, may precipitate the onset of PMR in genetically predisposed individuals [1,3]. The exact nature of these triggers remains unclear. Some studies have suggested seasonal variations in the incidence of PMR, with higher rates of diagnosis in the winter months. This could be related to environmental factors like infections. PMR has been reported following influenza B infection and, more recently, after SARS-CoV-2 infection [15,16].

PMR is characterized by pain and stiffness in the shoulders and proximal parts of the arms, the hip girdles and proximal parts of the thighs, and the neck [17,18]. Diagnosing PMR is usually straightforward in typical patients who exhibit hip and shoulder involvement, along with elevated levels of erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). However, besides the frequent association with giant cell arteritis (GCA), several conditions may mimic PMR or present with PMR features [19]. On the other hand, in some cases, PMR can present with normal levels or with a slight increase in acute phase reactants, which makes diagnosis difficult [20]. Therefore, an adequate diagnosis of this condition is usually required.

2. PMR, a Condition Associated with Bursal Involvement

Arthroscopic examinations have revealed mild synovitis in the proximal joints of people with PMR. The inflammatory infiltration observed in the synovial membranes of the shoulder and other affected joints mainly consisted of macrophages and CD4 T lymphocytes [21]. However, this mild synovitis does not fully account for the musculoskeletal manifestations and diffuse pain involving the periarticular structures in patients with PMR. In this context, magnetic resonance imaging (MRI) and ultrasonography (US) investigations have identified subacromial/subdeltoid bursitis and biceps tenosynovitis, along with the synovitis of the glenohumeral joints in these individuals [17]. These observations support the idea that the involvement of extra-articular structures may contribute to the development of PMR [21–24].

In this sense, in addition to subacromial bursitis, both hip joint effusion and pelvic bursitis can also occur in PMR. Trochanteric bursitis, as well as the less common iliopsoas and ischiogluteal bursitis, have also been observed as part of the disease spectrum. [25]. In this regard, ischiogluteal bursitis is quite specific for PMR. Interspinous bursitis affecting the cervical and lower lumbar spine has been documented in patients with PMR and could potentially contribute to the neck and back pain reported by these individuals [26–28].

The 2012 EULAR/ACR preliminary classification criteria for PMR have included, for the first time, the use of US data whenever this information is available.

They highlight the importance of ultrasound findings showing bilateral subacromial/subdeltoid bursitis and trochanteric bursitis in diagnosing PMR in patients experiencing inflammatory pain in the shoulder or pelvic girdle [29]. The use of US enhanced the specificity of the updated 2012 EULAR and ACR criteria [30]. However, if there are no other suggestive clinical features present, isolated US abnormalities should not be sufficient to support a diagnosis of PMR [31].

3. Is PET-CT Useful for the Diagnosis of PMR?

For the purposes of this review, a literature search was conducted in PubMed through May 2024. The terms used for this search included “PET” or “positron emission tomography” or “FDG” or “fluorodeoxyglucose”, combined with “PMR” or “polymyalgia”.

Taking into account that the inflammation of large joints and periarticular structures is common in PMR, the visualization of inflammation in periarticular structures is of great help for diagnosis. Because of that, positron emission tomography/computed tomography (PET-CT) has proved to be a useful tool for the diagnosis of PMR [32,33]. In this regard, PET-CT uses the radioactive tracer fluorodeoxyglucose (18F-FDG), which accumulates in areas with high glucose metabolism, such as inflamed tissues. PET allows the identification

of augmented metabolism in peripheral cells involved in inflammation, such as neutrophils, lymphocytes, monocytes, and macrophages. As discussed before, inflammation in PMR primarily affects the bursae, synovial joints, and tendons, and PET-CT can clearly visualize the areas of increased metabolic activity [34,35]. PET-CT can detect inflammatory changes before structural changes become apparent in conventional imaging like X-ray or magnetic resonance imaging. This early detection is crucial for initiating prompt treatment and managing symptoms effectively [36–38].

An important point to be kept in mind is that a wide spectrum of conditions can mimic PMR [17,39–41]. Among them, inflammatory arthritis, particularly late-elderly-onset rheumatoid arthritis that often presents with a polymyalgic phenotype, as well as other rheumatic conditions such as spondyloarthropathies, crystal-induced arthropathies, connective tissue diseases, or the remittent seronegative symmetrical synovitis with pitting edema (RS3PE) syndrome as well as infections and malignancies, may resemble isolated PMR [17]. Unlike these conditions, PMR presents with a well-defined periarticular inflammatory pattern that corresponds largely to the inflammation of bursal structures, which we will discuss below. PET-CT may also disclose the coexistence between PMR and GCA [40].

A few years ago, van der Geest et al. performed an extremely interesting systemic review on the diagnostic value of 18F-FDG-PET-CT in PMR. The review article included a meta-analysis that encompassed 20 studies [42]. Nine studies, encompassing 636 patients, were deemed eligible for inclusion in the meta-analysis [42]. The study confirmed a high prevalence of 18F-FDG uptake in several sites, including the interspinous bursae, hips, ischial tuberosities, shoulders, and sternoclavicular joints. The likelihood ratios for positive uptake in these areas were statistically significant, indicating their diagnostic value. The interspinous bursae showed the highest positive likelihood ratio, followed by uptake in the hips, ischial tuberosities, and shoulders [42]. However, the authors highlighted the moderate to high heterogeneity of these studies, which was attributed to variations in patient selection, scanning procedures, and interpretation criteria. Because of that, van der Geest et al. emphasized the need for standardized protocols in using 18F-FDG-PET/CT for diagnosing PMR [42].

Camellino et al. assessed the relationship between clinical symptoms and findings from FDG-PET-CT scans in patients with PMR [43]. These authors found a significant correlation between the clinical symptoms of PMR and increased FDG uptake in specific regions, such as the shoulder and hip girdles, indicating inflammation. Increased FDG uptake in vascular structures was also observed, suggesting a potential overlap with GCA, which often coexists with PMR.

The study reinforced the role of FDG-PET-CT in diagnosing and managing PMR by highlighting its ability to detect metabolic changes consistent with the disease's clinical manifestations [43].

Kim and Kim analyzed the diagnostic accuracy of FDG-PET-CT for PMR by synthesizing data from multiple studies [44]. To investigate this, the authors conducted a systematic review and meta-analysis of the studies employing FDG-PET-CT for diagnosing PMR. Their findings indicated that FDG-PET-CT demonstrated high sensitivity and specificity in detecting PMR [44]. These results advocate for incorporating this imaging technique into PMR diagnostic protocols. [44].

4. How Can We Detect the Presence of Inflammation in PMR Using PET?

There are two main methods for evaluating PET scans: visual evaluation and semi-quantitative evaluation. Here are the key differences between these methods:

Visual evaluation is based on the interpretation of PET images by a radiologist or nuclear medicine physician. This method is inherently subjective, as it depends on the experience and judgment of the observer. It involves visually inspecting the PET images for areas of increased uptake, which indicate inflammation. The intensity and pattern of uptake are assessed qualitatively, often using standardized criteria or scoring systems. It provides information on the number of sites with significant uptake equal to or greater than

hepatic uptake [45]. Because of that, this method is relatively easy to evaluate and does not require complex software or extensive processing. It can be performed immediately after examination and often allows visual findings to be effectively correlated with clinical symptoms and other diagnostic information, making this method valuable in routine clinical practice.

The alternative method to PET evaluation in PMR is the semi-quantitative method that involves measuring standardized absorption/uptake values (SUVs) in specific regions of interest. In this semi-quantitative analysis, the mean maximum standardized uptake value (SUVmax) is determined. Receiver operating characteristic curves are used to establish optimal cutoffs for both the visual score and SUVmax in diagnosing PMR [45]. This provides a more objective measure of inflammation by quantifying the amount of radiotracer uptake. The semi-quantitative evaluation is more reproducible than visual assessment because it is based on standardized measurements rather than subjective interpretation. This reduces variability between observers. However, it requires additional time and resources, including specialized software and expertise in quantitative image analysis. It may not be immediately available in all clinical settings. Semi-quantitative methods can provide detailed information on the extent and intensity of inflammation, which may be particularly useful in research settings or for tracking disease progression over time. In clinical practice, these methods are often used complementarily. Visual assessment can quickly identify areas of concern, while semi-quantitative analysis can provide detailed information to confirm findings and track changes. In certain scenarios, such as ambiguous cases or research studies, a semi-quantitative assessment may offer additional value by providing precise data that can influence clinical decision-making. The choice between visual or semi-quantitative assessment depends on the clinical context, available resources, and the specific needs of the patient and healthcare provider. Integrating both methods can enhance diagnostic accuracy and provide a comprehensive evaluation of disease activity. Amat et al. confirmed that both methods are useful to identify PMR among patients presenting with rheumatic conditions [45]. In this regard, these authors assessed 222 18F-FDG PET-CT scans from two hundred and fifteen patients, of which 161 scans were performed on patients diagnosed with inflammatory rheumatic diseases, fifty-seven of them with PMR. The identification of PMR based on the presence of significant uptake in at least three sites showed a sensitivity of 86% and a specificity of 85.5%. The mean SUV max cutoff for diagnosing PMR was 2.168, with a sensitivity of 77.2% and a specificity of 77.6% [45].

5. PET-Scores: Useful to Differentiate PMR from Other Conditions

To improve the accuracy of 18F-FDG-PET-CT in distinguishing PMR from conditions that resemble PMR, various composite scores and algorithms have been proposed based on FDG uptake at specific sites. Typically, these scores evaluate the FDG uptake at targeted regions relative to liver uptake, with uptake equal to or higher than the liver uptake considered positive. The Leuven score evaluates twelve predefined anatomical sites (cervical spinous processes, lumbar spinous processes, left and right sternoclavicular joints, left and right ischial tuberosities, left and right greater trochanters, left and right hips, and left and right shoulders) using a three-point system: 0 (no elevated FDG uptake), 1 (moderately elevated FDG uptake, but less than the average liver uptake), or 2 (intense FDG uptake, equal to or greater than the average liver uptake) [46]. A modified version, the Leuven/Groningen score, showed similar accuracy with a simplified analysis focusing on four regions (sternoclavicular joints, interspinous lumbar processes, hips, and ischial tuberosity) [47]. The Leuven/Groningen score aggregates values, resulting in a total score that spans from 0 to 14 [47].

The Besançon index is another scoring system used in the assessment of inflammatory activity in patients suspected of having PMR. It evaluates inflammation in a wider range of anatomical sites compared to the Leuven score. Unlike the Leuven score, which evaluates twelve anatomical sites, the Besançon index assesses seventeen anatomical sites. It includes regions commonly affected by PMR, such as the shoulders, hips, spine, and

other large joints, which are visually graded from 0 to 3 (0: no inflammation observed; 1: mild inflammation; 2: moderate inflammation; 3: severe inflammation). A grade of two or higher at any site indicates the presence of inflammation. This scoring system assists healthcare providers in diagnosing and managing PMR effectively. The Besançon score helps clinicians quantify the extent of inflammation in patients with PMR, aiding in the diagnosis and monitoring of disease activity. A higher total score indicates more widespread inflammation, potentially guiding treatment decisions [48].

The Saint-Étienne algorithm is another diagnostic tool used for assessing inflammatory activity in patients suspected of having PMR. This algorithm focuses on only two anatomical sites: the interspinous bursa and the trochanteric bursa. The presence of inflammation is typically assessed visually [47,49,50]. Another diagnostic tool used for evaluating inflammatory activity in patients with suspected PMR is the Heidelberg. Unlike the Saint-Étienne algorithm, it assesses five anatomical sites (interspinous bursa, trochanteric bursa, glenohumeral joint, hip joint, and ischial tuberosity). Similar to the Saint-Étienne algorithm, a grade of two or more at any of the assessed anatomical sites is considered positive for inflammation [47,49,50]. Both the Heidelberg and the Saint-Étienne algorithms provide a simplified approach to diagnosing PMR based on the presence of inflammation at specific anatomical sites. They offer a standardized method for clinicians to assess inflammatory activity, aiding in diagnosis and treatment decision making. Van der Geest et al. conducted a comparison of these scores and algorithms, revealing that the Leuven score exhibited the highest diagnostic utility [47]. Furthermore, the Leuven/Groningen score, which targets four predefined regions (sternoclavicular joints, interspinous lumbar bursae, hips, and ischial tuberosities), showed similar diagnostic accuracy with the added advantage of simplified analysis [47].

Recently, Brinth et al. evaluated the established scoring systems alongside a novel simplified scoring system called the Copenhagen score. This system employs either the visual or semi-quantitative analysis of periarticular FDG uptake in the shoulders and at the ischial tuberosities [51]. For the semi-quantitative analysis, the SUV peak at the target site was compared to the mean SUV of the superior vena cava and liver, and then converted into a three-point scoring system. As previously noted by Van der Geest et al. [47], all the scoring systems, including the simplest ones focusing on a few anatomical regions, exhibited good diagnostic performance for PMR in patients not treated with glucocorticoids [51].

Ikuma et al. conducted a study to identify key sites for distinguishing PMR from rheumatoid arthritis (RA) using 18F-FDG-PET-CT. The study involved 35 patients with PMR and 46 patients with RA. Their findings indicated that FDG uptake in the shoulder joints, lumbar vertebrae spinous processes, pubic symphysis, sternoclavicular joints, ischial tuberosities, greater trochanters, and hip joints helped differentiate PMR from RA. Specifically, FDG uptake in at least one of the ischial tuberosities showed the highest diagnostic value for distinguishing between the two conditions [52].

6. What about Other Clinical Studies?

Several clinical studies have assessed the role of PET in patients with PMR. In this regard, Casadepax-Soulet et al. conducted a retrospective study with 85 patients with new-onset PMR and 75 controls who underwent 18F-FDG PET-CT [53]. They performed both the quantitative and semi-quantitative analyses of FDG uptake at sixteen sites. They found that the patients with new-onset PMR had a higher mean number of sites with significant FDG uptake than the controls, particularly in the hips, shoulders, and ischial tuberosity [53].

Shoulder involvement is a hallmark of PMR as confirmed by Sondag et al. [48], Henckaerts et al. [54], and Yamashita et al. [55].

We investigated the effectiveness of 18F-FDG-PET-CT in detecting PMR in patients with large vessel GCA [56]. To explore this and identify the best predictors for diagnosing PMR using 18F-FDG-PET-CT in patients with large vessel GCA, we analyzed a cohort of 54 patients diagnosed with large vessel GCA at our hospital [56,57]. We assessed nine

extravascular areas, encompassing 16 potential sites: acromioclavicular and sternoclavicular joints (2 each), hips (2), shoulders (2), greater trochanters (2), ischial tuberosities (2), symphysis pubis entheses (2), and cervical and lumbar interspinous processes. Each patient was assigned a total score ranging from 0 to 16, based on the sum of all the sites demonstrating significant FDG uptake [57]. Twenty-one of the fifty four patients with large vessel GCA had been clinically diagnosed as having PMR [56]. The patients with a clinical diagnosis of PMR more commonly exhibited significant extravascular FDG uptake at the sites examined. This was particularly evident in the shoulders, where 76.2% of the patients with PMR showed significant FDG uptake compared to 24.2% of those without PMR. Other areas, such as the cervical and lumbar interspinous processes, hips, and greater trochanters, also exhibited a higher frequency of significant FDG uptake in the patients with PMR ($p < 0.05$ for all the comparisons). Consequently, the total score of significant FDG uptake (SCORE 16) was higher in the patients with large vessel vasculitis-GCA and PMR compared to those without PMR (5.10 ± 4.05 vs. 1.73 ± 2.31; $p < 0.001$). These findings indicate that the number of affected extravascular sites was greater in patients with PMR [57]. According to our data, significant 18F-FDG-PET-CT uptake in the shoulder, greater trochanter, and lumbar interspinous areas may facilitate the identification of PMR in patients with large-vessel GCA. All of these observations are in line with the recommendations put forward by van der Geest et al., who highlight the importance of evaluating multiple anatomic sites, including the shoulders, sternoclavicular joints, interspinous bursae, ischial tuberosities, hips, and greater trochanters using 18F-FDG PET-CT to detect suspected PMR. As these authors concluded, the significant FDG uptake at multiple anatomic sites is a strong indication of PMR [42,58]. In this regard, Slart et al. confirmed that 18F-FDG PET-CT is highly effective to identify inflammation in large vessels, offering precise imaging that correlates well with clinical and histopathological findings [58]. Moreover, this imaging technique was also found to be very useful for detecting inflammation in characteristic areas such as the shoulders, hips, and ischial tuberosities. Therefore, this approach is highly valuable for distinguishing PMR from other inflammatory or degenerative conditions and for assessing the extent of the disease [58].

7. When Do We Have to Perform 18F-FDG PET-CT?

A potential limitation of the use of 18F-FDG-PET-CT in patients with suspected PMR is that this is an expensive technique not available in many centers yet. Moreover, some authors have emphasized that the routine use of 18F-FDG-PET/CT should not be recommended in the typical cases of PMR [41]. However, these authors suggest considering 18F-FDG-PET-CT in cases where patients with PMR present atypical features, lack elevated laboratory markers of inflammation, or have a history of cancer [58]. In this regard, a diagnosis of PMR in patients presenting with normal acute-phase reactants may be a challenge [20]. This is also the case for patients with a previous history of cancer [39,40]. With respect to this, it is true that patients with cancer often present with atypical features such as a lack of morning stiffness; more widespread pain, not only located in the shoulder and hip girdles; and poor response to glucocorticoids [39]. However, there are situations where a patient previously treated for cancer may genuinely have PMR. In such cases, it is crucial to rule out cancer relapse and accurately diagnose new-onset PMR.

Figure 1 shows the results of 18F-FDG PET-CT of an 82 year old woman diagnosed with PMR. Ten years earlier she had been diagnosed with breast cancer, treated with surgery, chemotherapy, and radiotherapy, currently in remission. PET-CT revealed increased FDG uptake in the shoulders, cervical and lumbar spine, and hips. These findings were consistent with PMR.

Interestingly, in a recent study that included 220 patients with suspected PMR and/or GCA over a two-year period, malignancy was only confirmed in seven patients (3.2%). Three of them were diagnosed with PMR concurrently with malignancy. These findings suggest that not all the patients suspected of having PMR/GCA need to undergo FDG-PET-CT systematically to rule out malignancy [59].

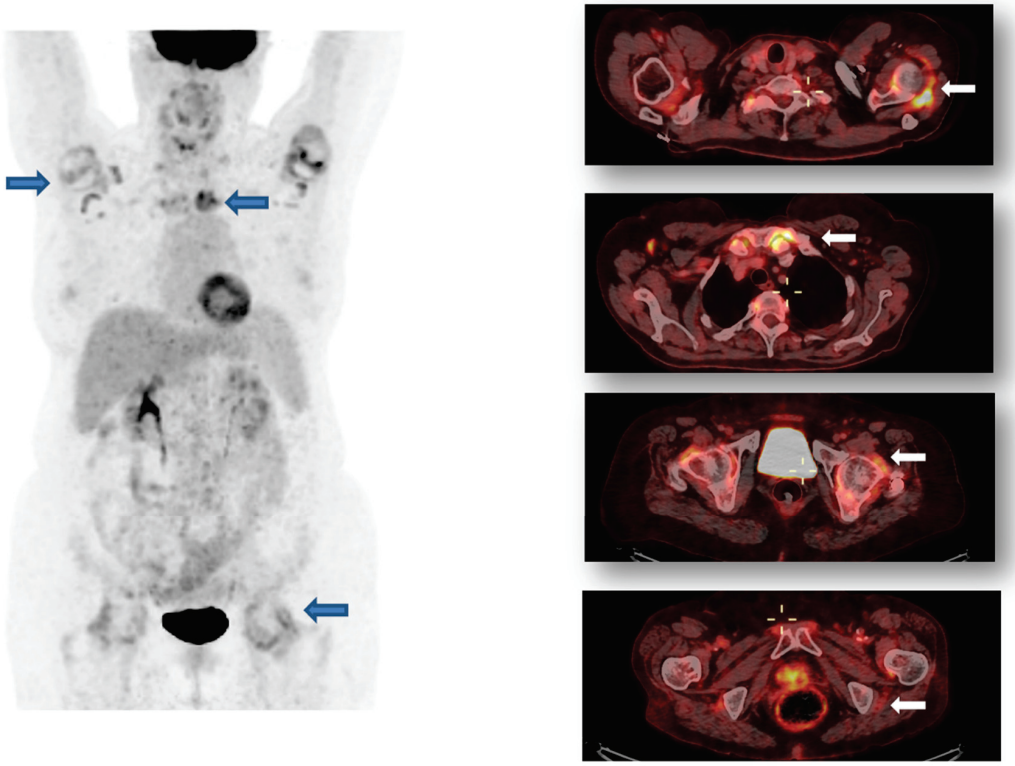

Figure 1. 82 year old woman with significant FDG uptake around the glenohumeral, sternoclavicular, costovertebral joints, lumbar interapophyseal spaces, coxofemoral joints, ischial tuberosities, and pubis, suggestive of diffuse osteoarticular pathology with an inflammatory component, in the context associated with PMR. Blue arrows: FDG uptake around glenohumeral, sternoclavicular and coxofemoral joint. White arrows: FDG upatake around glenomeral, esternoclavicular, coxofemoral and ischial tuberosities.

At this point, it is interesting to remark that the immune checkpoint inhibitors (ICIs) used in cancer patients can cause the appearance of a wide spectrum of musculoskeletal symptoms, sometimes indistinguishable from primary PMR (PMR-like syndrome) [60,61]. In these patients, PET may be useful to discriminate between primary PMR and those associated with ICI treatment. With respect to this, Vermeulen et al. suggest that ICI-PMR may show a milder course with less inflammation than primary PMR on 18F-FDG-PET-CT. As a result, patients with ICI-mediated PMR may be managed with a relatively low glucocorticoid dose, less than what is typically needed for patients with primary PMR [62].

18F-FDG PET-CT has proven valuable in identifying patients with a predominantly extracranial pattern of GCA [63–65]. More than 80% of the patients with GCA demonstrate increased FDG uptake on PET imaging, particularly affecting the thoracic and abdominal aorta. Additionally, this technique can detect vascular inflammation in the lower extremity arteries of GCA patients [65,66]. GCA may initially manifest as PMR, and imaging techniques, especially PET-CT, can reveal large vessel vasculitis in at least one-third of the patients initially diagnosed with isolated PMR [17]. Figure 2 illustrates increased FDG uptake in the aorta, indicating the presence of large vessel vasculitis in a patient with PMR who did not exhibit the ischemic manifestations of GCA.

EULAR experts also suggest that FDG-PET and MRI are effective tests for detecting large vessel involvement in patients presenting with PMR or systemic symptoms where GCA is a potential diagnosis [67]. However, further research is needed to determine whether PET-CT should be routinely performed in patients with PMR. Based on our clinical experience, we recommend considering PET-CT for patients with PMR who are resistant to prednisone doses of 15–20 mg/day or who present with atypical manifestations such as

predominant symptoms in the pelvic girdle [68]. In some of these cases, an extracranial large-vessel GCA may be found.

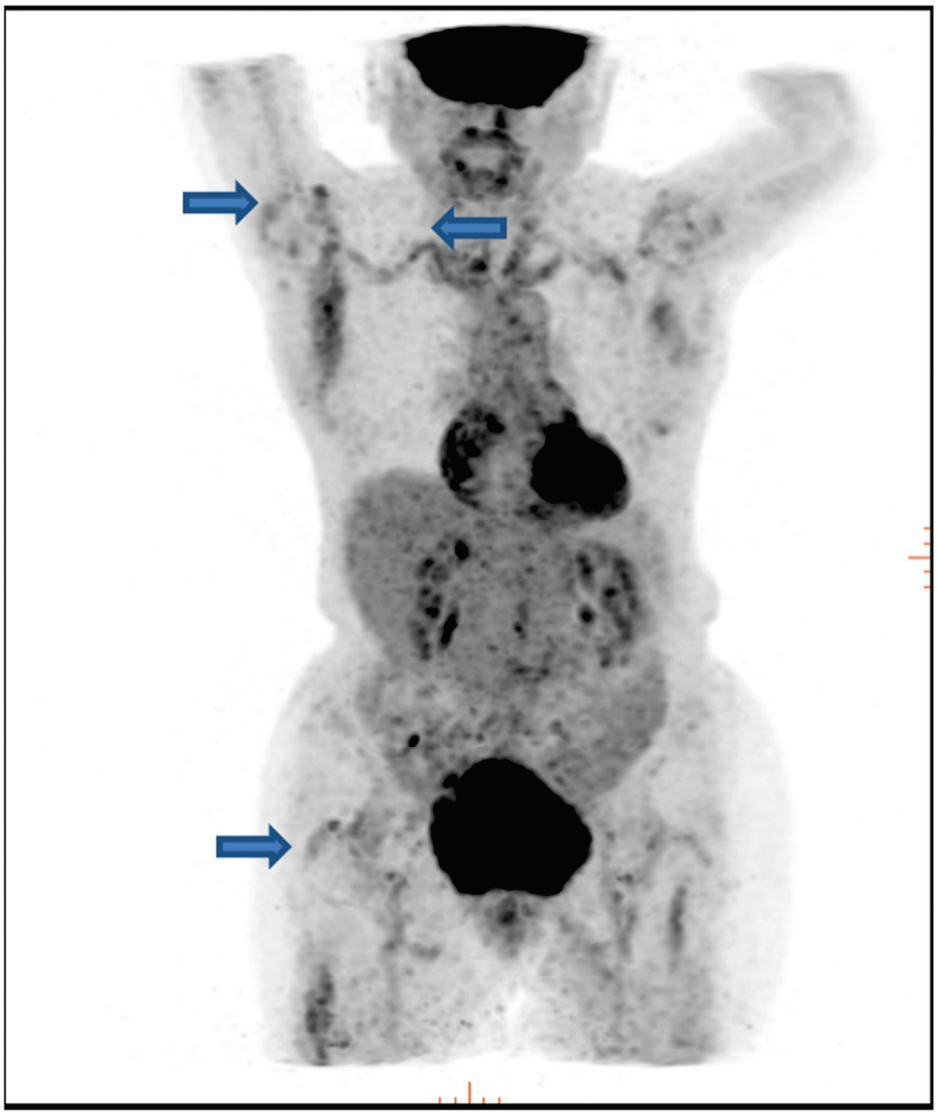

Figure 2. 65 year old woman with significant FDG uptake around the glenohumeral and coxofemoral joints (arrows) along with large vessel vasculitis.

8. Strengths and Weaknesses of PET-CT in Patients with PMR

18F-FDG PET-CT has been shown to be highly sensitive in detecting metabolic activity associated with inflammation, allowing for the early identification of inflammatory processes in PMR. Furthermore, this imaging technique can often identify "silent" extracranial large-vessel GCA, which is particularly useful for patients with PMR with atypical symptoms such as severe inflammatory low back pain or limb claudication. In these cases, PET-CT can reveal underlying vascular problems that might not be apparent by clinical examination alone [56,68].

Since FDG-PET-CT in the typical cases of PMR shows characteristic FDG uptake patterns in areas such as the ischial tuberosity, greater trochanter, lumbar or cervical spinous processes, and scapulohumeral joints [69,70], these findings help differentiate PMR from other conditions, particularly RA [70].

Pean de Ponfilly Sotier et al. assessed the effectiveness of 18F FDG PET CT imaging in distinguishing between PMR and atypical spondyloarthritis [71]. These authors found that PET-CT images provide distinctive uptake patterns that help differentiate these

two conditions, which often present with overlapping symptoms. This diagnostic tool may help clinicians make more accurate diagnoses and ultimately improve patient management and treatment outcomes.

However, there are limitations to the use of PET-CT in patients with PMR. One of them is the cost and accessibility of the technique. Furthermore, PET-CT involves exposure to ionizing radiation, which constitutes a risk, especially with repeated use. This is a crucial consideration for patients who require multiple scans over time. Furthermore, while PET-CT is sensitive to inflammation, it is not specific to PMR. Increased FDG uptake can be seen in several other conditions, including infections, malignancies, and other inflammatory diseases, which may lead to false positives and unnecessary additional testing [72].

Another limitation is the use of glucocorticoids prior to performing FDG-PET-CT. In this sense, the use of glucocorticoids may reduce the sensitivity of this imaging technique [48,73]. With respect to this, it has been found that within 3 days of high-dose glucocorticoid treatment, FDG-PET-CT can diagnose large-vessel GCA with high sensitivity [74]. However, the degree of 18-FDG uptake is reduced in patients with large-vessel GCA after 72 h of treatment with high doses of glucocorticoids, and the results may be falsely negative if the PET-CT is performed ten days after the initiation of glucocorticoids [38]. Regarding isolated PMR, some experts consider that if FDG-PET-CT is performed for diagnostic purposes, glucocorticoids should be discontinued to improve diagnostic accuracy [75]. However, other experts consider that although the effect of prednisone/prednisolone at a dose of 15 mg/day, which is the average initial dose generally used in patients with isolated PMR, may lead to a reduction in FDG uptake, the distribution of uptake on PET-CT remains consistent with that observed in patients with PMR without prior glucocorticoid therapy [38].

Another point of debate is whether PET-CT should be used in the management of PMR. There are inconclusive results regarding its correlation with relapse risk or treatment response, and changes in FDG uptakes following corticosteroid treatment have been observed, indicating challenges in its utility for long-term management. In this regard, studies on repetitive 18-FDG-PET-CT in patients with isolated PMR before treatment with glucocorticoids was initiated, and then at 3 and 6 months it was indicated that the results of FDG-PET scans in patients with PMR did not correlate with their risk of relapse [76]. In addition, current guidelines do not universally recommend its use for all patients with PMR, especially in the absence of atypical symptoms or refractory disease, due to the aforementioned factors. Further research is needed to establish clear guidelines for its use in patients with PMR.

9. Potential Correlation between PET-CT and Ultrasonography (US) in PMR

PET-CT is highly sensitive in detecting inflammatory changes and, as previously discussed, can help differentiate PMR from other conditions such as GCA, which often coexists with PMR. However, it has limitations due to its high cost, limited availability, and radiation exposure. In contrast, musculoskeletal US is a non-invasive imaging technique that can visualize inflammation in joints and soft tissues. In PMR, US can detect bursitis, tenosynovitis, and synovitis, particularly in the shoulders and hips. Unlike PET-CT, US is cost-effective, widely available, and does not involve radiation exposure. It can provide real-time images and is useful for guiding joint aspirations or injections. However, US also has limitations, such as being operator-dependent and less effective at assessing deeper structures compared to PET-CT.

PET-CT and US can have complementary roles in managing patients with PMR. Both techniques can identify similar inflammatory changes, though through different ways. PET-CT provides a comprehensive overview of metabolic activity, while US offers a detailed structural imaging of superficial joints and tissues. Their combined use can increase diagnostic accuracy. Both PET-CT and US can detect bursitis in the shoulders and hips, which are the key diagnostic features of PMR. While PET-CT is highly sensitive, US is more practical for routine follow-up and monitoring.

In an interesting pictorial review on PET-CT in PMR, Rehak et al. reported on the use of 18F-FDG-PET-CT in a 55-year-old woman evaluated during a relapse of PMR to rule out co-incidental malignancy. PET-CT disclosed active inflammation in the shoulders, hips, and sternoclavicular joints, as well as near the ischial tuberosities and lumbar spinous interspaces. US confirmed these inflammatory changes. These findings support a good correlation between PET-CT and US [69].

10. Conclusions

In daily clinical practice, most patients with PMR are managed without the need of using PET-CT. In these cases, an appropriate clinical assessment and the routine laboratory markers of inflammation can help establish a diagnosis of PMR. However, PET-CT may be useful to establish a comprehensive evaluation of PMR [77].

Since PET-CT is not required for the diagnosis of PMR, clinicians must consider several situations in which this imaging technique may be used in patients with suspected PMR.

These situations are described below (Table 1):

Table 1. Situations in which we recommend performing PET-CT for identification of PMR.

Typical clinical manifestations but normal markers of inflammation
Patients with typical clinical features who do not experience adequate response to glucocorticoids
Patients with suspected PMR with atypical presentation
Suspected large vessel vasculitis indicative of extracranial GCA
To exclude other conditions that can mimic PMR (i.e., malignancies, infections, rheumatoid arthritis, and atypical spondyloarthritis)
PMR-like syndrome in cancer patients treated with immune checkpoint inhibitors (ICIs)

Abbreviations: PET-CT: positron emission tomography/computed tomography; PMR: polymyalgia rheumatica; GCA: giant cell arteritis.

Patients with typical clinical manifestations in which there is a shoulder inflammatory involvement associated with other clinical manifestations such as hip involvement but who have normal markers of inflammation [20,58].

An initial dose of prednisone/prednisolone ranging between 12.5 and 25 mg/day is recommended for the management of isolated PMR [78]. Following this procedure, most patients should improve. Consequently, FDG-PET-CT may be used in a patient with typical clinical features who does not experience adequate response (a remarkable improvement of symptoms within a week) after the onset of 15–25 mg of prednisone per day.

PET-CT may be also used in patients with suspected PMR with atypical presentations. It may also be the case in patients in whom the clinical picture is confusing and does not match common diagnostic criteria [39,58].

PET-CT may help us to exclude other conditions that present with similar symptoms, such as RA, malignancies, infections, or other inflammatory diseases [35,36].

Another indication may also be patients with suspected GCA as PMR and GCA are often overlapping conditions [38,79,80]. In this regard, PET-CT can be useful in detecting large-vessel inflammation in large vessels indicative of GCA [81,82]. With respect to this, a recent study that included a meta-analysis confirmed that 18F-FDG-PET-CT is a highly effective diagnostic tool for detecting extracranial large vessel vasculitis in patients with PMR. Its high sensitivity and specificity, coupled with its ability to provide a detailed visualization of vascular inflammation, make it a valuable addition to the diagnostic of conditions [83].

In summary, the search for a reliable diagnostic test is critical in patients with PMR, in particular in those who are not well-defined. As discussed by experts in the field [84], the use of 18F-FDG-PET imaging appears promising, offering detailed insights into inflammatory activity that may not be evident through traditional methods. However, while PET imaging shows potential, it is essential to weigh its cost, accessibility, and feasibility against

its diagnostic benefits. Further research and clinical validation are necessary to determine whether PET can become a standard diagnostic approach for PMR.

Author Contributions: Conception, design, and interpretation of the data: E.H.-R., T.B.-S., R.L., S.C. and M.Á.G.-G. Acquisition of the data:E.H.-R., T.B.-S., L.C.L.-K., M.M.d.B.-A., A.T.-R., F.R.-G., C.C.-S., R.L., S.C. and M.Á.G.-G. All the authors have agreed to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature. All authors have read and agreed to the published version of the manuscript.

Funding: Miguel Ángel González-Gay research was supported by the Spanish Red de Investigación RICORS RD21/0002/0025 of the Instituto de Salud Carlos III, Spain.

Institutional Review Board Statement: The study was a review article and ethical review and approval was not needed.

Informed Consent Statement: Informed consent was obtained from all the subjects involved in the study.

Data Availability Statement: The data sets used and/or analyzed in the present study are available from the corresponding author upon request.

Conflicts of Interest: The authors declare no conflicts of interest.

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diagnostics

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Review

Relapse Predictors in Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

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Abstract: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of rare diseases with a chronic and relapsing course. Recent treatment guidelines offer many therapeutic options depending mainly on the type of diagnosis and disease manifestations. Areas that remain under discussion include whether all patients diagnosed with AAV belong to a homogeneous group with a similar prognosis at baseline or if the type and duration of remission-inducing treatment should depend on factors other than just diagnosis and disease severity. The aim of this review is to present the recent literature on the tools available to use while evaluating the risk of relapse in patients upon presentation as well as potential biomarkers of proceeding flare in patients upon remission.

Keywords: vasculitis; relapse; predictors

1. Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) are a group of rare diseases with an incidence of 13–20 cases per million per year worldwide, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA) [1–4]. The incidence of AAV has grown markedly over the last 30 years, which might be explained by the availability of ANCA testing, growing awareness of the diseases and evolution of classification criteria [5]. AAV clinical manifestations mostly reflect the fact that inflammation affects small and medium vessels and includes mostly upper and lower respiratory tract involvement, glomerulonephritis, and skin, eye and neurological symptoms. Since their first description in the 1930s, advancements in research on the diagnosis and treatment of these diseases have transformed them from rapidly progressing fatal conditions into chronic ones [6,7]. The latest treatment guidelines offer many therapeutic options depending on the type of diagnosis, disease manifestations, and other clinical variables. The intensity of the initial immunosuppressive remission induction depends mainly on the initial diagnosis of limited or generalized form of the disease, while maintenance therapy intensity and duration is rather uniform [8]. The treatment recommendations provide guidance for therapeutic decisions but do not address all questions regarding the care of patients with AAV. Areas that remain under discussion include whether all patients diagnosed with AAV belong to a homogeneous group with a similar prognosis at baseline or if the type and duration of remission-inducing treatment should depend on factors other than just diagnosis and the differentiation between limited and generalized forms. Given that AAV exacerbations lead to the accrual of organ damage, another research aim is to create a set of diagnostic tools that, along with the form of the disease, could predict the long-term efficacy of the applied treatment or the likelihood and timing of relapse [9]. Another challenge in AAV management is the outpatient monitoring of those who have achieved remission. Commonly used disease activity assessment tools, which guide immunosuppressive treatment intensification, rely on a set of results,

including imaging, laboratory tests, and consultation outcomes. To obtain these results, it is necessary to repeat them regularly in asymptomatic patients or in an accelerated manner for patients reporting symptoms. The fact that some clinical manifestations, such as hematuria, may present with few symptoms can delay the recognition of disease relapse, thereby predisposing patients to persistent changes and the accumulation of irreversible organ damage. Some simple sets of laboratory tests are proposed to perform on a regular basis for an early relapse detection in patients upon remission, but other sensitive and specific tools are still under investigation [10,11].

It is worth emphasizing that EGPA is both pathogenetic and clinically different from other AAVs. Patients of this entity are rarely participants of the same clinical trials or other scientific studies assessing the course of exacerbations, so EGPA is not included in the study below.

2. Methodology

The methodology of this review was based on the literature search for the MEDLINE database including studies published before 30 May 2024. Only studies written in English were analyzed. The main search strategy included adult GPA, MPA and AAV cohorts combined with relapse terminology.

3. Baseline Relapse Risk Evaluation

The clinical manifestation at flare of AAV seems to play a role in predicting future exacerbation. Single-center experiences most commonly pointed at proteinase 3 (PR3) ANCA presence and lung involvement as factors predictive of relapse [12,13]. Large multicenter clinical trials have delivered further data to analyze the set of basic risk factors of relapse in AAV. In 2008, a group of patients in the Glomerular Disease Collaborative Network (GDCN, $n = 350$) in the southeastern US was compared with a group of patients in the French Vasculitis Study Group (FVSG, n = 434). During a mean follow-up of 45 months, the risk of exacerbation in the GDCN group was shown to coexist with the presence of anti-PR3 antibodies (HR 1.68), lung involvement (HR 1.68), and upper respiratory tract involvement (HR 1.58) [14]. Pooled results from NORAM, CYCAZAREM, CYCLOPS and MEPEX (>500 patients) (pooled trials cohort) showed that 38% of patients experienced relapse during the observation period (between 36 and 132 months). Anti-proteinase 3 antibodies and cardiovascular involvement were found to be independently associated with a higher risk of relapse, while a creatinine level more than 200 μmol/L at baseline was strongly associated with a reduced risk of flare [15]. A meta-analysis of 16 trials published in 2021 confirmed that significant risk factors for relapse include the presence of anti-PR3 ANCA positivity [HR 1.69], cardiovascular involvement [HR 1.78], creatinine >200 μmol/L [HR 0.39] and creatinine 101–200 μmol/L [HR 0.81] [16].

Similar observations were made in a meta-analysis searching for relapse predictors in cyclophosphamide-treated patients by He et al. A lower level of baseline serum creatine, proteinase 3 (PR3)-ANCA positivity at diagnosis and extrarenal organ involvement (lung, cardiovascular, upper respiratory, and gastrointestinal involvement), were found risk factors for an exacerbation at baseline [17]. A significant role of creatinine level on relapse risk was also confirmed in a big Polish cohort analysis. Also, skin, ENT and eye involvement were found to increase the risk of flare [18].

3.1. ANCA Testing

ANCA antibodies are an important pathogenetic element in the development of vasculitis with high sensitivity and specificity for AAV diagnosis [19,20]. Actual guidelines suggest using one-step antibody testing as a rapid, non-invasive tool in the diagnosis of patients with suspected vasculitis, based on the EUVAS study comparing the performance of ANCA IF and immunoassays and the subsequent changes introduced by the revised 2017 international consensus on the testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis [21,22]. Their identification is important in the process of classify-

ing patients with a histopathological diagnosis of small vessel vasculitis [23–25]. However, it should be noticed, on the one hand, that some patients diagnosed with GPA, MPA and EGPA remain seronegative, and on the other hand, ANCA positivity is observed also in other diseases such as inflammatory bowel disease or drug-induced [26–28]. It is also worth emphasizing that racial differences are observed in the distribution of AAV serotypes in various populations, e.g., Caucasian patients diagnosed with GPA are mainly anti-ANCA-PR3-positive (65–75%), while in the Chinese population, the majority of patients with GPA show myeloperoxidase (MPO) positivity (71%) [29,30]. Overall, it should be concluded that while ANCA testing is an indispensable diagnostic tool in suspected AAV and has an important role in the classification process, it also has some limitations [31]. The performance of ANCA testing, its type and titer in predicting the recurrence of relapsing AAV patients remains debatable. The first reports regarding the potential role of ANCA titer in predicting exacerbations date back to the 1990s. The Kyndt team monitored disease status over 22 months in groups of patients completing remission-inducing treatment for GPA (then Wegener's granulomatosis, n = 21) and MPA (n = 17). They observed that the baseline ANCA pattern (IF) did not differentiate relapsers from non-relapsers; however, relapses occurred more frequently in patients with initial lung involvement [16 of 23 (70%) vs. 6 of 20 (30%)] and persisting ANCA presence (86% vs. 20% in the ANCA-negative group) [32]. The following years brought further evidence of the usefulness of dividing patients with AAV in terms of antibody specificity in stratifying the risk of exacerbations [33–36]. Lionaki's group compared this stratification system to the disease classification criteria and Chapel Hill Consensus Conference (CHCC) definitions, indicating that ANCA's specificity had the best relapse predictive model fit of all the tested methods [37]. Similar observations were provided by the first large clinical trials comparing different treatment regimens to induce and maintain remission in AAV. A cluster analysis of the results of five such studies (n = 673) selected the following clusters: 'renal AAV with PR3-ANCA positivity (40% of subjects), 'renal AAV without PR3-ANCA' (32%), 'non-renal AAV' (12%), 'cardiovascular AAV' (9%) and 'gastrointestinal AAV' (7%), differing from each other in both overall survival and the percentage of patients experiencing disease relapse, indicating the first subgroup as having the highest risk of recurrence [38]. In 2013, a retrospective analysis was conducted on factors responsible for not achieving disease remission within 6 months in the RAVE study (CYC/AZA vs. RTX in AAV). Among the study participants, 19% experienced disease relapse after initial improvement but before the 6-month mark of induction treatment. Among those who had severe flares, 92% were PR3-ANCA-positive, and 83% had GPA. A history of disease exacerbations prior to starting induction therapy was also considered an additional risk factor for early disease relapse at that time [39]. Not all analyses regarding the relationship between antibody type and disease relapse have been consistent. In a Japanese study from 2015, it was shown that both ANCA-PR3+ GPA and ANCA-MPO+GPA patient groups relapsed more frequently than MPA patients. It is worth noting, however, that this study involved a smaller group of patients compared to other studies on this topic and focused on a Japanese population characterized by significant differences in the type of antibodies present in GPA compared to Caucasian populations [40]. A pooled analysis from two large RCTs, RAVE and WGENT, found in 2016 that the risk of exacerbations in the MPO-ANCA-positive GPA and PR3-positive GPA groups did not differ from each other, but in the former group, it was higher than in the MPO-positive MPA group at both 12 and 18 months of follow-up. The risk of relapse in this cohort study was associated more closely with disease type rather than ANCA type [41]. A similar observation was made from a retrospective analysis of patients from Caen University Hospital (n = 150). Relapse-free survival was shorter in the group of patients with GPA than for patients with MPA; however, no differences in the risk of exacerbation were observed between patients with PR3+ and MPO+ [42]. The differences between the findings of these studies and earlier reports may stem from several factors. Firstly, the analyzed groups differ demographically and clinically. Some study populations include participants from clinical trials, which could impact the generalizability of findings

to broader patient populations. Additionally, there are significant differences in cohort creation methodologies, such as the proportion of patients with new diagnoses versus those experiencing disease exacerbations. Moreover, variations exist in the speciality of medical centers recruiting patients (e.g., nephrology vs. rheumatology). These factors collectively contribute to the variability in study outcomes observed across different research efforts. Important answers to questions about the prognostic value of ANCA's baseline status were eventually provided by an analysis of a large population from the French Vasculitis Study Group registry. The study unequivocally demonstrated that while the group of patients with seronegative AAV did not differ in terms of 5- or 10-year relapse-free rates from the group of GPA and MPA patients with antibodies, a detailed analysis of PR3-ANCA-positive patients showed a higher frequency of vasculitis exacerbations compared to the rest of the AAV population. It is important to note, however, that this relationship did not impact differences in overall survival [43]. Summarizing, it can therefore be concluded that not the presence of ANCA antibodies but their specificity may be helpful in stratifying the risk of relapse in patients who achieve AAV remission. Together with phenotypic analysis, it may in the future be a tool for classifying patients with individual clusters in terms of the risk of recurrence and be the basis for differentiating the treatment model in individual groups. The impact of such changes on overall survival would need to be verified but could be helpful in reducing the immunosuppressant's exposure.

3.2. Cell Count, Genetics, Infections, Histopathology and Other Predictors at Baseline

Flow cytometry studies also allowed us to identify cell populations that may predict resistance to induction treatment. These include the population of CD27+CD38hi B cells, an increased percentage of which in the relapsers group was observed in both peripheral blood and urine. Their presence in the study material was interpreted as the result of migration from the kidneys, as these cells were also observed in the kidney biopsies of patients in the active phase of the disease [44]. In 2015, Graysson et al. conducted a trial focusing on the hypothesis that low-density granulocytes (LDGs) contribute to gene expression signatures in AAV. The RNA sequencing of whole blood in patients with AAV was compared. Differential expression between responders (n = 77) and nonresponders (n = 35) was detected in 2346 transcripts at the baseline visit. The increased expression of a granulocyte gene signature was associated with disease activity and decreased response to treatment. The source of this signature was likely LDGs [45].

Genome-wide association studies in AAV have led to the identification of the genetic background of AAV susceptibility such as *CTLA-4*, *PTPN22*, *FCGR2A*, *SERPINA1* (an endogenous inhibitor of PR3), and TLR9 genetic variations. It was also proven that GPA is associated with *HLA-DP1*, MPA with *HLA-DQ*, and EGPA with *HLA-DRB4* [46]. This discovery aroused questions about potential treatment resistance predictors among genetic factors. The carriers of *TNFSF13B rs3759467* (a single-nucleotide polymorphism) and homozygous carriers of *HLA-DPB1*04:01* were found to relapse earlier than non-carriers [47–49]. As genetic testing is not available in every clinical center and is also relatively complex and expensive, these research results seem to be more informative than have presently a practical impact.

The role of infectious factors on AAV development and course was debated for a long time. Thirty years ago, it was proven that the chronic nasal carriage of *S. aureus* identifies a subgroup of GPA patients who are at risk of relapses of the disease, suggesting a role for *S. aureus* in its pathophysiology and a possible clue for treatment [50,51]. This early observations were also supported by the fact that treating GPA patients with trimethoptim–sulfamethoxazole reduced the incidence of relapses [52]. An explanation of this phenomenon is complex and still not well described, but it is worth noting that GPA exhibits molecular features that allow its differentiation from other inflammatory disorders with nasal involvement and that a mucosal disbalance might orchestrate primary inflammation on site [53,54]. It has also been shown that in mice models, staphylococcus aureus

plasmid-encoded 6-phosphogluconate dehydrogenase can induce anti-MPO autoimmunity, pointing at a possible molecular mimicry mechanism [55].

Most studies validating the histopathological classification of ANCA-associated glomerulonephritis focused on renal survival, although renal relapse probability was separately analyzed in a pooled cohort of patients from MEPEX and CYCAZAREM trials. Both clinical and histological parameters were taken under investigation. In this trial, sclerotic class ANCA-associated glomerulonephritis and the lack of interstitial infiltrates in baseline renal biopsies increased the instantaneous risk of renal relapse [56–59].

Some other relapse predictors at AAV flare have also been proposed: CCL18 serum levels, calprotectin at month 2 and 6 after RTX administration and a low number of circulating endothelial progenitor cells (EPCs) [60–62].

4. Relapse Predictors on Remission

Although cheap and easy to obtain, simple biomarkers of inflammation, like ESR, CRP, IL-6, IL-8, IL-15, IL-18BP, and matrix metalloproteinase-3 [MMP-3], seem to have a correlation with AAV activity and fail to predict relapse in longitudinal observations [63,64]. It raises questions about other possible tools for monitoring remission in order to early detect upcoming relapse.

4.1. ANCA Testing

Antibodies against PR3 most probably induce inflammation by directing the cells they bind to towards apoptosis, whereas antibodies against MPO stimulate cells to produce reactive oxygen species [65]. In vivo experiments have subsequently demonstrated that anti-MPO antibodies alone have the ability to induce full-blown vasculitis, whereas anti-PR3 antibodies have this potential only under specific conditions and typically induce milder forms of the disease [66–70]. These observations led to the hypothesis that an increase in ANCA titer may herald impending vasculitis exacerbations in patients who have achieved clinical remission, particularly in those with dominant capillaritis rather than granulomatous inflammation. Such measurements are cost-effective and non-invasive tools for monitoring patients in outpatient settings [71]. The initial reports on the predictive role of serial ANCA measurements in patients in remission suggested their high specificity. In a study by Tervaert et al., all exacerbations observed in the cohort of patients were preceded by a significant rise in ANCA titers [72]. In 1999, a serial analysis of ANCA levels in a group of patients with AAV showed that a significant titer increase was observed in 73% of exacerbations in patients with anti-MPO antibodies but only in 33% of exacerbations in those with anti-PR3 antibodies. This supports the hypothesis that the role of ANCA in monitoring remission in patients with AAV may vary depending on the disease phenotype [32]. Such observations were confirmed by subsequent studies. In a cohort of 166 patients with AAV, serial measurements of ANCA antibodies over a mean follow-up time of 49 ± 33 months revealed that a significant titer increase predicted vasculitis exacerbation primarily in patients with renal involvement (hazard ratio [HR], 11.09) and to a much lesser extent in patients with the involvement of other organs (HR, 2.79]) [73]. Additional information came from an extended analysis of the RAVE study (rituximab versus cyclophosphamide for remission induction), in which a rise in anti-PR3 antibodies was monitored. An increase measured by direct ELISA was associated with subsequent severe flare, especially in cases with renal involvement (HR, 7.94) and alveolar hemorrhage (HR, 24.19). This observation occurred only in the group of patients treated with rituximab, indicating that monitoring anti-PR3 levels may be applicable in a selected group of patients. It is also worth noting that a better predictive value was observed using the ELISA direct method than ELISA capture [74].

4.2. B-Cell Reconstitution

Over the past 15 years, rituximab has been increasingly playing a significant role in the treatment of AAV. As an antibody targeting B lymphocytes, it has not only proven to

be non-inferior to conventional remission-inducing therapies but has also solidified its advantage as a maintenance therapy for sustaining remission [75–78]. It brought attention to B lymphocyte count as a predictive tool on remission. In the analysis of disease relapse during the first 6 months of remission induction therapy in the RAVE study, no correlation was observed between an increase in B cell count and subsequent exacerbation. None of the patients experiencing disease relapse within the first 6 months in the RTX-treated group had detectable B cells. Conversely, 47 out of 197 (24%) patients in the study had peripheral B cells present for up to 6 months of remission induction therapy but did not experience vasculitis relapse [39]. However, this observation changed from 6 months to 18 months of treatment where disease relapses were rare in the group of patients with B cell depletion [79]. In a long follow-up of RTX treatment, 71% of patients experienced B cell return at the time of relapse [80]. These observations were continued in the MAINRITSAN2 study. It compared two maintenance treatment regimens using rituximab for sustaining remission: fixed-dose maintenance (500 mg every 6 months) versus personalized dosing based on ANCA seroconversion, a 2-fold increase in ANCA titers, or the return of the peripheral B lymphocyte population. Both groups did not differ significantly in terms of relapse rates, but the personalized rituximab dosing group had reduced exposure to immunosuppression. Therefore, it can be inferred that these markers are useful for monitoring patients in remission to optimize treatment outcomes and cost-effectiveness [81]. Rituximab causes depletion not only of effector B lymphocytes but also of regulatory B cells. In a 2015 study by Bunch et al., the immunophenotypic profile of this cell lineage was observed, indicating that patients in remission of AAV who experienced a decrease in CD5+ regulatory B cells to less than 30% of all B lymphocytes tended to experience vasculitis exacerbations more quickly compared to those with CD5+ above 30% (median = 16 months versus 23 months, respectively) [82]. Other interesting observations focused on different B cell subtypes during remission. Naïve B cell repopulation appears to play a protective role against exacerbations, while an increase in PR3+ plasmablast populations signals exacerbation in patients treated with rituximab for remission induction [83]. Therefore, the immunophenotypic analysis of total B cell numbers appears to be an alternative or complementary approach to measuring ANCA levels as a potential predictor of exacerbation.

4.3. Other Potential Markers

Another proposed relapse predictor upon remission was a myelopoiesis gene signature in circulating leukocytes. In fact, PR3/MPO mRNA levels were not associated with future relapses in the analyzed cohort, but the authors hypothesized that undergoing steroid therapy might have affected the results [84]. Among other potential mechanisms in AAV etiopathogenesis, altered IgG glyco- and galactosialylation levels have also been debated. Those changes in the Fc region have been found to have an impact on IgG effector functions [85]. It was first described that in mass spectroscopy, low galactosylation and sialyation in total IgG1 but not PR3-ANCA IgG1 predicts disease reactivation in patients with GPA [86]. It was later shown by Wojcik et al. in a longitudinal observation that PR3-ANCA patients who experienced an ANCA rise and relapsed shortly thereafter presented lower IgG Fc-fucosylation levels compared to non-relapsing patients already 9 months before relapse [87]. Although the cost of such testing is relatively high, it is worth noting that the test was only performed as the second step in patients who experienced ANCA rise during follow-up. All these above mentioned methods are difficult to perform in the setting of everyday clinical practice.

Among other possible markers of upcoming flare, it is worth mentioning some simple and relatively cheap ones like urinary CD4+ count and persisting hematuria [88,89].

There are some combined relapse-predicting scores used to evaluate the treatment failures proposed, with the REACT score as the most recent one, and it is worth discussing the possibility of adding it to the baseline evaluation while starting treatment [90,91].

5. Discussion

All discussed markers are presented in Table 1.

Table 1. AAV relapse predictors.

Relapse Predictors	Well Described	Proposed
At baseline	antiPR3 presence	CD27+CD38hi B cells low-density granulocytes TNFSF13B rs3759467 (snp) HLA-DPB1*04:01
	respiratory tract and cardiovascular involvement	CCL18 calprotectin endothelial progenitor cells (EPCs)
	S. aureus carriage	sclerotic class glomerulonephritis lack of interstitial infiltrates on renal biopsy
Upon remission	ANCA reappearance	galactosylation and sialyation in IgG1 IgG Fc-fucosylation
	B cell reconstitution	urinary CD4+ count persisting hematuria

A series of analyses of potential relapse predictors in remission patients discussed in the literature prompts a consideration of whether using any of these predictors individually or in combination could justify intensifying treatment or if the optimal practice relies on an observation of clinical symptoms of disease relapse followed by implementing more aggressive therapy. It remains unclear how frequently follow-up visits should occur for patients exhibiting only serologic markers indicating impending exacerbation and whether the delayed recognition of subtly symptomatic disease recurrence may lead to increased chronic organ damage and consequently poorer outcomes. Additionally, it is unclear how often such markers should be measured and how to establish a cutoff for significant increases without raising false-positive prediction rates. It is worth noting that none of the analyzed potential relapse predictors demonstrate 100% specificity, and certainly, not every patient showing changes in these markers will develop vasculitis exacerbation or will do so with significant delay. It is also reasonable to evaluate potential differential diagnoses, like IgG4-related disease or malignancy, and overlapping syndromes, mainly treatment complications when early relapse occurs, especially in seronegative patients. The most challenging symptoms are those of the respiratory tract in patients with ENT involvement as infections might mimic disease progression or they coexist. It is still not well explored which of the discussed tools are disease-specific and distinguish between these two conditions.

6. Conclusions

Taking into consideration the heterogeneity of AAV, we can define, on the one hand, a subgroup with a low risk of relapse (female, anti-PR3-negative, high creatinine, no ENT involvement) who will be candidates for withdrawing the maintenance treatment, and on the other hand, the phenotype requiring probably lifelong maintenance therapy (male, PR3+, ENT, skin, eye involvement, low creatinine). But the majority of patients' risk will be in between and will require real-time monitoring using a clinical observation, self-reporting and laboratory parameters monitoring to decide about maintenance therapy duration or intensification. Patients for whom the search for potential relapse markers has yielded less significant results so far include seronegative patients, the EGPA group, those with non-renal forms, and those treated with medications other than anti-CD19. There are several potential biomarkers proposed in the literature to evaluate relapse potential both at flare and upon the remission of AAV and they will need additional validation.

Author Contributions: Conceptualization, K.W.-A. and K.W.; methodology, K.W.-A.; formal analysis, K.W.; investigation, K.W.-A.; resources, K.W.-A.; writing—original draft preparation, K.W.-A.; writing—review and editing, K.W.-A. and K.W.; visualization, K.W.-A.; supervision, K.W., J.M. and M.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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Review

Neutrophils and Platelets as Key Players in the Pathogenesis of ANCA-Associated Vasculitis and Potential Sources of Disease Activity Biomarkers

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Abstract

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) is a heterogeneous group of small-vessel vasculitides, characterized by the presence of antibodies binding to myeloperoxidase (MPO) and proteinase-3 (PR3) found in neutrophil granules. Apart from being the target of ANCA, neutrophils actively contribute to the vicious cycle of inflammation and vascular damage in AAV. On the other hand, platelets have recently been recognized as essential for thrombosis and as inflammatory effectors that collaborate with neutrophils, reinforcing the generation of reactive oxygen species (ROS) and the formation of neutrophil extracellular traps (NETs) in those diseases. Neutrophils exhibit morphological and functional heterogeneity in AAV, reflecting the complexity of their contribution to disease pathogenesis. Since long-term immunosuppression may be related to serious infections and malignancies, there is an urgent need for reliable biomarkers of disease activity to optimize the management of AAV. This review summarizes the current understanding of the role of neutrophils and platelets in the pathogenesis of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), focusing on their crosstalk, and highlights the potential for identifying novel biomarkers relevant for predicting the disease course and its relapses.

Keywords: ANCA-associated vasculitis (AAV); neutrophils; platelets; myeloperoxidase (MPO); proteinase-3 (PR3); neutrophil extracellular traps (NETs); extracellular vesicles (EVs); biomarkers

1. Introduction

The anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) comprises a group of autoimmune diseases characterized by inflammation of small and medium-sized blood vessels, often leading to multi-organ damage. According to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature, AAV encompasses three main subtypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1], with EGPA being the rarest and most distinct form due to its eosinophilic component. The

presence of ANCA is a characteristic feature of AAV, with PR3-ANCA (proteinase-3 ANCA) associated with GPA and MPO-ANCA (myeloperoxidase ANCA) observed in MPA. Unlike GPA and MPA, where ANCA is detected in approximately 90% of cases, only 30–40% of EGPA cases are ANCA-positive, primarily with MPO-ANCA [2,3]. The heterogeneity of AAV presents significant challenges in diagnosis and management, as symptoms and disease severity vary.

Although any tissue can be involved, the respiratory tract and kidneys are most frequently affected, with complications such as pulmonary hemorrhage and rapidly progressive glomerulonephritis (RPGN) posing serious risks, including death [3–5]. Additionally, some patients exhibit overlapping features of different AAV subtypes, further complicating classification and prognosis [2,6,7]. Finally, the clinical presentation and disease trajectory may also change, making the long-term prognosis and treatment plans complex and challenging [8].

Given the typical relapse-remission pattern of AAV, remission induction and remission maintenance are fundamental paradigms in management. Remission induction in GPA and MPA depends on the severity of disease presentation. For patients with life- or organ-threatening manifestations, both the 2021 American College of Rheumatology/Vasculitis Foundation (ACR/VF) [9] and 2022 European Alliance of Associations for Rheumatology (EULAR) guidelines [10] recommend a combination of glucocorticoids (GC) and either rituximab (RTX) or cyclophosphamide (CYC). Maintenance of remission relies on intensive and long-term immunosuppression. In GPA and MPA, maintenance treatment with repeated doses of RTX is superior to azathioprine (AZA) and methotrexate (MTX) in reducing relapse rates, while AZA and MTX are recommended when RTX is contraindicated [11,12]. Mycophenolate mofetil (MMF) is considered a third-line treatment [9,10]. However, in some patients, discontinuing GC despite immunosuppressive therapy use may still be unfeasible [10].

Immunosuppressive treatment in AAV patients is associated with various complications, some of which can be severe and potentially fatal, particularly during long-term maintenance therapy. It has been shown that infections and malignancies rank among the top three long-term causes of death in AAV, being surpassed only by cardiovascular diseases, whose risk increases dose-dependently with GC use [13–15]. Therefore, it is crucial to balance therapy to reduce the risk of disease relapse and also minimize the side effects and toxicity of immunosuppression. Since no reliable clinical parameters are available, laboratory biomarkers are urgently needed to predict clinical trajectory and disease relapse.

Vasculitides are related to the inflammatory process that damages the walls of small and medium-sized blood vessels, resulting in impaired blood flow and ischemia [16,17]. The exact mechanisms underlying immunologic and cell responses, including preliminary triggers, have not been fully understood; however, the central role of neutrophils in the pathogenesis of AAV is unquestionable [18–21]. Platelets, on the other hand, have recently been considered as potential contributors to the inflammatory process underlying AAV. Moreover, there is growing evidence of crosstalk between neutrophils and platelets in various conditions [22–24], including AAV [25–28]. Given the relatively novel evidence on platelet involvement in AAV pathogenesis, we aim to review that issue. Furthermore, we recapitulate the known facts on the interplay between neutrophils and platelets in AAV and highlight the impact of this novel research on disease prognosis and optimal therapeutic approach in those patients.

2. Materials and Methods

A literature search was performed on PubMed and Embase for studies published in English up until April 2025, using MeSH and Emtree terms related to ANCA-associated

vasculitis, neutrophils, and platelets. The titles and abstracts were screened for relevance to the review topic. Articles that did not provide new insights were excluded. Additional relevant articles were identified through citation searching. Due to substantially different pathogenesis and rarity, this review did not include data on EGPA.

3. Pathogenesis of ANCA-Associated Vasculitis—An Overview

The pathogenesis of AAV involves a complex interplay between innate and adaptive immunity. While ANCA and neutrophils are central to this process, their pathogenicity is modulated and amplified through interactions with monocytes, macrophages, B and T lymphocytes, the complement and coagulation systems, as well as platelets.

Monocytes and macrophages also contribute to vascular damage and immune activation. Circulating monocytes infiltrate inflamed tissues, differentiate into macrophages, and promote granulomatous inflammation. Monocytes are stimulated by ANCA to produce proinflammatory cytokines, such as TNF and IL-6 [29], and are a major source of tissue factor (TF) that links inflammation to thrombosis [30]. They also play a role in impaired clearance of apoptotic neutrophils, which may perpetuate inflammation and interfere with resolution [31]. Additionally, macrophages may respond to NET-derived molecules [32,33] and participate in antigen presentation and T-cell activation, thus bridging innate and adaptive immunity [34].

B cells are essential for the production of ANCA and also serve as antigen-presenting cells. Abnormal B-cell activation and survival, enhanced by elevated B-cell activating factor (BAFF), are observed in AAV and correlate with disease activity [35]. The clinical efficacy of rituximab confirms their crucial pathogenic role in AAV [36]. T cells, including Th1, Th17, CD8+, and regulatory T-cell subsets, are actively involved in both granulomatous inflammation and humoral activation. Dysregulated T-cell function contributes to ANCA production, tissue infiltration, and loss of tolerance. IL-17-producing Th17 cells are increased in active disease, and T cells specific for complementary PR3 peptides (cPR3) have been detected in patients with PR3-ANCA vasculitis [37,38].

The complement system is a crucial amplifier of inflammation. C5a promotes neutrophil priming and chemotaxis [39]. Crosstalk between complement and coagulation systems facilitates thrombin generation and propagates endothelial injury [40]. The coagulation cascade is closely intertwined with immune activation. AAV patients exhibit increased thrombotic risk, associated with neutrophil- and monocyte-derived tissue factors and thrombin-mediated platelet activation [30,41]. Thrombin not only promotes fibrin formation but also stimulates inflammation through PAR signaling, further connecting thrombosis and vasculitis pathophysiology [26,42].

4. Neutrophils

4.1. Cytokine-Dependent Regulation of Neutrophil Production Is Abnormally Upregulated in AAV

Neutrophils, or polymorphonuclear (PMN) leukocytes, are the most abundant type of leukocytes, constituting 50–70% of their total population. The average lifespan of neutrophils is relatively short, limited by programmed cell death, ranging from 7 to 9 h [43] to over 5 days [44]. Therefore, to maintain their count, about 1–2 $\times$ 10^{11} neutrophils are produced daily in the bone marrow via neutropoiesis [45], a process dependent on granulocyte colony-stimulating factor (G-CSF) activity [46]. After maturation, neutrophils are retained in bone marrow for the next 4–6 days, forming a reserve pool, ready to be deployed in case of an infection, inflammation, or trauma [47]. Neutrophil retention and release are regulated by chemokine signaling, the expression of which is controlled also by G-CSF [48]. In MPA, high initial levels of circulating G-CSF were associated with the severity of central nervous system involvement and disease activity, according to the Birmingham Vasculi-

tis Activity Scale (BVAS) [49]. After fulfilling a biological function, neutrophils undergo apoptosis in the bone marrow, spleen, or liver. Then, they are cleared by macrophages through efferocytosis [31], which modulates the neutropoiesis by a negative feedback loop. Macrophages release large amounts of interleukin (IL)-23, triggering IL-17 production by T, NK, and NKT cells, and further increasing G-CSF production. Interestingly, phagocytosis of neutrophils reduces IL-23 production by macrophages, leading to diminished neutropoiesis and cell release to the peripheral blood. On the other hand, when inflammation is amplified, the same cytokine axis intensifies neutrophil proliferation and maturation [50,51]. Patients with AAV exhibit a markedly elevated circulating neutrophil count [52]. In AAV, according to the study by Nogueira et al. [53], serum IL-17A levels were significantly higher in the acute phase of GPA than in healthy controls. Moreover, in the same study, patients with elevated IL-23 had more active disease and higher ANCA titers. Additionally, a study by Huang et al. documented a positive correlation between the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) and an inverse with C3 level in those with MPO-ANCA [54]. Interestingly, a threshold NLR of at least 5.9 was related to increased disease severity and risk of relapse in follow-up [55]. Furthermore, an elevated delta neutrophil index (DNI) of at least 0.65, reflecting the proportion of immature granulocytes within the total neutrophil count, was associated with more severe disease at diagnosis; thus, it could likely serve as a predictor of relapse in GPA or MPA [56].

4.2. Neutrophil-Endothelium Interactions Mediate Adhesion, Migration and Inflammatory Amplification in AAV

As vascular wall damage in small vessels plays a key role in AAV, interactions between neutrophils and the endothelium are crucial to its pathogenesis. Under physiological conditions, neutrophils do not adhere to resting endothelium. Upon exposure to inflammatory stimuli, neutrophils migrate towards the inflammation site, where they undergo adhesion cascade and extravasation (Figure 1) [57–59].

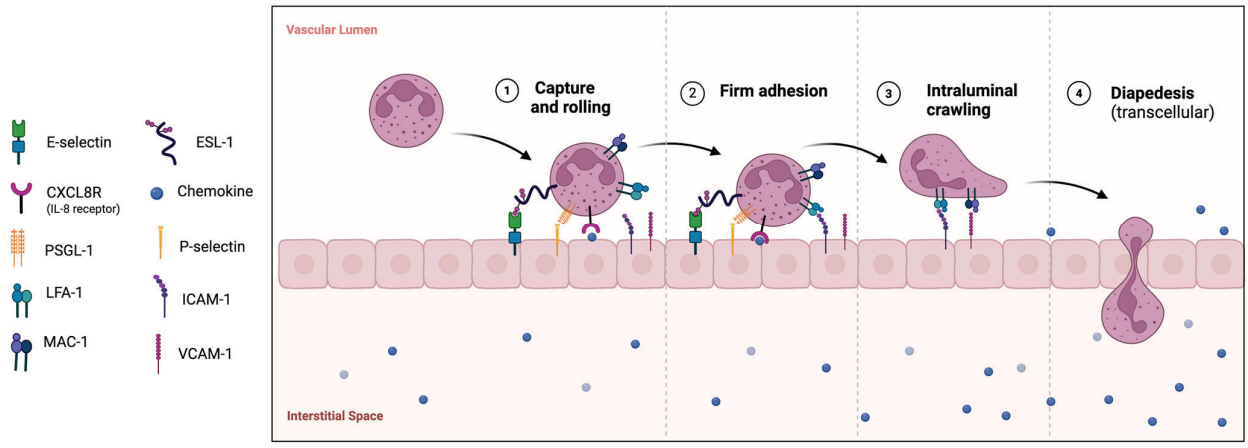

Figure 1. Neutrophil adhesion cascade preceding extravasation. This process involves capture, rolling, activation, firm adhesion, and intraluminal crawling. It depends on interactions of neutrophil glycoproteins with endothelial E- and P-selectins, whose expression is upregulated in inflammatory loci. Firstly, E- and P-selectin capture circulating neutrophils to the surface of endothelium by interacting with E-selectin ligand-1 (ESL-1) and P-selectin glycoprotein ligand 1 (PSGL1), respectively. The interaction of β_2 integrins, namely lymphocyte function-associated antigen-1 (LFA-1, $\alpha_L\beta_2$, CD11a/CD18) and macrophage-1 antigen (Mac-1, $\alpha_M\beta_2$, CD11b/CD18) with ligands such as vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule-1 (ICAM-1, CD54), and ICAM-2 on endothelial cells, ensures firm adhesion of neutrophils.

The expression of adhesion molecules, along with the deposition of plasma fibronectin on leukocytes, is enhanced by inflammation and endothelial damage. Both ANCA and tumor necrosis factor (TNF) increase β_2 integrin expression on neutrophils, further promoting their attachment and neutrophil aggregation, enhancing trapping of cell aggregates in capillaries [60]. Adhesion of neutrophils is followed by crawling along the surface of the endothelium, following the gradient of chemoattractants, adhesion receptors, and endothelial stiffness. Finally, neutrophils travel through the vascular wall via paracellular or, to a lesser extent, transcellular routes in the process of diapedesis, facilitated by the interaction of β_2 integrins, ICAM-1, platelet endothelial cell adhesion molecule 1 (PECAM-1), and junctional adhesion molecules [61]. In this context, the biological role of CD177, a novel IgG Fc receptor found on the neutrophil surface, should also be considered. It has been demonstrated that CD177 ligation causes the migratory arrest of neutrophils, likely triggered by β_2 integrins as signaling partners, including their higher expression and affinity, reduced internalization, and extracellular signal-regulated kinases (ERK)-driven suppression of chemoattractants stimuli, potentially leading to endothelial injury [62]. Next, studies on murine models and in vitro have shown that some adhesive molecules can increase neutrophil extracellular trap (NETs) formation, a process essential to AAV pathogenesis and tremendously enhancing local inflammatory response. For instance, Mac-1 augments lipopolysaccharides (LPSs)-related NET formation (NETosis), P-selectin after ligation to PSGL-1, while the β_2 integrin subfamily when triggered by β-glucan [60].

Semaphorin A4D (SEMA4D) is a glycoprotein engaged in neutrophil-endothelium interactions, considered a potential biomarker of disease activity. In typical physiological conditions, the membrane complex of CD100/SEMA4D serves as an inhibitory receptor on neutrophils, where it interacts with plexin-B2 (PLXNB2) expressed by endothelial cells. This interaction shields the endothelium from damage, mainly by suppressing neutrophil-driven immune responses by reducing the production of reactive oxygen species (ROS) and NETosis [63]. A disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) is a protease responsible for cleavage membrane-bound proteins, including SEMA4D, converting it to a soluble form [63,64]. A study by Bertram et al. [64] has reported a higher circulating ADAM17 concentration in patients with active PR3-AAV with kidney involvement compared to those in remission or with nonvascular kidney diseases. Similarly, markedly elevated serum SEMA4D levels have been demonstrated in patients with AAV, depicting a positive association with the BVAS score, and they were higher than in other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus (SLE) [63]. Furthermore, Wang et al. [65] demonstrated that neutrophils from AAV patients exhibited a notable reduction in cell-surface SEMA4D compared to healthy controls. These findings suggest increased proteolytic shedding of SEMA4D in AAV, likely mediated by ADAM17. Since membrane-bound SEMA4D contributes to endothelial protection by regulating neutrophil activation, its loss from the cell surface, resulting in elevated levels of soluble SEMA4D, may impair this regulatory mechanism and promote neutrophil-mediated vascular injury.

4.3. Neutrophil Granule Proteins, Reactive Oxygen Species Production and Extracellular Vesicles Shape the Inflammatory Environment in AAV

Neutrophils possess an armamentarium of mechanisms aimed at pathogen detection and destruction. Neutralization of ingested particles and pathogens relies on two main cytotoxic mechanisms—ROS generation in the oxidative burst, catalyzed by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [66], and activity of antibacterial proteins, originating from neutrophil granules [67].

Depending on the stage of neutrophil differentiation, the granules can be divided into four main types—azurophil, specific, gelatinase, and secretory [68]. Degranulation

through exocytosis also serves as a targeted, defensive mechanism and further enhances inflammatory response, with secretory granules being the most available for exocytosis [69]. Azurophil granules, however, are particularly relevant in the context of autoimmune vasculitis. Among various potent antimicrobial proteins—such as defensins, cathelicidins, cathepsin B, and lysozyme—they also include MPO and PR3 [70–72]. This phenomenon is mainly related to epigenetic dysregulation [73]. Furthermore, expression of these proteins on the neutrophil surface is augmented upon stimulation by complement component 5a (C5a) and cytokines released after ANCA binding [74].

ROS damage cellular components by causing double-stranded DNA breaks [75], inducing lipid peroxidation that compromises membrane integrity [76], and oxidizing proteins, leading to their misfolding and loss of function [77]. Hydroperoxides of amino acids and their residues are generated during oxidative modification driven by ROS, propagating oxidative damage further within proteins [78]. In addition to direct endothelium damage, oxidative burst might play a role in the stimulation of NETosis [79] (Figure 2), as its inhibition decreases NET formation [80]. A study by Hilhorst et al. [81] suggested that kidney damage in AAV depends on an imbalance between ROS and antioxidant defenses. Oxidative burst and hypochlorous acid (HOCl) production in neutrophils due to MPO activation at diagnosis have been linked to the presence of active cellular crescents in MPA, whereas higher serum thiol concentrations correlated with fewer cellular crescents and reduced interstitial fibrosis. According to the same study, MPA patients display higher oxidative stress, characterized by increased serum HOCl and advanced oxidation protein products (AOPP) concentration compared to healthy individuals. Interestingly, Sun et al. [82] reported a decrease in AAV-associated organ damage and MPO deposition in the kidneys and lungs of rat models treated with astaxanthin, a potent antioxidant. Therefore, the level of systemic oxidative stress response could reflect disease activity in AAV, making it a promising direction for further research.

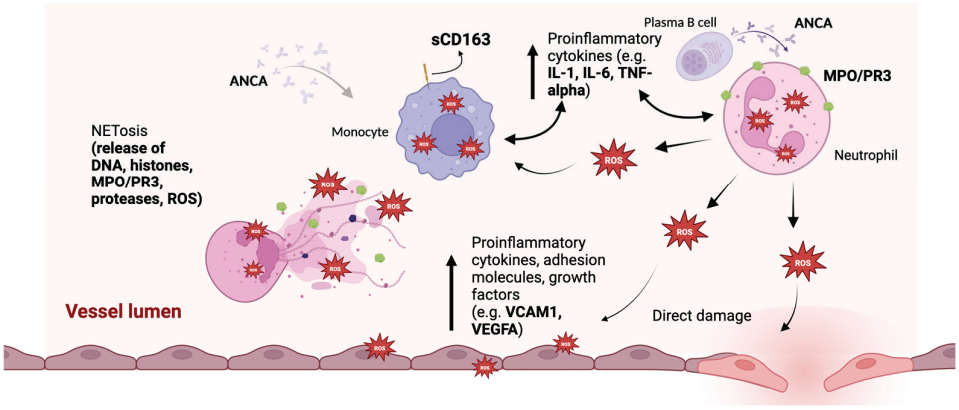

Figure 2. Reactive oxygen species (ROS) play a critical role in AAV. In addition to direct endothelial damage and perpetuating the inflammation via cytokine release, ROS generation is crucial for initiating NETosis. Monocytes and macrophages stimulated by ANCA, ROS, and inflammatory mediators release soluble CD163, which urine levels are a relatively novel biomarker of kidney vasculitis flare [83].

Beyond degranulation and ROS production, neutrophils also mediate inflammation via extracellular vesicles (EVs). EVs are an umbrella term for phospholipid bilayer-enclosed vesicles released by eukaryotic cells. Depending on their size, EVs can be divided into exosomes (50–150 nm) and microparticles (100–1000 nm) [84]. EVs regulate cell-to-cell communication, with different stimuli influencing the composition of their cargo, including proteins, nucleic acids, and lipids [85]. EVs cargo has been profiled in numerous studies investigating potential biomarkers in various conditions, such as cancer [86,87], neurologi-

cal disorders [88], autoimmune diseases [89,90], and thrombosis [91]. Neutrophil-derived EVs were shown to carry ANCA-antigens, proinflammatory miRNA, and oxylipins. Interestingly, studies report a positive correlation between the BVAS and the levels of C3a, C5a, pentraxin 3 (PTX3) [92], and high mobility group box 1 (HMGB1) expressed on MPO-positive microparticles [93,94]. A recent study by our team [95] has reported that EVs from GPA patients, likely originating from neutrophils, encompass higher leukotriene B_4 (LTB_4) and 5-oxo-eicosatetraenoic acid (5-oxo-ETE) content compared to EVs from healthy controls. This study also shows that primed neutrophils stimulated with LTB_4 or 5-oxo-ETE exhibit a concentration-dependent increase in ROS production and dsDNA release. Another study of ours [96] shows that EVs released by IgG anti-PR3-activated neutrophils induce human umbilical vein endothelial cells (HUVECs) to produce proinflammatory cytokines via their miRNA content (most notably miR-223-3p and miR-142-3p). Furthermore, the expression of EVs-derived miR-223-3p and miR-664a-3p has been elevated in active GPA and correlated positively with BVAS, but also with circulating DNA-MPO complexes, suggesting a link to NETosis [97]. In a study by Glémain et al. [98], miR-142-3p and miR-451 from neutrophil-derived EVs have been implicated in promoting endothelial inflammation and damage. Furthermore, increased expression of miR-223, miR-142-3p, and miR-451 has been observed in peripheral blood of those with kidney involvement, suggesting their role in AAV progression.

4.4. Phenotypic Diversity of Neutrophils, Including CD177$^+$ and Low-Density Subsets, Is Associated with Disease Activity in AAV

In the past, neutrophils were thought to form a homogenous population of cells possessing uniform properties. However, this view has been challenged by findings enabled by the advent of high-resolution technologies [70]. Despite their short lifespan, neutrophils change in the process of aging. In addition to downregulating CXCR2 and L-selectin, it manifests by upregulating CXCR4, CD11b, and CD49 [99], accompanied by increased capacity to form NETs. These processes can be linked to the activation of pathogen-recognition receptors by pathogen associated molecular patterns (PAMPs) [100] and depend on changes in cortisol level and expression of circadian-clock genes, remaining in relation to circadian rhythm [101]. The abovementioned alterations promote neutrophils' homing and infiltrating tissues, where they act as sentinels. In the lungs, for instance, neutrophils adhere to the vascular lumen and reside in the interstitial spaces, retained by a mechanism that depends on CXCR4, making them a possible destination for aged neutrophils [102]. Evidence indicates that neutrophils might display differences in phenotype also across tissue [103,104]. Moreover, neutrophils display substantial diversity in morphology and function in pathological contexts of inflammation, infection, and cancer [105]. For instance, the proportion of circulating neutrophils expressing CD177 remains stable within an individual, regardless of age, gender, or activation state. However, their percentage can increase during pregnancy [106], GM-CSF therapy, or in patients with polycythemia vera [107]. Studies have revealed that variability in CD177 expression affects the surface display of PR3 [108]. Only CD177(+) neutrophils express PR3, and an increased proportion of these cells is linked to a higher risk of developing AAV [109] and a higher risk of relapse in GPA [110]. Stimulation of CD177 triggers degranulation and ROS production, especially in neutrophils expressing high levels of CD177 and PR3 [111]. Interestingly, that effect is attenuated by blocking the complement receptor integrin Mac-1 [112]. On the other hand, neutrophils of MPO-ANCA-positive individuals exhibit higher expression of LFA-1 compared to PR3-ANCA-positive ones, with this integrin expression associated with systemic and pulmonary components of the BVAS [113]. Furthermore, in AAV, neutrophils coexpressing CD177, LFA-1, Mac-1, CD80, CD86, CD100/SEMA4D, class II major histo-

compatibility complex (MHC II), TNF receptor (TNFR)1, and TNFR2 are detected in higher percentages, also in positive correlation with the BVAS [63,113–115].

Among neutrophil subsets described in a pathological context, particular attention is given to low-density neutrophils (LDNs), first identified in individuals with SLE [116]. LDNs can be separated from other granulocytes using a discontinuous density gradient and exhibit a density comparable to peripheral blood mononuclear cells (PBMCs). They have been observed in various conditions, including cancer [117], infections [118], and autoimmune disorders, such as rheumatoid arthritis [119] and psoriasis [120]. Studies based on autoimmune conditions suggest that LDGs are characterized by more pronounced proinflammatory properties [121,122], a higher tendency to undergo NETosis [123,124], and better promotion of Th17 cell differentiation compared to other subsets of neutrophils [125]. Interestingly, LDGs consisting of both mature CD10(+) and immature CD10() cells have been identified in AAV [126]. The CD10(−) subset displays downregulated CD16 and CD88/C5aR expression, an immature nuclear structure, and diminished responsiveness to stimulation by MPO-ANCA, which undermines their relevance in AAV pathogenesis [126]. On the other hand, LDGs co-expressing CD10, CD16, and CD88/C5aR can be induced by ANCA stimulation and likely play a role in activating the alternative complement pathway [127]. LDGs have been reported to correlate with disease activity in AAV [128]. However, it is important to note that LDNs encompass a broad spectrum of neutrophil phenotypes and have been observed in lower fraction also in healthy individuals [129]. The actual distinctiveness and relevance of neutrophil phenotypes have been questioned and attributed to the limitations of cell isolation methodology, making it one of the most controversial current aspects of neutrophil research [130,131].

4.5. Neutrophils Exhibit a Decreased Rate of Spontaneous Apoptosis and Enhanced NETosis in AAV

After completing their function, senescent neutrophils are removed from the inflamed tissue to avoid unnecessary perpetuation of the inflammation [70]. Besides homing to undergo apoptosis and efferocytosis, they can migrate in reverse or perish via different death processes, including pyroptosis, ferroptosis, necroptosis, necrosis, and NETosis [132]. In AAV, neutrophils show a decreased rate of spontaneous apoptosis in vitro, resulting in a prolonged lifespan, which suggests a tendency to accumulate at the inflammation site in vivo [133]. Delayed apoptosis observed in neutrophils of GPA patients involves both the intrinsic and extrinsic pathways and is likely driven by elevated levels of circulating factors such as GM-CSF, TNF, and soluble Fas cell surface death receptor (sFas) [134]. On the other hand, the opposite situation occurs in the case of NETosis in AAV. NETosis is a distinct form of cell death—as opposed to apoptosis, it involves the disintegration of neutrophil cell membrane paired with the release of NETs, which consist of granule contents combined with double-stranded DNA. This process is initiated by ROS generated through NADPH oxidase, which stimulates MPO to activate neutrophil elastase (NE) and promotes its translocation from azurophilic granules into the nucleus. There, NE cleaves histones and facilitates chromatin decondensation, aided by MPO, which acts synergistically. To reach the nucleus, NE must first degrade cytoplasmic F-actin. Notably, during NETosis, plasma membrane permeabilization occurs in a programmed manner, not due to physical disruption by expanding chromatin [135]. Upon release, chromatin immobilizes pathogens, and granule-derived proteins exert their antimicrobial effect, making this process a type of cell death and an effector neutrophil mechanism [136]. Moreover, it has been observed that, as in the case of unregulated necrosis, NETosis can drive a proinflammatory response instead of mitigating it, contributing to organ injury [137]. In AAV, neutrophils display enhanced NETosis compared to healthy individuals [138,139]. Although NET formation in AAV is often driven by ANCA, Kraaij et al. [139] suggest it can occur independently of them.

Even when IgG and IgA were depleted from AAV patient serum, NETosis still occurred in vitro, indicating the presence of additional humoral factors contributing to neutrophil activation and disease progression. MPO and PR3 are integral components of NETs, so their exposure may further drive ANCA production. In AAV, NETs enriched with PR3 and MPO have been detected in kidney tissues during active disease [140,141]. Interestingly, while both MPO and PR3 can form complexes with DNA, a study by our group [138] shows that MPO-DNA complexes are consistently present in all GPA patients, whereas PR3-DNA complexes can be detected only in some. Considering this, PR3-DNA complexes are of limited utility as NET formation markers in AAV, while MPO-DNA complexes appear to serve as a universal circulating marker of NET formation. In the same study, patients with active GPA exhibited elevated circulating levels of serine proteases, DNA-histone complexes, and MPO-DNA complexes. However, DNA-histone complexes were similarly elevated in GPA patients in remission and did not correlate with the BVAS score, further supporting the role of MPO-DNA complexes as a more reliable marker of NETosis. Additionally, increased levels of free circulating mitochondrial and genomic DNA have been identified as serum markers of GPA. Elevated circulating nucleosome levels, previously observed in AAV, further highlight the role of NETosis in disease pathology [142]. Moreover, fibrous DNA deposits containing PR3 and MPO can activate plasmacytoid dendritic cells (pDCs) and autoreactive B cells through a Toll-like receptor 9 (TLR-9)–dependent mechanism [143], potentially amplifying the autoimmune response. Interestingly, NET formation is not inextricably associated with cell death, as it can also occur via vital NETosis, contributing to the persistent, pathological immune response [144].

4.6. Neutrophil Effector Functions as an Emerging Therapeutic Target in AAV

In addition to their diagnostic and prognostic relevance, neutrophils and their proteases have gained attention as potential therapeutic targets in AAV. Rather than broadly suppressing immune responses, novel approaches aim to selectively inhibit neutrophil effector functions responsible for vascular injury. Preventing NETosis, for instance by PAD4 inhibitors, which prevent chromatin decondensation and NET release [145], seems particularly potential, but has not been evaluated in AAV yet. Similarly, inhibitors of neutrophil serine proteases [146,147] appear to be a compelling research direction in the search for agents to attenuate the inflammatory process in AAV. Although such inhibitors have not yet been evaluated in AAV, a study by Jerke et al. [148] on neutrophils derived from patients with Papillon-Lefèvre syndrome, who have a genetic deficiency in cathepsin C and consequently reduced protease activity, showed impaired neutrophil activation, lower surface expression of PR3, and significantly less endothelial damage. The same study further demonstrated that in human stem cell-derived neutrophils, where a specific cathepsin C inhibitor reduced levels of neutrophil serine proteases, membrane PR3 expression, PR3-ANCA-induced activation, and the transfer of active proteases to glomerular microvascular endothelial cells, which are the primary target in ANCA-induced necrotizing crescentic glomerulonephritis. Small-molecule inhibitors of spleen tyrosine kinase (Syk), central to ANCA-induced neutrophil activation via Fcγ receptors also bear a potential to become a new therapeutic target [149,150]. Notably, avacopan, an oral C5aR1 antagonist that has become a therapeutic option in AAV, prevents neutrophil priming and recruitment [151,152].

5. Platelets

Platelets are small, anucleate cells circulating for about 7–10 days in humans before being cleared in the spleen and liver. Platelet production, or thrombopoiesis, takes place primarily in the bone marrow. This process begins with hematopoietic stem cells (HSCs)

differentiating into large, polyploid megakaryocytes, which then extend long, cytoplasmic protrusions known as proplatelets, ultimately demarcating their tips and releasing platelets into circulation [153]. Approximately 10^{11} platelets are produced daily [154]. While the roles of platelets in hemostasis and thrombosis have been extensively studied, their contributions to the immune response, particularly in autoimmune diseases, have only recently been recognized.

Although platelet counts are higher in patients with GPA compared to healthy individuals, no significant difference has been observed between those in remission and those with active disease [138,155]. Proposed mechanisms of count increase comprise interactions between platelet-derived sCD40L and matrix metalloproteinase-9 (MMP-9) [155] and between platelet-derived CCL5 and megakaryocytes [156]. A recent study by Lee et al. [157] has proposed a novel predictor based on platelet, neutrophil, monocyte, and lymphocyte counts—pan-immune-inflammation value (PIIV = neutrophil count ($\times 1000/m^3$) $\times$ monocyte count ($\times 1000/m^3$) $\times$ platelet count ($\times 1000/mm^3$)/lymphocyte count ($\times 1000/m^3$)). A high PIIV (cut-off point of at least 1011.3) at the onset of AAV has been postulated as an independent risk factor for all-cause mortality. Additionally, patients with GPA and MPA—especially those with kidney and pulmonary involvement—exhibit significantly elevated peripheral blood platelet count and platelet-to-lymphocyte ratio (PLR). PLR of 272.0 or greater has been linked to more severe disease activity [158,159]. On the other hand, in a study by Jin et al., lower platelet counts at presentation (cut-off point of 264.5 $\times$ 109/L) are suggested to be a predictor of worse kidney function, including end-stage kidney disease (ESKD), and death [160]. This observation is supported by a study by Sánchez Álamo et al., where lower platelet count was a predictor of mortality in AAV; however, the cut off value was within normal limits as well [161].

Platelets possess granules of three types: (1) alpha granules containing chemokines (CXCL7, CXCL4/PF4, CXL1/GROα, CXCL5, CCL5/RANTES, CCL3/MIP1α) [162], coagulation factors, PDGF receptors, TGF-β, P-selectin, fibrinogen, von Willebrand factor (vWF), and fibronectin; (2) dense granules storing calcium, magnesium, nucleotides (ADP, ATP), serotonin, and histamine; and (3) lysosomal granules, including glycohydrolases and proteases such as cathepsin, acid phosphatase, collagenase, and elastase. Dense bodies play a role in vasoconstriction and cytokine production primarily due to their high serotonin content [163,164]. In addition, platelets participate in immune responses by producing and releasing proinflammatory cytokines, most notably IL-1β [165]. They interact with specific receptors on leukocytes, such as monocytes, leading to cell activation. Platelets also express a diverse range of immune receptors, including chemokine receptors [166], Fc receptors [167], TLRs [24,168], and complement receptors [169–171]. The complement system plays a vital role in the pathogenesis of AAV [172]. Activation of the complement pathway leads to deposition of membrane attack complex (MAC) on the platelet surface and generation of C3a and C5a, further stimulating platelets [26].

In response to vascular damage, platelets undergo immediate changes in shape and function to participate in hemostasis or contribute to thrombosis in an unfavorable scenario. However, as platelets form heterogeneous subpopulations, chronic diseases involve shifts in their composition, altering platelet phenotypes [173]. Changes in platelet phenotypes can be driven by interactions between fully formed platelets and circulating inflammatory molecules or cells and by modulating platelet production by alterations in the megakaryocyte microenvironment. Such observations have been made in several disorders characterized by prolonged systemic inflammation, such as SLE [174], systemic sclerosis [175], and cancer [176]. For instance, chronic inflammatory states are characterized by increased platelet receptor expression and activity and the loss of surface receptors

through cleavage and shedding [173]. However, as this is a relatively novel topic, it remains understudied and highlights a new direction for research in AAV monitoring.

6. Neutrophil-Platelet Crosstalk

Recent studies have shown that the progression of AAV involves interactions between activated platelets and neutrophils, as well as the interplay between the coagulation and complement systems

A study by Miao et al. [27] has investigated in AAV platelet-derived microparticles (PMP) containing proinflammatory cytokines, adhesion molecules, and growth factors, and has shown a positive correlation between PMP levels and erythrocyte sedimentation rate (ESR), CRP concentrations, and the BVAS score, particularly in relation to kidney involvement. The PMP level was also positively associated with both platelet and neutrophil counts and the percentage of neutrophils among leukocytes during the active phase of AAV. Upon exposure to cytokines such as TNF, but also C5a, and ANCA, neutrophils undergo an oxidative burst and degranulate, releasing microparticles containing tissue factors, which enhance NET formation. In turn, NETs not only enhance platelet adhesion [177] and aggregation [135], but also contribute to the activation of the coagulation cascade [178].

Both tissue factor and NETs components initiate the coagulation cascade, ultimately generating thrombin [22]. Thrombin then activates platelets through protease-activated receptors (PARs), leading to platelet degranulation and the release of P-selectin. Platelet receptors facilitate interactions with neutrophils, promoting ROS generation and further NET formation (Figure 3) [25,28]. These interactions damage the endothelium and trigger vWF release, which mediates platelet adhesion and aggregation, exacerbating vascular injury. Meanwhile, the activated neutrophils and platelets, through their membranes, microparticles, and NETs, stimulate the alternative complement pathway, increasing C5a levels. This positive feedback loop amplifies thrombin production and platelet/endothelial activation, perpetuating the inflammatory processes [179,180]. Activated platelets with bound fibrinogen can stimulate neutrophils, triggering an oxidative burst and facilitating neutrophil extravasation. Elevated plasma levels of platelet-derived soluble CD40L and CD62P/P-selectin complex correlate with disease activity in GPA [181]. The interaction between soluble CD40L and CD40 facilitates communication between platelets and endothelial cells, triggering the production of proinflammatory cytokines, such as IL-1β, IL-2, and TNF. This signaling also upregulates the expression of endothelial adhesion molecules, including ICAM-1, VCAM-1, and P-selectin, promoting the recruitment of leukocytes to the site of vascular damage. The sCD40L increases endothelial tissue factor expression and contributes to endothelial dysfunction by stimulating neutrophil ROS production. sCD40L can directly activate neutrophils, trigger ROS release, and upregulate Mac-1 [182]. It has been suggested that soluble P-selectin can serve as a biomarker of platelet activation [183]. The interaction of neutrophils and platelets mediated by P-selectin and PSGL enables their aggregation [184]. Patients with active GPA have more platelet-neutrophil aggregates and higher CD11b expression on neutrophils compared to healthy individuals. The percentage of platelet-neutrophil aggregates among neutrophils increases with BVAS [138]. The release of P-selectin from platelets stimulates NET formation; moreover, blocking its interaction with PSGL-1 substantially inhibits platelet-mediated NETosis [185]. In addition, according to a study by Matsumoto et al., platelets activated through TLR9 signaling release CXCL4, which in turn promotes the formation of NETs [28]. Interestingly, the TLR9–CXCL4 axis is upregulated in AAV. Platelets promote the formation of NETs also via activating neutrophils by TLR4 [168]. HMGB1 is a protein derived from platelets, capable of activating TLR4-dependant NETosis [186]. Higher serum levels of HMGB1 have also been linked to AAV with kidney involvement [187].

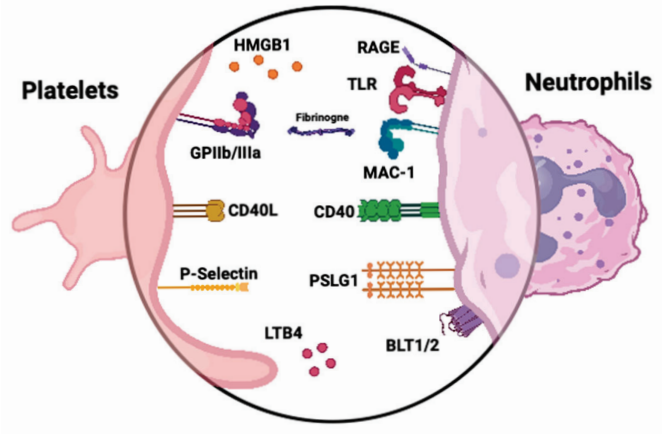

Figure 3. Platelet-neutrophil surface interactions in AAV. Upon activation, platelets express adhesion molecules and release inflammatory mediators that engage corresponding receptors on neutrophils. Notable interactions include P-selectin binding to PSGL-1 and platelet-derived HMGB1 engaging RAGE and TLRs on neutrophils, amplifying the inflammatory response through signaling pathways such as NF-κB and MAPK. Additionally, neutrophil MAC-1 interacts with platelet GPIIb/IIIa, facilitating firm adhesion. Leukotriene B4 (LTB4) and its receptors BLT1/2 contribute to neutrophil recruitment and activation.

Finally, the abovementioned CD177 has been shown not only to recognize β_2 integrins but also to bind to PR3 and PECAM-1, an immunoglobulin family protein found on endothelial cells, platelets, and neutrophils. However, evidence does not confirm its role in binding platelets to neutrophils or enhancing their interactions [62,188]. Further studies are needed to clarify that issue.

7. Biomarker Candidates in AAV Related to Neutrophils and Platelets

A summary of candidate biomarkers discussed in this study was presented in Table 1.

Table 1. An overview of neutrophil- and platelet-related biomarker candidates in AAV.

Biomarker	Source	Detection Method	Mechanism	Clinical Correlation and Relevance
ANCA	Autoantibodies	ELISA, IIF	Directly activate neutrophils via PR3/MPO binding	Established diagnostic and classification marker; titers may correlate with relapse [189].
MPO-DNA complexes	NETs	ELISA	Marker of NETosis, MPO bound to extracellular DNA	Correlate with disease activity and organ involvement [138].
Pentraxin-3 (PTX3)	NETs, activated neutrophils	ELISA	Acute-phase protein associated with NETs	Elevated in active disease; correlates with BVAS [92].
High Mobility Group Box 1 (HMGB1)	Neutrophils, platelets	ELISA	DAMP/alarmin promoting inflammation and NETosis	Increased in active AAV with kidney involvement [187].
Neutrophil-to-lymphocyte ratio (NLR)	Peripheral blood	Hematologic index	Indicator of systemic inflammation and neutrophil burden	Correlates with disease severity and relapse (cut-off $\geq$ 5.9) [55,190].
Delta Neutrophil Index (DNI)	Peripheral blood	Automated hematology analyzer	Reflects immature granulocyte population	Associated with relapse and severity (cut-off $\geq$ 0.65) [56].
$CD177^{+}PR3^{+}$ neutrophils	Neutrophils	Flow cytometry	Subset expressing surface PR3; more responsive to ANCA	Higher percentage in relapse-prone patients [110].
Low-density neutrophils (LDNs)	Neutrophils	Centrifugation in density gradient and flow cytometry	More pronounced proinflammatory properties and tendency to undergo NETosis	Correlates with BVAS [128], although it is unclear if LDNs form a truly distinct subset.
miR-223, miR-142-3p, miR-664a-3p	Neutrophil-derived EVs	RT-qPCR, miRNA sequencing	Proinflammatory miRNAs from neutrophile-derived vesicles	Correlate with BVAS and NETs [97].
P-selectin/sCD40L	Platelets	ELISA	Markers of platelet activation and endothelial crosstalk	Elevated in active GPA and correlate with NETs [180,184].

Table 1. *Cont.*

Biomarker	Source	Detection Method	Mechanism	Clinical Correlation and Relevance
Platelet-derived microparticles (PMPs)	Platelets	Flow cytometry, ELISA	Include TF, cytokines; promote NETs, coagulation	Correlate with ESR, CRP, BVAS, kidney involvement [27].
SEMA4D (soluble)	Neutrophils	ELISA	Cleaved from surface; loss facilitates NETosis	Elevated in active PR3-AAV [63].
Pan-Immune Inflammation Value (PIIV)	Peripheral blood	Hematologic index	Composite marker of neutrophil/monocyte/platelet burden	Predicts mortality risk (cut-off $\geq$ 1011.3) [158].

Although multiple studies have identified potential biomarker candidates in AAV, further research is necessary to confirm their clinical relevance and facilitate implementation, as most have not progressed beyond the discovery phase. Key challenges include standardizing assay methodologies, defining cut-offs, and verifying their added value in larger cohorts. International collaborative efforts, along with the development of integrative biomarker panels that combine multiple candidates, could accelerate the translational process.

8. Conclusions

Growing evidence shows that all essential neutrophil functions can be altered in AAV and are actively involved in disease pathogenesis. Furthermore, platelets play a crucial role in neutrophil activation and NET formation, ultimately leading to vascular damage. Potential predictors of AAV prognosis and biomarkers of disease activity related to neutrophils and platelets include indices calculated from blood counts (e.g., PLR), serum cytokine levels, surface antigen expression, and NET-associated components. However, further research is necessary to confirm their clinical relevance and facilitate implementation, especially as panels of multiple biomarkers. Neutrophil and platelet phenotypes represent a relatively novel and understudied area; therefore, changes in their composition and activation status may not only offer insights into AAV pathogenesis but also hold potential for disease monitoring.

Author Contributions: Conceptualization, A.D. and K.W.; methodology, A.D. and K.W.; software, M.S.; investigation, A.D. and S.B.-S.; writing—original draft preparation, A.D.; writing—review and editing, K.W., M.S., S.B.-S., K.W.-A., M.K. and J.M.; visualization, M.S.; supervision, K.W., M.S., K.W.-A., M.K. and J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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Distribution of Airway Findings in ANCA-Associated Vasculitis: A 20-Year Observational Analysis

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Abstract: Objective: Pulmonary involvement is commonly observed in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), presenting with manifestations such as diffuse alveolar hemorrhage, inflammatory infiltrates, pulmonary nodules, and tracheobronchial disease. We aimed to identify distinct subgroups of tracheobronchial disease patterns in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) using latent class analysis (LCA), and to evaluate their clinical characteristics and outcomes. **Methods:** We conducted a retrospective cohort study using electronic medical records of patients aged >18 years diagnosed with AAV and tracheobronchial disease between 1 January 2002 and 6 September 2022. Patients with follow-up <6 months were excluded. LCA was employed to identify disease subtypes based on 10 pre-defined indicators. Maximum likelihood estimation with 10 repetitions per model ensured robustness in model selection, guided by the Akaike information criterion (AIC). Patient and disease characteristics were summarized and compared across predicted classes. Statistical analyses included Kruskal–Wallis and Fisher's exact tests for continuous and categorical variables, respectively. The primary outcome was time to relapse of the tracheobronchial inflammation after starting immunosuppressive medication, analyzed using the Kaplan–Meier method and log-rank tests. Secondary outcomes included severity of pulmonary disease on pulmonary function tests, endoscopic interventions, tracheostomy, or mortality during follow-up. **Results:** Among 136 identified AAV patients assessed for tracheobronchial involvement, 111 (81.6%) were included after excluding 25 without tracheal or bronchial disease. Predominant findings included subglottic stenosis (91.0%), lower tracheal stenosis (16.2%), and bronchial stenosis (17.1%). LCA identified a three-class model as optimal: tracheal predominant (n = 94), tracheobronchial (n = 12), and bronchial predominant (n = 5). Tracheal predominant patients showed reduced risk of ear, eye, and lower respiratory manifestations, with milder obstruction on pulmonary function testing (PFT). Tracheobronchial-class patients were prone to saddle nose deformity (50%), extensive lower respiratory involvement (91.7%), and renal disease (66.7%). Bronchial predominant patients exhibited severe obstructive disease (median forced expiratory volume in 1 s (FEV1)% predicted: 58, IQR 34–66; FEV1/forced vital capacity (FVC) ratio: 56.9, interquartile range (IQR) 43–63.3) but lacked systemic AAV manifestations. LCA classes did not predict outcomes such as endoscopic intervention, tracheostomy, recurrent tracheobronchial narrowing, or mortality. **Conclusion:** LCA shows promise in subtype

stratification of AAV patients, yet its utility in predicting outcomes and guiding treatment remains limited based on our analysis. Future studies with enhanced phenotypic data and larger cohorts are warranted to improve predictive accuracy.

Keywords: ANCA vasculitis; granulomatosis with polyangiitis; prognostication; tracheobronchial; subglottic stenosis; latent class analysis

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of disorders including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [1,2]. These illnesses are complicated by small-vessel vascular inflammation that is associated with ANCA antibodies specific for proteinase-3 and myeloperoxidase.

GPA and MPA, and to a lesser degree EGPA, are well known to cause upper and lower respiratory manifestations [3] These can include pulmonary nodules, tracheobronchial involvement, diffuse alveolar hemorrhage, and less commonly, interstitial lung disease or bronchiectasis [4]. These manifestations can cause a variety of symptoms including hoarseness, cough, dyspnea, stridor, hemoptysis, and wheezing with upper airway involvement. Hemoptysis, pleuritic chest pain, and shortness of breath are common with lower airway involvement. Specifically, tracheobronchial disease has been reported in 19.3–23% of patients with AAV. In particular, subglottic stenosis, defined as narrowing of the airway between the vocal cords and the lower cricoid cartilage, is the most common manifestation of tracheobronchial AAV [5–10]. These are devastating complications which can lead to upper airway obstruction and potentially life-threatening disease [5–9]. Bronchial involvement occurs in approximately half of those with tracheal disease [7,11]. Despite the frequent upper airway involvement in AAV, there is a dearth of data about its epidemiology, outcomes, and prognosis, with only a few studies providing information about this manifestation.

Identification of patient subsets at particular risk for airway disease is a significant unmet need in AAV. The prevalence of tracheobronchial disease in patients with GPA has been the focus of a recent cohort where subglottic stenosis and endobronchial disease were reported in 10% and 6% of patients with GPA, respectively [7]. Interestingly, the tracheobronchial disease was reported to occur without disease activity in other organs and did not necessarily correlate to disease activity overall. This study suggested that certain epidemiologic characteristics of the patient, such as female sex and younger age of onset, may be associated with the phenotype of tracheobronchial disease and outcomes.

In contrast, a much higher prevalence of upper airway involvement of 70% was reported from a cohort in Iran but the involvement was not well defined [8,12]. In this cohort, upper airway involvement was associated with a higher disease-associated damage and worse outcomes. In a separate cohort from Turkey, ear–nose–throat (ENT) involvement that included bloody nasal discharge, sinusitis, subglottic stenosis, otomastoiditis, or hearing loss was 37%, but the individual prevalence was not defined [13]. ENT involvement was felt to be associated with better outcomes, but no differentiation was made regarding specific manifestations.

Lastly, in a separate cohort from Australia, the prevalence of tracheobronchial disease manifesting as subglottic and main bronchial airway stenosis was described in 17.1% of patients with GPA [14]. Many patients required multiple therapeutic endobronchial interventions to alleviate symptomatic airway obstruction. This report also highlighted the

clinical dilemma that the stenotic lesion may result from ongoing active inflammatory disease or be related to exaggerated post-inflammatory cartilaginous fibrosis and structuring. It is unclear if these are amenable to immunosuppressive treatment with recent reports showing benefit with immunosuppressive therapy, particularly rituximab, as maintenance therapy [15,16].

The existence of specific subgroups within ANCA-positive patients experiencing tracheobronchial involvement that could guide prognostication and therapy remains unknown. Determining these phenotypic groups can prognosticate the outcomes and improve management decisions. LCA is a method used to differentiate potential groups and has been applied in similar instances [5,10]. LCA is considered superior to standard statistical methods for utilizing complex data to evaluate for "latent", or hidden subgroups that can be clinically relevant. Gu et al. utilized LCA to differentiate radiographic manifestations of microscopic polyangiitis, proposing a four-class model ("infiltrative", "fibrotic", "bronchiectatic", and "nonspecific") that correlated with disease manifestations, relapse rates, and cumulative survival [5]. Survival rates at one year were lowest for the infiltrative (51.9%) and fibrotic (62.5%) classes compared with the nonspecific (74.0%) and bronchiectatic (85.7%) classes. However, their analysis did not include tracheobronchial disease as a variable.

LCA has also been utilized in relapsing polychondritis, another disease process that can affect the tracheal and bronchial airways and is akin to ANCA vasculitis [17]. In this evaluation of 73 patients, LCA identified three subgroups which correlated with involved airway distribution, time to diagnosis, and disease severity.

We aimed to identify distinct subgroups of tracheobronchial disease patterns in patients with AAV using LCA, and to evaluate identified subgroups in regards to clinical characteristics and outcomes.

2. Patients and Methods

We conducted a retrospective cohort study using electronic medical records from three institutional Mayo Clinic sites (Minnesota, Florida, and Arizona). Patients aged >18 years diagnosed with AAV, based on the revised 2012 International Chapel Hill Consensus Nomenclature, and diagnosed with tracheobronchial disease between 1 January 2002 and 6 September 2022, were included. The diagnosis was based on a combination of histopathology findings and the type of ANCA involvement. Patients who were difficult to classify based on the Chapel Hill Consensus Nomenclature were labeled as "unspecified ANCA disease".

Evaluation for tracheobronchial disease could have been performed with laryngoscopy by otolaryngology or bronchoscopy with a pulmonologist. Patients with <6 months of follow-up were excluded. Clinical characteristics, pertinent serologic markers, and chest computed tomography (CT) findings were documented. Immunosuppressive regimens were documented along with the start date, end date, and reason for discontinuation. Immunosuppressive regimens included cyclophosphamide, rituximab, and methotrexate and these could be documented as induction agents or maintenance. Induction agents included rituximab or cyclophosphamide and were required to have been used within 6 months of the maintenance agent. Maintenance agents could include rituximab, methotrexate, mycophenolate, or azathioprine. Pulmonary function testing results included forced expiratory volume in the first second (FEV1) percent predicted and forced vital capacity (FVC), when available. Various demographic and clinical variables were collected and summarized as mean, standard deviation, median, interquartile range, and range for continuous variables, while categorical variables are summarized as count and percentage.

LCA was employed to identify disease subtypes using 10 pre-defined indicator variables: tracheal involvement, bronchial involvement, ANCA subtype (negative ANCA, PR3/C-ANCA, MPO/P-ANCA, or "other ANCA"), saddle nose deformity, presence of lung nodules and/or ground-glass opacities, symptoms in the eye, ear, or cardiovascular/gastrointestinal/nervous systems, renal involvement, and cutaneous involvement. Other ANCA was defined as any alternative combination of positive ANCA testing. Maximum likelihood estimation was performed with 10 repetitions per model. Models ranging from one to eight classes were estimated; models with more than eight classes were unstable and not considered further. Model selection was based on the AIC, with lower values indicating better fit. Additional fit and diagnostic criteria were assessed but did not influence the final model selection.

Patient and disease characteristics were summarized and compared across predicted classes using Kruskal–Wallis tests for continuous variables and Fisher's exact tests for categorical variables. Time to recurrence was defined as the duration from the initiation of first-line medication (including methotrexate, azathioprine, rituximab, or cyclophosphamide) to the first confirmed recurrence of airway inflammation observed during laryngoscopy or bronchoscopy. Patients without recurrence were censored at their last follow-up. Survival curves were estimated using the Kaplan–Meier method, and differences in survival among latent classes were assessed using log-rank tests. Analysis was performed in R version 4.2.2. and SAS version 9.4. LCA analysis was performed using the poLCA package [18].

3. Results

A total of 136 patients with AAV who had undergone assessment for tracheobronchial involvement (Figure 1) with laryngoscopy or bronchoscopy were identified. After excluding 25 who did not have identified tracheal or bronchial disease, 111 were included.

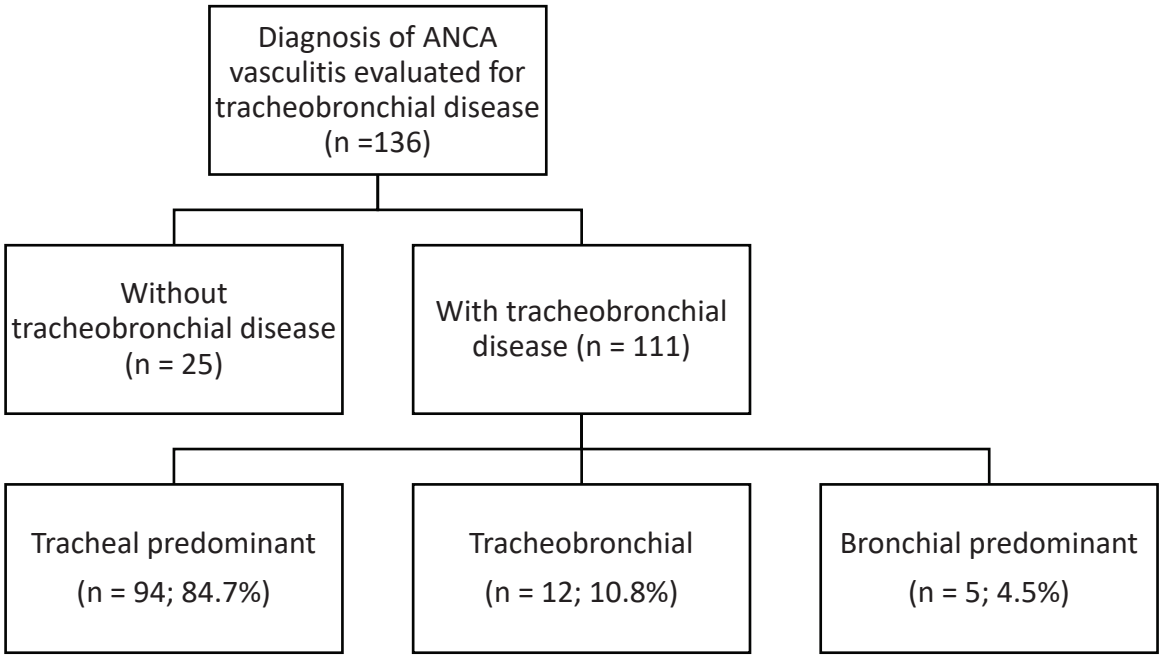

Figure 1. Flow chart of the study population.

3.1. Latent Classes Identified

A three-class model was deemed to be the best fit (Table 1). Table 2 identifies the baseline characteristics in each sub phenotype. The predicted probabilities of observing 10 variables per LCA classification are shown in Table 3. The first class identified, referred to as "tracheal predominant", was a group of 94 patients with mostly subglottic involvement

without bronchial inflammation and with less lower respiratory disease (Table 3). The second group "tracheobronchial" consisted of 12 patients with a higher percentage (50%) exhibiting concomitant tracheal disease with bronchial inflammation and lower respiratory disease. The third group "bronchial predominant" held five patients. These patients lacked subglottic involvement.

Table 1. Model fit statistics for latent-class models from one to eight classes.

# of Classes	DF	AIC	BIC	Likelihood Ratio	Entropy
1	99	1173.376	1206	268.141	-
2	86	1160.303	1228	229.0679	1
3	73	1154.798	1258	197.5627	0.874
4	60	1166.587	1305	183.3519	0.81
5	47	1179.841	1353	170.606	0.779
6	34	1194.037	1403	158.802	0.816
7	21	1207.58	1451	146.3447	0.853
8	8	1221.306	1500	134.0711	0.879

Akaike Information Criterion (AIC) had the lowest value with the 3-class model indicating best fit. The entropy level for the 3-class model was also the highest at 0.874, suggesting that there was strong distinction between classes. This was coupled with a Bayesian information criterion (BIC) lower than that of models with higher number of classes, which suggests that further classification did not improve distinction between models. Additional abbreviations: DF, degrees of freedom.

Table 2. Baseline characteristics by predicted class assignment.

	Predicted Class				
Demographics	**Tracheal Predominant (N = 94)**	**Tracheo-Bronchial (N = 12)**	**Bronchial Predominant (N = 5)**	**Total (N = 111)**	***p*-Value**
Age at vasculitis diagnosis					0.171 [1]
Mean (SD)	42.3 (17.58)	32.8 (17.38)	35.8 (17.68)	41.0 (17.69)	
Median (IQR)	44.6 (26.5, 55.8)	27.0 (18.7, 46.9)	33.7 (25.1, 52.4)	43.6 (25.4, 55.1)	
Sex, n (%)					0.888 [2]
Female	72 (76.6%)	10 (83.3%)	4 (80.0%)	86 (77.5%)	
Male	22 (23.4%)	2 (16.7%)	1 (20.0%)	25 (22.5%)	
Ethnicity, n (%)					1.000 [2]
Caucasian	82 (87.2%)	11 (91.7%)	5 (100.0%)	98 (88.3%)	
Hispanic	7 (7.4%)	1 (8.3%)	0 (0.0%)	8 (7.2%)	
African American	2 (2.1%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	
Native American	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	
Other	2 (2.1%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	
Length of follow-up (weeks)					0.817 [1]
mean (SD)	480.1 (314.22)	504.9 (473.81)	409.4 (341.21)	479.6 (332.34)	
Median (IQR)	437.1 (209.0, 680.0)	299.9 (171.0, 977.8)	310.6 (111.4, 687.0)	420.9 (186.4, 697.1)	
Disease Characteristics					
Tracheal stenosis, n (%)	94 (100.0%)	12 (100.0%)	0 (0.0%)	106 (95.5%)	<0.001 [2]
Bronchial stenosis, n (%)	8 (8.5%)	6 (50.0%)	5 (100.0%)	19 (17.1%)	<0.001 [2]
Diagnosis, n (%)					>0.999 [2]
GPA	88 (93.6%)	12 (100.0%)	5 (100.0%)	105 (94.6%)	
MPA	4 (4.3%)	0 (0.0%)	0 (0.0%)	4 (3.6%)	
Unspecified ANCA-associated vasculitis	2 (2.1%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	
ANCA, n (%)					0.098 [2]
negative ANCA	13 (13.8%)	0 (0.0%)	2 (40.0%)	15 (13.5%)	
PR3/C-ANCA	37 (39.4%)	8 (66.7%)	3 (60.0%)	48 (43.2%)	
MPO/P-ANCA	34 (36.2%)	2 (16.7%)	0 (0.0%)	36 (32.4%)	
Atypical ANCA	10 (10.6%)	2 (16.7%)	0 (0.0%)	12 (10.8%)	
Specific Organ Involvement					

Table 2. *Cont.*

Demographics	Predicted Class				
	Tracheal Predominant (N = 94)	Tracheo-Bronchial (N = 12)	Bronchial Predominant (N = 5)	Total (N = 111)	*p*-Value
Cutaneous, n (%)	9 (9.6%)	5 (41.7%)	0 (0.0%)	14 (12.6%)	0.019 [2]
Ear, n (%)	15 (16.0%)	12 (100.0%)	2 (40.0%)	29 (26.1%)	<0.001 [2]
Eye, n (%)	7 (7.4%)	2 (16.7%)	2 (40.0%)	11 (9.9%)	0.042 [2]
Saddle nose deformity, n (%)	13 (13.8%)	6 (50.0%)	0 (0.0%)	19 (17.1%)	0.011 [2]
* Lower respiratory, n (%)	34 (36.2%)	11 (91.7%)	4 (80.0%)	49 (44.1%)	<0.001 [2]
Renal, n (%)	14 (14.9%)	8 (66.7%)	0 (0.0%)	22 (19.8%)	<0.001 [2]
** Systemic, n (%)	12 (12.8%)	2 (16.7%)	0 (0.0%)	14 (12.6%)	0.828 [2]

[1] Kruskal–Wallis *p*-value; [2] Fisher's exact *p*-value; comparison of baseline characteristics by predicted class assignment. Abbreviations: SD, standard deviation; IQR, interquartile range; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; ANCA, anti-neutrophil cytoplasmic antibody; PR3, proteinase-3; c-ANCA, cytoplasmic ANCA; MPO, myeloperoxidase; p-ANCA, perinuclear ANCA. *—indicates nodules, interstitial lung disease, or alveolar hemorrhage. **—indicates cardiac, nervous system, or renal involvement secondary to vasculitis.

Table 3. Probabilities of disease characteristics by predicted sub-phenotype classes.

Disease Characteristics	Bronchial Predominant	Tracheobronchial	Tracheal Predominant
Atypical ANCA	0.000	0.184	0.104
PR3	0.600	0.636	0.397
MPO	0.000	0.180	0.360
Negative ANCA	0.400	0.000	0.138
Subglottic involvement	0.000	1.000	1.000
Bronchial involvement	1.000	0.476	0.088
Saddle nose	0.000	0.458	0.143
Cutaneous	0.000	0.369	0.102
Ear	0.400	1.000	0.159
Eye	0.400	0.158	0.075
Lower respiratory involvement	0.800	0.911	0.362
Renal	0.000	0.618	0.155
Systemic	0.000	0.188	0.125

Class-conditional outcome probabilities were estimated from LCA modeling. Value in each cell is the probability of observing the disease characteristic for an individual in the predicted sub-phenotype. Cell color is determined by the value of the probability, with high probabilities given a darker shade and low probabilities given a lighter shade. Abbreviations: ANCA, anti-neutrophil cytoplasmic antibody; PR3, proteinase-3; MPO, myeloperoxidase.

3.2. Baseline Characteristics by Predicted Class Assignment

Table 2 summarizes the demographic and clinical characteristics of the cohort. Average age was 41.0 years, 86 (77.5%) patients were female, 98 (88.3%) were White. The majority, 105 (94.6%) patients, held a diagnosis of GPA as opposed to MPA or unspecified ANCA vasculitis. A total of 96 (86.5%) patients were positive for any ANCA type, 106 (95.5%) of patients had tracheal stenosis, and 19 (17.1%) had bronchial stenosis. Age, sex, and ethnicity were similar between predicted classes (Table 4). The median time of follow-up was 8.1 years (IQR 3.6–13.4).

Table 4. Outcomes by predicted class assignment.

	Predicted Class				
	Tracheal Predominant (N = 94)	**Tracheo-Bronchial (N = 12)**	**Bronchial Predominant (N = 5)**	**Total (N = 111)**	***p*-Value**
Pulmonary Function Tests					
Available data, n (%) ****	72 (76.6%)	7 (58.3%)	5 (100.0%)	84 (75.7%)	0.201 [2]
FEV1% predicted					0.024 [1]
mean (SD)	86.8 (23.01)	77.1 (20.80)	55.4 (23.64)	84.0 (23.92)	
Median (IQR)	89.0 (73.0, 103.0)	75.0 (70.0, 95.0)	58.0 (34.0, 66.0)	88.0 (69.0, 102.0)	
FVC % predicted					0.505 [1]
mean (SD)	97.4 (18.87)	96.9 (6.07)	85.2 (24.14)	96.6 (18.52)	
Median (IQR)	100.5 (84.5, 109.5)	98.0 (90.0, 101.0)	92.0 (76.0, 96.0)	99.0 (85.5, 108.5)	
FEV1/FVC ratio					0.031 [1]
Mean (SD)	69.4 (13.48)	64.6 (15.86)	52.4 (17.12)	67.9 (14.37)	
Median (IQR)	73.0 (63.4, 78.3)	67.0 (58.7, 69.4)	56.9 (43.0, 63.3)	71.0 (60.4, 78.0)	
Tracheobronchial Interventions					
Endoscopic dilation, n (%)	54 (57.4%)	9 (75.0%)	3 (60.0%)	66 (59.5%)	0.497 [2]
Number of dilations, n (%)					0.765 [2]
1	21 (38.9%)	3 (33.3%)	2 (66.7%)	26 (39.4%)	
2	9 (16.7%)	2 (22.2%)	0 (0.0%)	11 (16.7%)	
3	9 (16.7%)	3 (33.3%)	0 (0.0%)	12 (18.2%)	
4	15 (27.8%)	1 (11.1%)	1 (33.3%)	17 (25.8%)	
Number of dilations					0.863 [1]
Mean (SD)	2.3 (1.26)	2.2 (1.09)	2.0 (1.73)	2.3 (1.24)	
Median (IQR)	2.0 (1.0, 4.0)	2.0 (1.0, 3.0)	1.0 (1.0, 4.0)	2.0 (1.0, 4.0)	
Tracheostomy, n (%)	6 (6.4%)	1 (8.3%)	0 (0.0%)	7 (6.3%)	0.699 [2]
Mortality					
Death during follow-up period, n (%)	2 (2.2%)	0 (0.0%)	0 (0.0%)	2 (1.9%)	1.000 [2]
Missing	2	1	0	3	

[1] Kruskal–Wallis *p*-value; [2] Fisher's exact *p*-value; **** Among patients in the tracheal predominant group who had PFTs, 3 were missing FEV1% predicted, 4 were missing FVC% predicted, and 5 were missing FEV1/FVC ratio. Abbreviations: FEV1, forced expiration volume over one minute; SD, standard deviation; IQR, interquartile range; FVC, forced vital capacity.

3.3. Immunosuppressive Management Within Cohort

Of the 111 patients, 44 (39.6%) utilized rituximab induction and maintenance in combination with another agent such as mycophenolate or methotrexate. Twenty-six (23.4%) patients utilized rituximab monotherapy as both induction and maintenance. Fifteen (13.5%) patients were treated with methotrexate without induction. Eight (7.2%) patients received induction therapy without maintenance. Of these 8 patients, 6 utilized rituximab, 1 utilized cyclophosphamide, and 1 was on a combination of rituximab and cyclophosphamide. Six (5.4%) patients were managed with azathioprine or mycophenolate without induction. Three (2.7%) patients utilized cyclophosphamide induction within 6 months of starting a maintenance agent (azathioprine, mycophenolate, or a combination). Four (3.6%) patients were not initiated on systemic immunosuppression. Three (2.7%)

patients were maintained on an immunosuppressive agent not previously listed. Two (1.8%) patients did not have medication history available.

3.4. Probabilities of Disease Characteristics by Predicted Sub-Phenotype Classes

Class 1, tracheal predominant, was noted to have the highest prevalence of anti-MPO positivity (36.2%), though this was not statistically significant. Ear and eye involvement were less frequent than in other classes (16.0% and 7.4% prevalence, respectively). Lower respiratory involvement was less common (36.2%).

Class 2, tracheobronchial, had the highest prevalence of saddle nose deformity (50%) and lower respiratory (91.7%), renal (66.7%), cutaneous (41.7%), and other systemic manifestations (16.7%) out of all three classes. This severity with widespread disease was not linked to specific ANCA status.

Class 3, bronchial predominant, had frequent lower respiratory involvement (80%) and lacked saddle nose deformity, cutaneous disease, renal involvement, or other systemic ANCA manifestations.

3.5. Outcomes by Predicted Class

Time to recurrence of tracheobronchial inflammation after initiating immunosuppressive therapy, defined as the time from first medication start date to first recurrence (or loss of follow-up), was compared between classes (Figure 2) without significant difference. Secondary outcomes are shown in Table 4. Endoscopic intervention was common (59.5%) though rates did not differ significantly between classes. The infrequent occurrences of tracheostomy and death were not different between classes (6.3% and 1.8%, respectively).

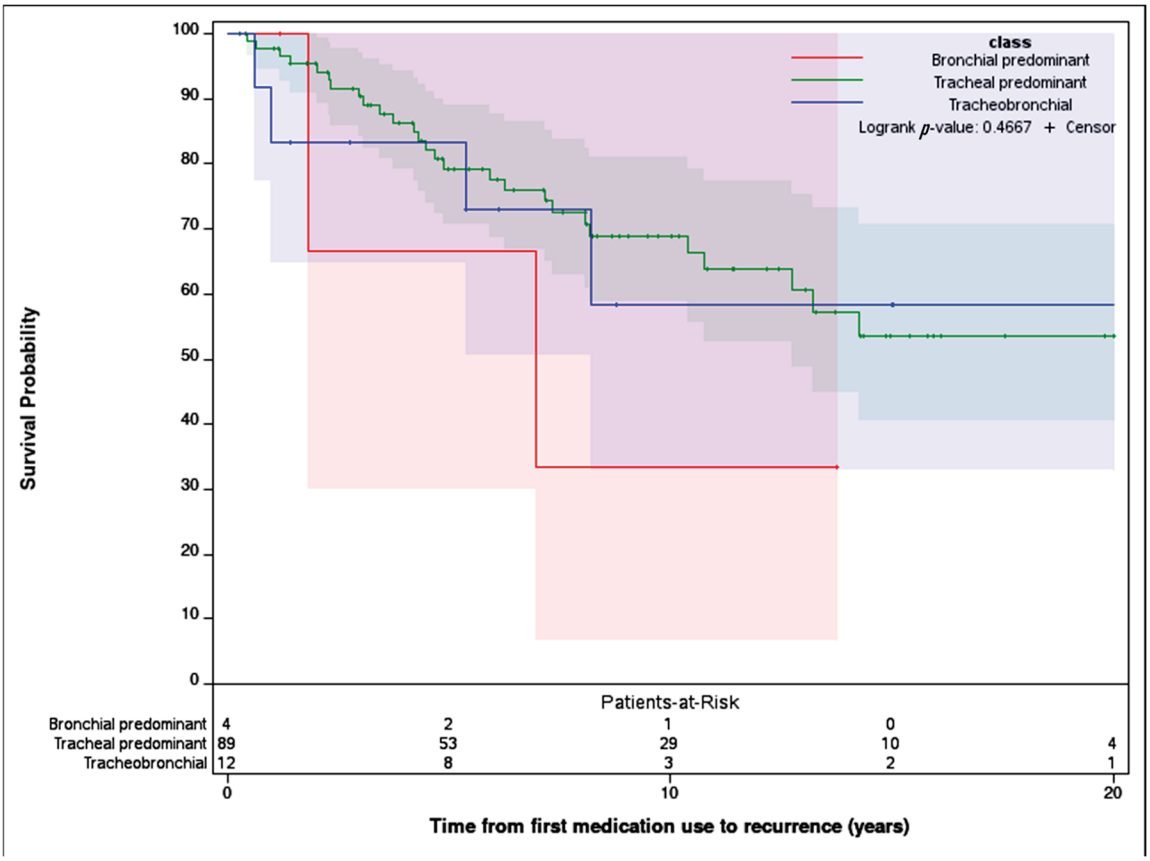

Figure 2. Relapse-free survival of tracheobronchial disease by predicted class. Shading represents the 95% confidence interval.

In the 84 (75.7%) patients who had pulmonary function testing available it was noted that median FEV1 percent predicted decreased with class allocation (89.0, 75.0, and 58.0, respectively, with a p value of 0.24). The FEV1/FVC ratio was also statistically significant across classes 1, 2, and 3 (73.0, 67.0, and 56.9, respectively, with a p value of 0.31).

4. Discussion

Tracheobronchial disease is a recognized consequence of ANCA-associated vasculitis, particularly GPA, and in this report, we have described a cohort of patients with AAV-associated tracheobronchial disease. Our findings align with previous reports, indicating that upper tracheal (subglottic) inflammation and stenosis are common [3,5–12,19,20].

As highlighted previously, there is a paucity of data regarding the epidemiology and outcomes of tracheobronchial disease in AAV with a limited number of studies available, and those that are available provide conflicting information [7,11–14]. The prevalence of tracheobronchial disease is felt to be around 20% but has been reported to be as high has 70% [8,12]. Previously, it has been reported that in patients with GPA, the subglottic stenosis variant of tracheobronchial disease may be more prevalent in younger and female patients with GPA and those with severe, destructive, sinonasal disease but a lack of renal disease [7]. Endobronchial disease was more prevalent in younger patients with positive PR3-ANCA, and those who has a history of ENT involvement. It remains unclear if the upper airway involvement is associated with a severe disease [7,8,10].

This analysis further builds on existing data and highlights the presence of sub-phenotypes within these cohorts. Patients with tracheal predominant disease were noted to have the highest prevalence of anti-MPO positivity and less common involvement of ear, eye, or lower respiratory tract. Tracheobronchial disease was associated with saddle nose deformity and lower respiratory, renal, cutaneous, and other systemic manifestations but not with specific ANCA status. The bronchial predominant subset had frequent lower respiratory involvement with obstructive lung disease, and lacked cutaneous, renal, or other systemic ANCA manifestations.

Most notably, systemic disease was seen in patients with more diffuse airway involvement, i.e., tracheobronchial disease, and less with isolated bronchial disease. These findings suggest that severe systemic presentation may herald a more severe upper airway involvement and vice-versa. The more frequent occurrence of renal disease in patients presenting with tracheobronchial disease suggests that this subset of patients should also be monitored closely for renal disease. Additionally, the degree of obstruction observed in pulmonary function tests was linked to both the tracheobronchial and bronchial predominant subgroups. Though the bronchial predominant group was small, there was an indication that those with isolated bronchial disease may have had less systemic manifestations.

It is important to note that this study observed less frequent involvement of the lower airways compared to earlier literature, with lower tracheal and bronchial disease each affecting less than 20% of the population. This discrepancy may be attributed to our study including patients who had undergone either laryngoscopy or bronchoscopy. Without bronchoscopy or chest computed tomography read by a skilled radiologist, the prevalence of lower airway involvement might have been underestimated.

Despite this limitation, LCA revealed three distinct subgroups with different phenotypic characteristics a useful construct that can be used during evaluation of these patients as well as for future research.

These innovative findings provide significant insight into the heterogeneity of the airway involvement in AAV and highlight the presence of three different phenotypic subgroups with prognostic and therapeutic implications. Clinicians can use these results to stratify the patients during evaluation to aggressively assess and closely follow for

systemic disease and saddle nose deformities in patients with tracheobronchial disease, and potentially intervene early to improve the outcome. Furthermore, the findings provide a direction for additional studies in the future.

However, it is important to note that the phenotypic subgroups identified in this study did not show a correlation with outcomes outside of the degree of obstructive disease on pulmonary function testing, which seemed to be associated with bronchial airway involvement. Other outcomes, such as relapse rates of tracheobronchial disease following the initiation of immunosuppressive therapy or the necessity for endoscopic interventions like dilation and injection, did not correlate strongly. This lack of correlation is likely due to the small sample size, particularly in the bronchial predominant subgroup. Alternatively, this may also be due to a less aggressive use or the limited effectiveness of standard immunosuppressive therapies for tracheobronchial disease. The benefits of systemic immunosuppressive therapy for airway involvement are questionable based on current literature but there are instances of improved outcome with aggressive immunosuppressive therapy in addition to endoscopic or surgical interventions. Two recent studies show that immunosuppressive treatment, and in particular rituximab, may reduce the need for endoscopic interventions, supporting their use in AAV [15,16].

5. Conclusions

This LCA of patients with tracheobronchial disease and ANCA vasculitis identified distinct phenotypic subgroups, each characterized by unique disease features and association with distinct non-airway clinical manifestations. Despite these differences, our analysis did not reveal a significant association between these subgroups and clinical outcomes such as disease relapse or the need for endoscopic interventions. These findings suggest that while phenotypic heterogeneity exists, it may not directly translate into differences in clinical outcomes with the current treatment approaches. Future research should focus on further exploring the underlying mechanisms driving these subgroups and investigating whether more tailored or novel therapeutic strategies might improve outcomes for specific phenotypes. This could provide valuable insights for optimizing patient management and advancing personalized treatment in ANCA-associated tracheobronchial disease.

Author Contributions: Conceptualization, M.M.S. and V.M.; Methodology, M.M.S., A.A., and V.M.; Formal analysis, C.M.-H.; Data curation, M.M.S. and M.D.M.; Writing—original draft, M.M.S., R.B., B.W., C.M.-H., A.A. and V.M.; Writing—review & editing, M.M.S., H.B., A.I., R.B., B.W., F.B., A.A. and V.M.; Supervision, H.B., B.W. and F.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved under an exempt status by the Institutional Review Board of Mayo Clinic (protocol code 22-009660 on 10/13/2022).

Informed Consent Statement: Patient consent was waived due to the minimal risk status of the study and was performed as a retrospective chart review.

Data Availability Statement: Data can be provided by the authors upon request, with removal of identifiable information and anonymization of dates.

Conflicts of Interest: The authors declare no conflicts of interest.

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Article

Comparative Analysis of Classification Criteria in IgG4-Related Disease and Evaluating Diagnostic Accuracy from a Retrospective Cohort in Clinical Practice

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Abstract: Introduction: We conducted a comprehensive comparative analysis of the Okazaki, Umehara, and American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for diagnosing immunoglobulin G4-related disease (IgG4-RD). Materials and Methods: A retrospective study was conducted in a single tertiary hospital, using expert clinical judgment as the gold standard. We compared the diagnostic accuracy of the Okazaki, Umehara, and ACR/EULAR criteria in a cohort of 41 patients with suspected IgG4-RD. We assessed sensitivity, specificity, and positive and negative predictive values for each criterion, and conducted a separate analysis based on four IgG4-RD subtypes. Results: A total of 30 patients were confirmed to have IgG4-RD and 11 were identified as mimickers. The Umehara criteria demonstrated the highest sensitivity (83.33%), followed by the ACR/EULAR 2019 (66.67%) and Okazaki (60.0%) criteria. All three criteria exhibited 100% specificity, with overall diagnostic accuracy ranging from 70% to 88%. The areas under the curve (AUC) were 0.917 (Umehara), 0.800 (Okazaki), and 0.833 (ACR/EULAR 2019), indicating significant diagnostic effectiveness ($p < 0.000$). Subtype analysis revealed that the Umehara and ACR/EULAR 2019 criteria were more effective in diagnosing pancreato-hepato-biliary involvement (subtype 1), while the Okazaki and ACR/EULAR 2019 criteria were more effective in diagnosing retroperitoneal fibrosis and/or aortitis (subtype 2). Conclusions: Our study provides valuable insights into the diagnostic performance of the Okazaki, Umehara, and ACR/EULAR criteria for a cohort of patients with suspected IgG4-RD. The Umehara criterion demonstrated the highest sensitivity, suggesting its potential utility for screening purposes, while all three criteria showed consistent specificity.

Keywords: IgG4; diagnostic criteria; ACR/EULAR

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated chronic disorder characterized by intense inflammation, fibrosis, infiltration, and elevated IgG4 levels in peripheral blood affecting multiple organs [1–3]. This fibroinflammatory condition is characterized by an initial inflammatory phase driven by antigen-experienced lymphocytes secreting pro-fibrotic molecules, followed by a fibrotic phase marked by dense stromal reactions and leading to tissue distortion and organ damage.

While IgG4 antibodies normally resolve inflammation, in IgG4-RD, they may synergize with cytotoxic T cells to induce tissue injury. The antigens triggering the disease and the reasons for organ specificity remain unclear but suggest a breach of immunological tolerance as the potential initiating event [4]. IgG4-RD poses diagnostic challenges as it is often confused with neoplasms, infections, or other immunological conditions due to shared clinical, serological, and pathological features [5].

Although the prevalence of IgG4-RD in Europe has not specifically been described to date, it is estimated to be around 4.6 per 100,000 individuals, with a higher incidence among persons aged over 60 [6]. A multicenter observational study by Fernandez et al. [7] identified 55 Spanish patients with IgG4-RD, making this the largest series reported in Spain and contributing to an understanding of the disease. Singly [1] published estimates suggesting that the average time from symptom onset to disease diagnosis is two years.

Despite growing interest and scientific advances, diagnosing IgG4-RD remains a significant challenge for clinicians due to its complexity and heterogeneity. Moreover, IgG4-RD requires an integrated approach, involving comprehensive evaluation and proper coordination among different medical specialties.

The organs most frequently affected are the pancreas, retroperitoneum, salivary glands, and lymph nodes [7]. The average number of affected organs is 2.9 and isolated involvement of a single organ is very uncommon [4].

The IgG4-RD predilection for certain organs has been known since early on, although comprehensive assessments of consistent patterns in clinical manifestations were lacking until 2019, when, applying latent class analysis to an international cohort, the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) developed classification criteria for four homogeneous phenotypes of IgG4-RD, as follows: pancreato-hepato-biliary disease (31%), retroperitoneal fibrosis and/or aortitis (24%), head/neck-limited disease (22%), and Mikulicz syndrome with systemic involvement (22%) [1]. Notably, patients within each phenotype shared distinctive clinical, epidemiological, and serological features. Patients with head/neck limited disease were more likely to be female, Asian, and younger, and more frequently required histological confirmation for diagnosis. Patients with pancreato-hepatobiliary disease were more often referred to the emergency department due to symptom flare-ups. In the retroperitoneal fibrosis and Mikulicz syndrome patients, inflammatory markers were significantly higher and lower, respectively. Finally, patients with Mikulicz syndrome and systemic involvement had the highest median serum IgG4 concentrations [1]. This classification provides a framework for recognizing IgG4-RD phenotypes, enabling the description of biological differences, the assessment of biomarker performance in homogeneous cohorts, and the search for personalized follow-up and therapeutic strategies.

While no genetic risk factors have been definitively linked to gender differences in IgG4-RD, environmental factors like smoking and occupational exposures are more frequently observed in male patients, potentially contributing to the higher prevalence of the disease in men [8–11].

Definitive diagnosis requires rigorous clinical–pathological correlation, as clinical, laboratory, and imaging findings are often non-specific [12]. Serum IgG4 elevation (55–97% of cases) correlates with organ involvement but is of poor diagnostic utility [4,12]. The absence of disease-specific autoantibodies (e.g., ANCA, SSA/Ro, SSB/La, double-stranded DNA, RNP, and Sm), helps differentiate IgG4-RD from other autoimmune conditions [3]. Histological examination remains the diagnostic mainstay but can be challenging for

certain organs (such as the retroperitoneum and ocular cavity). Whole-body computed tomography (CT) or fludeoxyglucose F18 (18FDG)-positron emission tomography (PET) scans are recommended at diagnosis for staging and to identify accessible biopsy sites [13].

For the above reasons, classification criteria have been established based on joint evaluation of clinical, serological, and histological findings. The Okazaki criteria [14] (Appendix A), introduced in 2009, were the first to establish a standardized approach to IgG4-RD diagnosis. These criteria rely on a combination of clinical features, serological findings, and histological evidence. While their simplicity and high specificity make them suitable for initial screening, their low sensitivity requires further evaluation. The Umehara criteria [15] (Appendix B), proposed in 2012, expanded on the Okazaki criteria by incorporating additional clinical and serological parameters. They categorize cases into possible, probable, or definitive IgG4-RD. While this classification system has enhanced sensitivity compared to the Okazaki criteria, its complexity and lower specificity warrant cautious interpretation. Globally, despite clear clinical suspicion indicating the presence of the condition, neither of those diagnostic criteria are optimal, making accurate diagnosis and timely intervention not only challenging, but also underscores their inadequacy in terms of capturing the full spectrum of conditions and manifestations.

To adequately enhance the ability to identify and manage patients with IgG4-RD, the development of new criteria became imperative. In 2019, ACR/EULAR experts introduced novel classification criteria for IgG4-RD [16] (Appendix C), based on a three-stage approach that integrates clinical findings, serological data, and radiological findings. While the sensitivity (82–85%) of the ACR/EULAR 2019 criteria is the highest of the three sets of criteria, its complexity requires careful consideration. One notable advantage of the ACR/EULAR 2019 criteria is the ability to classify patients as having IgG4-RD even when obtaining a biopsy is challenging and/or serum IgG4 levels fall within the normal range despite clinical suspicion of IgG4-RD. Additionally, the ACR/EULAR 2019 criteria streamline the identification of homogeneous IgG4-RD cases in clinical trials, improving the availability and implementation of criteria in research settings.

While existing classification systems have individually advanced IgG4-RD diagnosis, a comprehensive comparative analysis of their clinical performance remains unexplored. As a rare, relatively novel, and often underdiagnosed condition due to low clinical suspicion and complex and unfamiliar classification criteria, IgG4-RD necessitates a thorough evaluation of existing diagnostic frameworks.

This study aims to address this critical knowledge gap by conducting a comparative analysis of the diagnostic performance (sensitivity, specificity, and accuracy) of the Okazaki, Umehara, and ACR/EULAR 2019 criteria for a cohort of confirmed IgG4-RD patients. The rationale for this research is multifaceted: (1) to optimize the diagnostic approach and facilitate timely and accurate diagnoses, crucial for appropriate management and prevention of organ damage; (2) to provide evidence-based guidance to clinicians on the most appropriate criteria for various clinical contexts, thereby potentially improving diagnostic accuracy and patient outcomes; and (3) to advance IgG4-RD research by identifying the most robust classification criteria, thereby enhancing the homogeneity of patient cohorts in clinical trials and observational studies, leading to more reliable and generalizable research findings. By offering a clearer understanding of the strengths and limitations of each set of criteria, we seek to contribute to more accurate diagnoses, more effective treatments, and better outcomes for patients with this challenging condition. Our comparative analysis is anticipated to offer valuable insights into the relative strengths and limitations of each set of criteria and provide a nuanced understanding of their applicability across diverse clinical scenarios. Ultimately, our study strives to fill a crucial knowledge gap, inform clinical practice, guide future research, and accelerate scientific progress regarding IgG4-RD, with the overarching goal of improving care for patients affected by this complex disorder.

2. Materials and Methods

2.1. Study Design and Setting

A retrospective cross-sectional study was conducted at the rheumatology outpatient clinic of a tertiary hospital designated as a Spanish national reference center for systemic autoimmune diseases (XUEC CSUR, Hospital Sant Pau i de la Santa Creu, Barcelona, Spain). The study was approved by the Hospital Sant Pau i de la Santa Creu ethics committee following the good clinical practices protocol (IIBSP-EIG-2022-92) and was performed in accordance with the tenets of the 1964 Helsinki Declaration and its subsequent amendments.

2.2. Patients

All patients aged 18 years and older with suspected IgG4-RD based on clinical grounds and elevated IgG4 levels (>135 mg/dL) were included from January 2000 to January 2024. The patients were evaluated by experienced rheumatologists and categorized into two groups based on expert clinical judgment: those diagnosed as having and not having IgG4-RD (IgG4-RD group and non-IgG4-RD group, respectively).

2.3. Procedures

Obtained retrospectively from the hospital's electronic healthcare records were patient demographic data (sex, age, race) and disease-related variables, including clinical and laboratory parameters, histological findings, previous neoplasia, cause of death (any cause), and prescribed treatments.

The following specific clinical manifestations were also recorded: glandular involvement, pulmonary involvement, retroperitoneal fibrosis, autoimmune pancreatitis, renal involvement, aortitis, inflammatory aortic aneurysm, lower back pain, constitutional symptoms, fever, hypophysitis, pachymeningitis, orbital pseudotumor, and ocular involvement. Visceral involvement was assessed through imaging techniques including CT, PET, and/or nuclear magnetic resonance imaging (nMRI).

Recorded laboratory data included hemogram; total IgG and IgG4, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and tests results for the presence or absence of anti-extractable nuclear antigens (ENA), rheumatoid factor, antinuclear antibodies (ANA), and various disease-specific autoantibodies (including anti-Ro/SSA, anti-La/SSB, anti-neutrophil cytoplasmic, anti-double stranded DNA, anti-RNP, anti-Sm, and plasmablasts). IgG4 quantification was performed from peripheral blood samples by turbidimetry using the Optilite kit. Reference values at our hospital were 3.9–86 mg/dL, though the upper limit of normal serum IgG4 concentration was set to 135 mg/dL, a threshold commonly used in Japanese diagnostic criteria for IgG4-RD [13,14]. Plasmablasts were identified through flow cytometry based on the expression of surface proteins (CD19 + IgM − IgD − CD27 + $CD38^{high}$).

The three classification sets of criteria (Okazaki: present or absent; Umehara: possible, probable, definitive; ACR/EULAR 2019: present or absent and quantitative according to a weighted numeric score) were evaluated across the entire patient cohort and compared for the four IgG4-RD subtypes (pancreatic-hepato-biliary disease; retroperitoneal fibrosis and/or aortitis; head/neck-limited disease, and Mikulicz syndrome with systemic involvement) [1].

Finally, histopathological confirmation, where available, was obtained for patients in both the IgG4-RD and non-IgG4-RD groups. However, in some cases, particularly those with deep-seated fibrotic disease such as retroperitoneal fibrosis, histological confirmation was not possible due to the invasive nature of biopsy procedures and the associated clinical risks, including bleeding and vascular complications. The presence of the following histopathological features was also recorded: lymphoplasmacytic infiltration, obliterative phlebitis, and/or glandular fibrosis.

2.4. Statistical Analysis

Patient demographic, clinical, and biochemical data were summarized using percentages, means, and standard deviations (SD), or medians and interquartile ranges (IQR), depending on the characteristics of the variable. Differences in values of continuous variables between IgG4-RD and non-IgG4-RD groups were analyzed by Student's *t*-test or the Mann–Whitney U test. Categorical variables were compared between groups using chi-square or Fisher's exact tests. IgG4 subtypes in terms of either demographic or laboratory values were compared by analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (PPV) were calculated for the Okazaki, Umehara, and ACR/EULAR 2019 criteria (note that, for the sensitivity analysis of the Umehara criteria, the possible, probable, and definitive categories were either analyzed separately or collapsed into a single disease-positive category). Values were summarized using contingency tables for true positive (T+), false positive (F+), true negative (T−), and false negative (F−) values to obtain full information on sensitivity, specificity, and diagnostic odds ratios. A receiver operator characteristics (ROC) curve was plotted, and the area under the ROC curve (AUC) was calculated to evaluate the IgG4-RD diagnostic performance of each set of criteria.

All analyses were conducted for a significance level of 0.05. Analyses were performed using R v. 4.3.1 (R Core Team (2022). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. General IgG4-RD Characteristics

Of the 41 patients with suspected IgG4-RD included in the study, 30 cases were confirmed as IgG4-RD based on expert clinical judgment and the remaining 11 cases were classified as non-IgG4-RD. The mean (SD) age at the time of IgG4-RD diagnosis was 61.79 (16.27).

Baseline characteristics for the IgG4-RD group and non-IgG4-RD group are described in Table 1. The definitive diagnoses of the 11 non-IgG4-RD patients were retroperitoneal fibrosis (n = 5), inflammatory aortic aneurysm (n = 3), autoimmune pancreatitis (n = 2), and hypophysitis (n = 1).

Table 1. Patient clinical characteristics (n = 41).

	IgG4-RD (n = 30)	**Non-IgG4-RD (n = 11)**	***p* Value**
Sex (male)	25 (83.3%)	4 (36.3%)	0.007
Race			
- Caucasian	28 (96.6%)	10 (90.9%)	0.47
- Asian	1 (3.4%)	1 (9.1%)	
Weight (kg), median (IQR)	83 (70.5–100.8)	84 (73.7–89.5)	0.665
Arterial hypertension	14 (46.7%)	4 (36.4%)	0.726
Dyslipidemia	14 (46.7%)	4 (36.4%)	0.726
Ischemic heart disease	6 (20%)	2 (18.2%)	1
Non-hematological neoplasia	1 (3.3%)	0 (0%)	1

Table 1. *Cont.*

	IgG4-RD (*n* = 30)	Non-IgG4-RD (*n* = 11)	*p* Value
Glandular involvement	4 (13.3%)		
- 1 set	2 (6.7%)	0 (0%)	1
- >2 sets	2 (6.7%)		
Pulmonary involvement			
- Peri-bronchovascular and septal thickening	5 (16.7%)	1 (9.1%)	
- Paravertebral-like thorax soft tissue	0 (0%)	0 (0%)	1
- Wall thickening of thoracic aorta	0 (0%)	0 (0%)	
Pancreatic involvement	10 (33.3%)	3 (27.27%)	
- Lobulation loss	1 (3.3%)	0 (0%)	
- Low density capsule edging	2 (6.7%)	2 (18.2%)	0.557
- Pancreatic and biliary injury	7 (23.3%)	1 (9.1%)	
Renal involvement	14 (46.7%)	1 (9.1%)	
- Hypocomplementemia	3 (10%)	0 (0%)	
- Thickening of renal pelvis	3 (10%)	1 (9.1%)	0.267
- Bilateral low-density renal cortex	8 (%)	0 (0%)	
Retroperitoneal involvement	17 (56.7%)	4 (36.4%)	
- Wall thickening of abdominal aorta	7 (23.3%)	2 (18.2%)	
- Iliac or infrarenal aortic soft peripheral tissue	10 (33.3%)	2 (18.2%)	0.593
Fever	3 (10%)	0 (0%)	0.551
Constitutional syndrome	3 (10%)	0 (0%)	0.551
Lower back pain	6 (20%)	0 (0%)	0.167
Hydronephrosis	3 (10%)	0 (0%)	0.551
Aneurysm	10 (33.3%)	3 (27.3%)	1
Hypophysitis	1 (3.3%)	1 (9.1%)	0.47
Pachymeningitis	1 (3.3%)	0 (0%)	0.268

Table 1. *Cont.*

	IgG4-RD (n = 30)	Non-IgG4-RD (n = 11)	p Value
Orbital pseudotumor	0 (0%)	0 (0%)	1
Uveal involvement	0 (0%)	0 (0%)	1
Sclera involvement	1 (9.1%)	0 (0%)	0.268
IgG, median (IQR)	1196 (979.2–1536.2)	1137 (1006.5–1250)	0.233
IgG4, median (IQR)	90.5 (40.8–154.5)	47.0 (33.5–86)	0.05
Plasmablasts, median (IQR)	993.0 (255.5–1628.2)	24 (0–101)	0.004

Comparative analysis of the IgG4-RD (n = 30) and non-IgG4-RD (n = 11) groups revealed several significant differences. In the IgG4-RD group, males were more prevalent (83.3% vs. 36.3%; p = 0.007), median serum IgG4 levels were higher (90.5 vs. 47.0; p = 0.05), and the median plasmablast count in peripheral blood was significantly more elevated (993.0 vs. 24; p = 0.004). These findings highlight the utility of elevated IgG4 as a biomarker for diagnosing IgG4-RD and underscore the importance of integrating both clinical characteristics with serological biomarkers for accurate diagnosis.

All 30 patients in the IgG4-RD group had negative results for rheumatoid factor, ANA, and ENA.

Histological data are summarized in Table 2. Samples were obtained from nine patients in the IgG4-RD group, compared to just one patient in the non-IgG4-RD group (34.6% vs. 9.09%; p = 1.000). A notable limitation of this study is the lack of histological confirmation for most of the non-IgG4-RD patients. This was primarily due to the clinical presentation of these subjects, who exhibited retroperitoneal fibrosis associated with aortic aneurysm and mildly elevated serum IgG4 levels. The potential risks of retroperitoneal biopsies in such cases, including bleeding and vascular complications, were deemed to outweigh the diagnostic benefits.

Table 2. Histological characteristics.

	IgG4-RD (n = 30)	Non-IgG4-RD (n = 11)	p-Value
Histology	9 (34.6%)	1 (9.09%)	1.000
Histological location			
- Liver	1 (11.1%)	1 (100.0%)	
- Adenopathy	1 (11.1%)		
- Salivary gland	2 (22.2%)		
- Abdominal mass	2 (22.2%)		
- Pleura	1 (11.1%)		
- Renal	2 (22.2%)		
Plasma cells	8 (88.9%)	1 (100.0%)	0.200
Phlebitis	2 (22.2%)	0 (0.0%)	1.000
Fibrosis	2 (22.2%)	0 (0.0%)	1.000

While no patients in the non-IgG4-RD group received intravenous methylprednisolone (IV-MTPD) boluses or steroid therapy, all patients in the IgG4-RD group underwent treatment with these interventions. This stark contrast in treatment approaches highlights a

key difference in the management of the two patient cohorts. Two patients (6.7%) in the IgG4-RD group who received IV-MTPD boluses followed by oral prednisone (median dose (IQR) 55 (30–60) mg) as initial treatment showed a statistically significant difference ($p < 0.001$) compared to the non-IgG4-RD group. Additionally, four patients (13.3%) required treatment with rituximab (500 mg), administered in two infusions separated by 15 days and a maintenance dose over two weeks every six months.

3.2. Okazaki, Umehara, and ACR/EULAR 2019 Criteria

We evaluated these criteria in a cohort of 41 patients, including 30 with confirmed IgG4-RD and 11 without IgG4-RD.

Of the 30 patients diagnosed with IgG4-RD, 18 (60%) met the Okazaki criteria; 25 (83.33%) met the Umehara criteria, including 6 (20%) definitive, 2 (6.7%) probable, and 17 (56.7%) possible cases; and 20 (66.7%) met the ACR/EULAR 2019 criteria, with a median (IQR) value of 20.0 (20–44).

Table 3 summarizes the diagnostic performance of the Okazaki, Umehara, and ACR/EULAR 2019 criteria.

Table 3. Okazaki, Umehara, and ACR/EULAR 2019 diagnostic performance.

METRIC	OKAZAKI	UMEHARA	ACR/EULAR 2019
Confirmed IgG4-RD patients ($n = 30$)	18 (60%)	25 (83.33%)	20 (66.67%)
Sensitivity [95% CI]	60% [40.6–77.34%]	83.33% [65.28–94.36%]	66.67% [47.19–82.71%]
Specificity [95% CI]	100% [71.51–100%]	100% [71.51–100%]	100% [71.51–100%]
Accuracy [95% CI]	70.73% [54.46–83.87%]	87.8% [73.8–95.92%]	75.61% [59.7–87.64%]
Positive predictive value [95% CI]	100% [81.47–100%]	100% [86.28–100%]	100% [83.16–100%]
Negative predictive value [95% CI]	47.83% [26.82–69.41%]	68.75% [41.34–88.98%]	52.38% [29.78–74.29%]
Negative likelihood ratio [95% CI]	40% [25.81–62%]	16.67% [7.49–37.1%]	33.33% [20.1–55.29%]

Note: CI = confidence interval.

For the 30 IgG4-RD patients, sensitivity was highest for the Umehara criteria (83.33%; 95% CI: 65.28–94.36%), which correctly identified 25 patients, followed by the ACR/EULAR 2019 criteria (66.67%; 95% CI: 47.19–82.71%), identifying 20 patients, and the Okazaki criteria (60%; 95% CI: 40.6–77.34%), identifying 18 patients. Further stratification of patients according to the Umehara criteria into possible, probable, or definitive IgG4-RD, the sensitivity values were 56.67% (95% CI: 37.43–74.54%), 6.67% (95% CI: 0.82–22.07%), and 20% (95% CI: 7.71–38.57%), respectively.

Specificity for all three criteria was 100% (95% CI: 71.51–100%), with all 11 non-IgG4-RD patients correctly identified, and resulting in a PPV of 100% for each set of criteria.

Accuracy was highest for the Umehara criteria, which correctly classified 87.8% (95% CI: 73.8–95.92%) of the patients, followed by the ACR/EULAR 2019 criteria (75.61%; 95% CI: 59.7–87.64%) and the Okazaki criteria (70.73%; 95% CI: 54.46–83.87%).

The NPV was highest for the Umehara criteria at 68.75% (95% CI: 41.34–88.98%), followed by the ACR/EULAR 2019 criteria, at 52.38% (95% CI: 29.78–74.29%), and the Okazaki criteria, at 47.83% (95% CI: 26.82–69.41%).

The AUC values (Figure 1) were 0.917 for the Umehara criteria, 0.800 for the Okazaki criteria, and 0.833 and 0.864 for the ACR/EULAR 2019 criteria and numeric score, respectively, with all values showing significant diagnostic performance ($p < 0.000$).

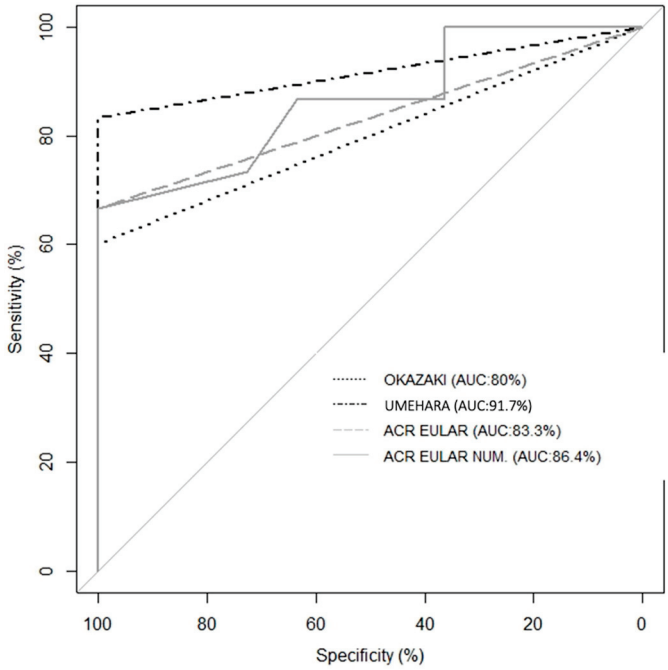

Figure 1. Area under the curve for the Okazaki, Umehara, and ACR/EULAR criteria.

3.3. Description of IgG4-RD Subtypes

The analysis of IgG4-RD subtypes revealed distinct patterns across four identified groups (Table 4). Subtype 1, comprising 26.7% of cases, was characterized by a strong male predominance (87.5%) and the most pronounced pancreatic involvement, with 75% of cases showing pancreatic–biliary injury. Subtype 2 was the most prevalent subtype, comprising 19 patients (63.3%). Was especially associated with hypertension (p = 0.066), aneurysms (47.4%) and retroperitoneal involvement. Pulmonary manifestations, specifically peribronchovascular and septal thickening, were exclusive to this subtype (26.3% of cases). Subtype 3 (head/neck-limited) was represented by a single case, limiting comparative analysis. Subtype 4 (Mikulicz-systemic involvement), with only two cases, showed a tendency for systemic manifestations, including aneurysm in one case.

Table 4. IgG4 subtypes.

	SUBTYPE 1 Pancreato-Hepato-Biliary *n* = 8 (26.7%)	**SUBTYPE 2 Retroperitoneal +/− Aortitis *n* = 19 (63.3%)**	**SUBTYPE 3 Head/Neck-Limited *n* = 1 (3.3%)**	**SUBTYPE 4 Mikulicz-Systemic Involvement *n* = 2 (6.7%)**	***p* Value**
Gender (male)	7 (87.5%)	16 (84.2%)	1 (100%)	1 (50%)	0.592
Race					
- Caucasian	8 (100%)	18 (94.7%)	1 (100%)	2 (100%)	1
- Asian	0 (0%)	1 (5.3%)	0 (0%)	0 (0%)	
Arterial hypertension	2 (25%)	12 (63.2%)	0 (0%)	0 (0%)	0.066
Dyslipidemia	3 (37.5%)	10 (52.6%)	0 (0%)	1 (50%)	0.83
Ischemic heart disease	0 (0%)	6 (31.6%)	0 (0%)	0 (0%)	0.321

Table 4. *Cont.*

	SUBTYPE 1 Pancreato-Hepato-Biliary *n* = 8 (26.7%)	**SUBTYPE 2 Retroperitoneal +/− Aortitis *n* = 19 (63.3%)**	**SUBTYPE 3 Head/Neck-Limited *n* = 1 (3.3%)**	**SUBTYPE 4 Mikulicz-Systemic Involvement *n* = 2 (6.7%)**	***p* Value**
Non-hematological neoplasia	0 (0%)	1 (5.3%)	0 (0%)	0 (0%)	1
Glandular involvement					
- 1 set	0 (0%)	2 (10.5%)	0 (0%)	0 (0%)	1
- >2 sets	1 (12.5%)	1 (5.3%)	0 (0%)	0 (0%)	
Pulmonary involvement					
- Peri-bronchovascular and septal thickening	0 (0%)	5 (26.3%)	0 (0%)	0 (0%)	0.483
- Paravertebral-like thorax soft tissue	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Pancreatic involvement					
- Lobulation loss	0 (0%)	1 (5.3%)	0 (0%)	0 (0%)	
- Low-density capsule edging	2 (25%)	0 (0%)	0 (0%)	0 (0%)	<0.001
- Pancreatic-biliary injury	6 (75%)	1 (5.3%)	0 (0%)	0 (0%)	
Renal involvement					
- Hypocomplementemia	1 (12.5%)	2 (10.5%)	0 (0%)	0 (0%)	
- Thickening of renal pelvis	0 (0%)	3 (15.8%)	0 (0%)	0 (0%)	0.914
- Bilateral low-density renal cortex	1 (12.5%)	6 (31.57%)	0 (0%)	1 (50%)	
Retroperitoneal involvement					
- Wall thickening of abdominal aorta	0 (0%)	7 (36.8%)	0 (0%)	0 (0%)	0.001
- Iliac and infrarenal aortic soft peripheral tissue	0 (0%)	10 (52.6%)	0 (0%)	0 (0%)	

Table 4. *Cont.*

	SUBTYPE 1 Pancreato-Hepato-Biliary *n* = 8 (26.7%)	**SUBTYPE 2 Retroperitoneal +/− Aortitis *n* = 19 (63.3%)**	**SUBTYPE 3 Head/Neck-Limited *n* = 1 (3.3%)**	**SUBTYPE 4 Mikulicz-Systemic Involvement *n* = 2 (6.7%)**	***p* Value**
Fever	0 (0%)	2 (10.5%)	0 (0%)	1 (50%)	0.293
Constitutional syndrome	0 (0%)	2 (10.5%)	0 (0%)	1 (50%)	0.293
Lower back pain	0 (0%)	6 (31.6%)	0 (0%)	0 (0%)	0.321
Hydronephrosis	0 (0%)	3 (15.8%)	0 (0%)	0 (0%)	0.663
Aneurysm	0 (0%)	9 (47.4%)	0 (0%)	1 (50%)	0.037
Hypophysitis	1 (12.5%)	0 (0%)	0 (0%)	0 (0%)	0.367
Okazaki 2009 criteria					
- Not met	4 (50%)	7 (36.8%)	0 (0%)	1 (50%)	0.902
- Met	4 (50%)	12 (63.2%)	1 (100%)	1 (50%)	
Umehara 2012 criteria					
- Not met	0 (0%)	5 (26.3%)	0 (0%)	0 (0%)	
- Possible	4 (50%)	10 (52.6%)	1 (100%)	2 (100%)	0.652
- Probable	1 (12.5%)	1 (5.3%)	0 (0%)	0 (0%)	
- Definitive	3 (37.5%)	3 (15.8%)	0 (0%)	0 (0%)	
ACR/EULAR 2019 criteria					
- Not met	2 (25%)	6 (31.6%)	1 (100%)	1 (50%)	0.653
- Met	6 (75%)	13 (68.4%)	0 (0%)	1 (50%)	
ACR/EULAR numeric value, median (IQR)	24.0 (19.8–34.0)	20.0 (12.0–23.5)	4.0 (4.0–4.0)	12.5 (8.2–16.8)	0.523
IgG, median (IQR)	1166.5 (853.2–1306.0)	1180.0 (985.5–1542.0)	1624.0 (1624.0–1624.0)	1355.5 (1261.8–1449.2)	0.390
IgG4, median (IQR)	72.0 (39.8–132.8)	84.0 (43.5–180.0)	153.0 (153.0–153.0)	297.0 (207.0–387.0)	0.45
Plasmablasts, median (IQR)	518.0 (0.0–862.2)	1005.0 (288.0–1657.5)	9680.0 (9680.0–9680.0)	1176.5 (1145.8–1207.2)	0.179

On comparing diagnostic criteria across groups, distinctive trends emerged. The diagnostic accuracies of Umehara's criteria and the ACR/EULAR 2019 criteria for subtype 1 were 50% and 75%, respectively. For subtype 2, ACR/EULAR 2019 demonstrated an accuracy of 68.4%, while the Okazaki's criteria exhibited an accuracy of 63.2%. These findings suggest that specific criteria may be more useful for the diagnosis of these particular subtypes. Finally, only the subtype 3 case met both Okazaki's and Umehara's criteria, while the two subtype 4 cases met Umehara's criteria.

4. Discussion

We evaluated the diagnostic performance of the Okazaki, Umehara, and ACR/EULAR 2019 IgG4-RD classification criteria for a cohort of 41 Spanish patients with suspected IgG4-RD, in 30 of whom the diagnosis was confirmed by expert clinical judgment. Sensitivity was highest for the Umehara criteria (83.3%), followed by the ACR/EULAR 2019 criteria (66.66%) and the Okazaki criteria (60.0%).

Regarding the Okazaki (2009) and Umehara (2011) criteria, sensitivity was suboptimal for our cohort, which would question their utility for IgG4-RD screening in clinical practice. For the ACR/EULAR 2019 criteria, our sensitivity value of 66.66% was lower than reported (85.5% and 82.0%) in the original validation studies [15]. This discrepancy can be attributed to several factors. Firstly, the inherent design of the ACR/EULAR 2019 criteria gives them a built-in advantage, as the pre-defined threshold values for sensitivity and specificity during the criteria development process effectively established a high pre-test probability. This approach inherently increased the likelihood of achieving superior diagnostic performance in the initial validation cohort. Secondly, our relatively small sample may have influenced our results, while potential differences between our cohort and the original validation cohorts (disease phenotypes, patient characteristics, geographic variations) may contribute to the observed differences. Consequently, the ACR/EULAR 2019 criteria may not achieve the same level of sensitivity when applied to different patient populations or in real-world clinical settings, as in our study. This underscores the importance of external validation studies in diverse populations to assess the true performance of diagnostic criteria outside their development cohort and to account for variations in patient demographics and clinical presentations across different settings.

Notably, in our cohort all three criteria demonstrated excellent specificity (100%) and PPV (100%). These findings align with previous studies highlighting the high specificity of these diagnostic criteria for IgG4-RD [13–15].

The Umehara criteria, when stratified into possible, probable, or definitive IgG4-RD categories, showed lower sensitivity than when stratified dichotomously (with/without IgG4-RD). This observation aligns with Carruthers et al. [11], who reported significantly reduced sensitivity (36%) when considering only the definitive category. These findings underscore the heterogeneous nature of IgG4-RD and the challenges associated with strict compliance with more stringent classification criteria in specific cases. To optimize diagnostic sensitivity and prevent the omission of true cases, our study highlights the importance of considering all classification criteria categories, rather than focusing solely on the category with the highest specificity.

Subgroup analysis revealed differing compliance patterns for the four IgG4-RD phenotypes (classified according to the Wallace et al. 2019 [1] categorization), suggesting the potential utility of applying specific criteria to identify certain disease subtypes.

In our cohort, retroperitoneal fibrosis and/or aortitis (subtype 2) was the most prevalent subtype, comprising 63.3% of our patients. This differs from the literature, which reports pancreato-hepato-biliary involvement (subtype 1) to be the most prevalent subtype, accounting for 31% of cases [1]. The greater prevalence of subtype 2 in our cohort can be attributed to the presence of a multidisciplinary specialized aorta monthly committee in our institution, which likely led to increased detection and referral of cases with retroperitoneal fibrosis and aortitis. The varying prevalence of subtypes in our cohort, along with differences in how well each subtype meets different diagnostic criteria, underscores the known heterogeneity of IgG4-related disease and highlights the challenges faced in creating universally applicable diagnostic criteria.

Aligning with previous reports advocating for customized diagnostic approaches based on phenotype-specific consideration [1,14,15], our findings underscore the importance of considering disease phenotypes when selecting appropriate diagnostic criteria. We found that the Umehara and ACR/EULAR 2019 criteria performed better for the pancreato-hepato-biliary subtype, whereas the Okazaki and ACR/EULAR 2019 criteria performed better for the retroperitoneal fibrosis and/or aortitis subtype [17]. Adams et al. [5] also found

that the ACR/EULAR 2019 criteria were more effective for both pancreato-hepato-biliary and retroperitoneal fibrosis and/or aortitis subtypes, corroborating Martinez-Calabuig et al. [18], who found that the ACR/EULAR 2019 criteria were superior to the Umehara and Okazaki criteria in diagnosing these subtypes. Those findings overall suggest that the ACR/EULAR 2019 criteria can play a crucial role in enhancing diagnostic accuracy for the IgG4-RD pancreato-hepato-biliary and retroperitoneal fibrosis and/or aortitis subtypes, thereby potentially improving patient care and outcomes.

The mean age of IgG4-RD diagnosis in our cohort was 61.79 years, which aligns with Brito-Zerón et al.'s [19] observation that the disease predominantly affects older adults.

Likewise, men predominated among our patients with an IgG4-RD diagnosis, highlighting potential sex-specific differences in disease presentation and susceptibility. Although no definitive disparity hypothesis is supported, men with IgG4-RD typically exhibit more a frequent involvement of organs such as the pancreas and kidneys, accompanied by a more active B-cell response [6].

The main strength of our study is the novelty of simultaneously comparing all three sets of criteria (Okazaki, Umehara, and ACR/EULAR 2019) in a cohort of IgG4-RD patients which, to our knowledge, is the first such comparison to date. While previous studies have compared the ACR/EULAR 2019 and the Umehara criteria separately, no single study has comprehensively evaluated the diagnostic performance of all three criteria sets concurrently. Additionally, our cohort includes patients representing all four IgG4-RD phenotypes, although, importantly, there was a significant imbalance in their distribution, in contrast with the leading ACR/EULAR groups [1]. In our cohort, subtypes 2 and 1 were predominant, while subtypes 3 and 4 were only anecdotally represented. This disproportionate distribution makes it challenging to draw robust conclusions regarding the latter two groups. Consequently, while our study provides some insights into the potential utility of specific criteria for different subtypes, the reliability of these insights varies considerably across subtypes.

The strict selection of patients with a high pretest probability of IgG4-RD (based on stringent inclusion criteria and comprehensive evaluation) likely contributed to the observed 100% PPV across all three criteria and minimized the inclusion of false negatives, while meeting the classification criteria significantly increased the likelihood of true positives. These findings highlight the clinical utility and reliability of the diagnostic criteria in accurately identifying IgG4-RD cases within our study cohort.

The main limitations are the small sample size, reflecting the low prevalence of the disease, and the single-center nature of our study. Further studies with larger sample sizes are necessary to achieve greater robustness. We plan to include all potential cases of IgG4-RD evaluated in our hospital for a future multicenter study to validate our results. Another key limitation was that enrolled patients were selected based on high clinical suspicion of IgG4-related disease and elevated IgG4 levels. This selection process may not have captured the full clinical spectrum of the condition, as patients presenting with subtle or atypical manifestations, or those with normal IgG4 levels despite active disease, could have been inadvertently excluded. To help mitigate this potential selection bias, the final diagnosis was determined through comprehensive evaluation by physicians with specialized expertise in IgG4-RD. However, this approach does not entirely eliminate the possibility that the study population may not be fully representative of the broader IgG4-RD patient population.

Additionally, since histopathological confirmation is crucial to diagnosing IgG4-RD in a non-negligible proportion of cases, a significant limitation was the small number of biopsies performed. Consequently, we may have inadvertently excluded a subset of patients with the disease. The paucity of biopsies in our cohort was due to the predominance of IgG4-RD subtype 2 (retroperitoneal fibrosis and aortitis). As reported in the literature, retroperitoneal fibrosis often presents with a fibrotic phenotype, meaning that tissue sampling is not only technically difficult (due to the deep-seated nature and proximity to vital structures) but may also yield limited diagnostic information (prominent fibrosis but

minimal inflammation) [20]. This makes diagnosis particularly challenging, especially in the absence of distinctive histopathological features. Therefore, despite the recognized importance of biopsy for definitive diagnosis, the anatomical and pathological characteristics of subtype 2 often render biopsies unfeasible or potentially hazardous, further complicating the diagnostic process. Consequently, while our study provides some insights into the potential utility of specific criteria for different subtypes, the reliability of these insights varies considerably across the subgroups due to their uneven representation.

5. Conclusions

This retrospective study provides a detailed comparative evaluation of the Okazaki, Umehara, and ACR/EULAR 2019 classification criteria for diagnosing IgG4-related disease (IgG4-RD) in a Spanish cohort. Although the overall sample size is small, our findings demonstrate that the Umehara criteria exhibit the highest sensitivity (83.33%), making them the most suitable for screening purposes. Meanwhile, all three sets of criteria showed perfect specificity and positive predictive value (PPV), effectively confirming the diagnosis of IgG4-RD.

The predominance of subtype 2 in our cohort, attributed to a specialized multidisciplinary approach at our center, further supports the importance of clinical context in the diagnosis of IgG4-RD. However, the uneven distribution of subtypes, particularly the underrepresentation of subtypes 3 and 4, limits the generalizability of our conclusions for these less prevalent subtypes.

The lack of histopathological confirmation in some cases, particularly in patients with deep-seated fibrotic disease, remains a limitation, emphasizing the need for alternative diagnostic strategies when biopsy is not feasible. Future multicenter studies with larger, more balanced cohorts and broader histopathological validation are needed to refine these diagnostic criteria and improve their applicability across different IgG4-RD phenotypes.

In summary, our results suggest that while no single set of criteria is universally optimal, the Umehara and ACR/EULAR 2019 criteria offer the highest diagnostic value, especially when applied to specific subtypes. The development of tailored diagnostic strategies based on disease phenotype, along with further validation in diverse populations, will be essential to improve the accuracy and utility of these criteria in clinical practice.

Author Contributions: Formal analysis, H.S.P.; Investigation, P.M.-A., M.C.M., S.C., H.C.-M., B.M., I.C., A.J.B.-M., A.L., C.D.-T., L.S., J.B., L.M.-M. and H.C.; Writing—original draft, M.L.-G. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Sociedad Española de Reumatología.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee (IIBSP-EIG-2022-92) in 2021 in Hospital Sant Pau i de la Santa Creu, Barcelona, Spain.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

Okazaki Criteria (Proposed by the Japanese Research Committee for IgG4-Related Systemic Sclerosing Disease) 2009

1. Focal or diffuse enlargement or lesions in one or more organs.
2. Serum IgG4 concentrations > 135 mg/dL
3. Histopathology
    (a) Lymphocytic and plasmocytic infiltrate with fibrosis, without neutrophilic infiltrate.

(b) IgG4 positive plasmocytic infiltrate greater than 10/cap or IgG4/IgG > 40% ratio of IgG4/IgG cells.
(c) Storiform fibrosis
(d) Obliterative phlebitis

The patient will be classified by meeting one of the following combinations of criteria:

- 1 + 2
- 1 + 3 (a + b)
- 2 + 3 (a + b)
- 3 (a + b + c + d)

Appendix B

Umehara Criteria 2011

1. Clinical examination showing characteristic diffuse/localized swelling or masses in one or more organs.
2. Hematologic examination showing elevated serum IgG4 concentrations (≥135 mg/dL).
3. Histopathologic examination showing:
   - Marked lymphocyte and plasmacyte infiltration and fibrosis.
   - IgG4-positive plasma cell infiltration: IgG4/IgG-positive cell ratio > 40% and >10 IgG4-positive plasma cells/high potency field (HPF).

The patient will be classified by meeting one of the following combinations of criteria: Definitive: (1) + (2) + (3); Probable: (1) + (3); Possible: (1) + (2)

Appendix C

ACR/EULAR 2019 Criteria

Exclusion Criteria

Clinical

- fever: recurrent temperature > 38 °C without clinical signs of infection
- lack of response to glucocorticoids at doses of at least 40 mg/day of prednisone (approx. 0.6 mg/kg/day) for 4 weeks

Serologic

- leukopenia or thrombocytopenia without alternative explanation
- peripheral eosinophilia > 3000 mm^3
- presence of ANCA antibodies
- presence of antinuclear antibodies anti-Ro, anti-La, anti-double-stranded DNA, anti-RNP, anti-Sm, anti-synthetase (e.g., anti-Jo1), antitopoisomerase III (Scl-70). This does not include antibodies of low specificity, such as rheumatoid factor, antinuclear antibodies (in screening), antimitochondrial antibodies, antimuscle smooth muscle antibodies, and antiphospholipid antibodies
- cryoglobulinemia.

Radiological

- radiological changes characteristic of neoplastic diseases or infections not sufficiently screened for
- rapid radiological progression
- anomalies in long bones compatible with Erdheim-Chester disease: multifocal osteosclerotic lesions in long bones
- splenomegaly: >14 cm without other explanations

Histopathologic

- cellular infiltrates that raise suspicion of a malignant neoplasm and have not been sufficiently analyzed

- markers related to an inflammatory myofibroblastic tumor
- evident neutrophilic inflammation
- necrotizing vasculitis
- evident necrosis (especially zonal necrosis)
- primary granulomatous inflammation
- characteristic signs of diseases related to macrophage/histiocyte disorders.

Histopathological

- cellular infiltrates that raise suspicion of a malignant neoplasm and have not been sufficiently analyzed
- markers related to an inflammatory myofibroblastic tumor
- evident neutrophilic inflammation
- necrotizing vasculitis
- evident necrosis (especially zonal necrosis)
- primary granulomatous inflammation
- characteristic signs of diseases related to macrophage/histiocyte disorders.

Exclusion of specific diseases

- multicentric Castleman's disease
- Crohn's disease
- ulcerative colitis
- Hashimoto's thyroiditis

Inclusion criteria: a point count should be performed.

Histopathology	
-biopsy that does not provide relevant information	0
-dense lymphocytic infiltrate	4
-dense lymphocytic infiltrate and obliterative phlebitis	6
-dense lymphocytic infiltrate and glandular fibrosis with or without obliterating phlebitis	13
Immunostaining	0–16
Serum IgG4 concentration	
-normal or undetermined	0
-above normal, but <2× upper limit of normal (ULN)	4
-from 2× to 5× LSN	6
≥5× LSN	11
Bilateral involvement of lacrimal glands, parotid, sublingual and submaxillary salivary glands	
-unaffected	0
-affectation of 1 pair	6
-involvement of ≥2 pairs	14
Chest	
-undetermined or none of the aforementioned elements are present	0
-peri-bronchovascular and septal thickening	4
-paravertebral band-like soft tissue in the thorax	10

Pancreas and biliary tract	
-undetermined or none of the aforementioned elements are present	0
-diffuse enlargement of the pancreas (loss of lobulation)	8
-diffuse enlargement of the pancreas and low-density capsule rim	11
-involvement of the pancreas (one of the above) and bile ducts	19
Kidney	
-undetermined or none of the aforementioned elements are present	0
-hypocomplementemia	6
-thickening of the renal pelvis/soft tissue	8
– bilateral areas of low density in the renal cortex	10
Retroperitoneum	
-undetermined or none of the aforementioned elements are present	0
-diffuse thickening of the wall of the abdominal aorta	4
-peripheral or anterolateral soft tissue around the infrarenal aorta or iliac arteries	8

IgG4-related disease classification criteria are met if the entry criterion is met, there are no exclusion criteria, and the total score is $\geq$20.

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Disease Course and Long-Term Outcomes in Adult IgA Vasculitis Nephritis: A Prospective Observational Study

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Abstract: Background/Objectives: A limited number of previous studies have reported high rates of end-stage renal disease (ESRD) in adults with IgA vasculitis nephritis (IgAVN). Despite the high prevalence of the disease and the high rates of ESRD reported in the literature, no specific guidelines for adult patients have been established and there is no consensus on the management of the disease. This study aimed to prospectively investigate adults with IgAVN from a broad perspective. **Methods**: This investigation was designed as a prospective observational study and was conducted between 01.02.2022 and 01.10.2024. A total of 49 newly diagnosed adult (>18 years) patients with IgAVN were regularly followed up. At the end of the study, the renal remission rates, factors influencing remission, treatment data, treatment-related adverse events, and disease outcomes were determined. **Results**: The median follow-up time was 22 (IQR: 11–24) months. A total of 42 patients (87%) received immunosuppressive treatment in addition to the initial glucocorticoid treatment. Azathioprine (AZA) was the preferred (41%) first steroid-sparing agent. ESRD occurred in only one patient (2%), while a total of ten patients (20%) had an unfavorable outcome. The rate of nephrotic-range proteinuria (NRP) was significantly higher in the patients who did not achieve renal remission at the end of the 12-month follow-up period (9,7% vs. 60%; $p = 0.02$) and NRP was an independent risk factor for unfavorable outcomes [OR: 17.18; 95% CI: 1.31–224.95; $p = 0.03$]. A total of 16% of the patients developed an infection that required hospitalization during follow-up; these patients had a higher rate of IgAVN-associated acute kidney injury (62.5% vs. 22%; $p = 0.02$) and were significantly older (mean: 46 ± 15.3 vs. 65 ± 13.3; $p = 0.002$). One patient died of sepsis at 4 months and another died of a myocardial infarction at 32 months. **Conclusions**: These results suggest that adults with IgVAN do not have a high rate of ESRD if they receive effective immunosuppressive therapy. However, immunosuppressive therapy is associated with an increased risk of infection, particularly in the elderly. The presence of NRP is associated with lower long-term remission rates and has a predictive value for unfavorable outcomes.

Keywords: IgA vasculitis; nephritis; prognosis; mortality; ESRD

1. Introduction

Immunoglobulin A vasculitis (IgAV), also known as Henoch–Schönlein purpura (HSP), is a type of primary vasculitis characterized by the deposition of IgA1-immune complexes in

small vessels [1]. Its annual incidence in adults has been reported to vary from 0.3/100,000 to 5.1/100,000 [2–4]. The disease classically involves the skin, joints, gastrointestinal tract, and kidneys. Renal involvement is the most common cause of morbidity and mortality and is the main determinant of the prognosis in patients with IgAV [5,6]. The renal involvement of the disease is essentially an immune complex glomerulonephritis and is termed IgA vasculitis nephritis (IgAVN) [7]. The rate of IgAVN in adult patients with IgAV has been reported to vary between 45% and 85% [8]. Hematuria is the most common and first manifestation of IgAVN, but proteinuria, nephrotic syndrome, nephritic syndrome, and acute kidney injury may also occur due to the disease [9]. Most of the data in the literature on IgAVN are derived from studies conducted in children. Studies comparing pediatric and adult patients with IgAVN have shown that the disease has a worse prognosis in adults [10,11]. The aim of this study was to prospectively investigate the disease course, outcomes, and treatment options in adults with IgAVN.

2. Materials and Methods

2.1. Study Design and Population

This investigation was designed as a prospective observational study and was conducted between February 2022 and October 2024 at the University of Health Sciences Başakşehir Çam and Sakura City Hospital Department of Rheumatology. A total of 49 patients aged ≥18 years with histopathological or clinically diagnosed IgAVN were included in the study. Patients with isolated IgA nephropathy and patients whose renal findings could be explained by another concurrent disease were excluded. All the patients were re-examined at 3-month intervals. Their renal functions, urine analysis results, proteinuria level, medications and doses, adverse events, and vasculitis damage scores were recorded at each visit. At the end of the study, the long-term (12-month) renal outcomes of the patients and the factors influencing these outcomes were determined. This study was approved by the hospital ethics committee (approval number: KAEK/2022.11.361) and was conducted according to the guidelines of the Declaration of Helsinki. Informed consent was obtained from all the patients.

2.2. Clinical Definitions

The EULAR/PRINTO/PRES classification criteria were used for the diagnosis of IgAV [12]. Renal involvement was defined as the presence of proteinuria (≥150 mg/24 h or ≥150 mg/g spot urine protein/creatinine ratio) and/or hematuria (≥5 red cells per high-power field). Acute kidney injury (AKI) was defined as an increase in serum creatinine of 0.3 mg/dL within 48 h or an increase in baseline serum creatinine of ≥50% within 7 days. The definitions of renal conditions (proteinuria, hematuria, AKI, CKD, and ESRD) were made in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [13–15]. Renal remission was defined as proteinuria <300 mg/g supcr with a GFR≥ 60 mL/min/1.73 m^2 and using a glucocorticoid dose of ≤5 mg/day of prednisolone or equivalent. A relapse was defined as a >50% increase in proteinuria with hematuria or the reappearance of hematuria that was not explained by another medical condition other than vasculitis during a period after remission in patients with at least 3 months of follow-up. The definition of renal remission was determined by the investigators specifically for this study. Unfavorable outcomes were defined as established CKD (G3a-G5), renal replacement therapy, persistent proteinuria >500 mg/g supcr at the end of the follow-up, relapse disease, IgAVN-associated death, or a vasculitis damage index (VDI) score ≥1 at the end of the follow-up period.

2.3. Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) 26.0 (IBM, Chicago, IL, USA). The Kolmogorov–Smirnov test and the Shapiro–Wilk test were used to assess the normality of the data. Continuous variables were summarized as the mean ± standard deviation or median [interquartile range (IQR)] and categorical variables were summarized as percentages. Comparisons of continuous variables between groups were performed using a *t*-test or the Mann–Whitney U test after the distribution was evaluated, and the chi-square (χ^2) test or Fisher's exact test were used to compare categorical variables. The binary logistic regression analysis and multivariate Cox regression analysis methods were used to determine the predictors. A Kaplan–Meier estimation was performed to calculate the rate of the endpoint.

3. Results

3.1. Patient Characteristics and Presentation Signs

This study enrolled 49 adult patients (30 male; mean age: 49 ± 2.3 years) with newly diagnosed IgAVN. The median follow-up time was 22 (11–24) months. Of a total of 49 patients, 46 (94%) had skin involvement, 16 (32.6%) had joint involvement, and 11 (22.4%) had gastrointestinal involvement. Palpable purpura (94%) was the most common clinical sign at initial presentation, followed by hematuria (73.4%) and proteinuria (69.3%). Eleven patients (22.4%) had no renal pathology at initial presentation but developed renal involvement during follow-up. In patients who subsequently developed renal findings, the median time between the first visit and the renal findings was 30 (8–49) days. Regarding the renal findings, the patients most commonly had non-nephrotic proteinuria (73.4%) with active urinary sediment, 16.3% had nephrotic-range proteinuria, and 28.5% had acute kidney injury. Renal biopsy was performed in 55% of patients and a skin biopsy was performed in 94%. In all the patients with renal biopsies, pathological examination revealed increased mesangial cells and IgA deposits; all patients had evidence of mesangioproliferative glomerulonephritis. Glomerular crescent formation was present in 41% of the patients, but none of them had a crescent rate of more than 50%. The details of the histopathological findings can be found in the Supplementary Materials. The baseline demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. Demographics and clinical characteristics of the patients.

	***N* = 49**
Age, year; mean ± SD	49 ± 2.3
Male; *n*/*N* (%)	30 (6.2)
Follow-up time, month; median (IQR)	22 (11–24)
Organ system involvement; *n*/*N* (%)	
Skin	46 (94)
Joint	16 (32.6)
Gastrointestinal	11 (22.4)
Renal	49 (100)
Overall renal involvement; *n*/*N* (%)	
Nephrotic-range proteinuria	8 (16.3)
Non-nephrotic proteinuria	36 (73.4)
Isolated hematuria	5 (10.2)
Acute kidney injury	14 (28.5)

Table 1. *Cont.*

	N = 49
Overall renal outcomes; *n*/*N* (%)	
Persistent proteinuria (>500 mg/24 h)	6 (12)
Relapse	3 (6)
Chronic kidney disease (G3a–G5)	4 (8)
G3a	1 (2)
G3b	1 (2)
G4	1 (2)
G5	1 (2)
Established renal replacement therapy	1 (2)
VDI score (≥1); *n*/*N* (%)	10 (20)
Mortality; *n*/*N* (%)	
Sepsis	1 (2)
Myocardial infarction	1 (2)

SD: standard deviation; VDI: vasculitis damage index; G3a-G5: Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease stages—G3a: GFR 45–59; G3b: GFR 30–44; G4: GFR15–29; G5: GFR < 15—IQR: interquartile range.

3.2. Immunosuppressive Management Within the Cohort

The drugs and drug doses used in the treatment were decided by the clinicians without any guidelines. All the patients received a glucocorticoid treatment (53.1% pulse methylprednisolone), and the median glucocorticoid dose was 500 mg/day of methylprednisolone. Azathioprine (AZA) was the most commonly preferred first glucocorticoid-tapering agent (41%), followed by cyclophosphamide (CYC) (31%) and mycophenolate mofetil (MMF) (6%). In seven patients (14%), the glucocorticoid-tapering agent was changed to another for various reasons. The drugs used in the treatment and their effects on the renal outcomes are shown in Table 2.

Table 2. Treatment data of the patients.

	All of the Patients *N* = 49	**Remission at 12 Months (+) vs. (−)/*p*-Value**	**VDI Score (≤1) vs. (>1)/*p*-Value**	**Unfavorable Renal Outcomes (+) vs. (−)/*p*-Value**
All of the steroid-sparing agents; *n*/*N* (%)				
CYC	16 (33)			
AZA	25 (51)			
MMF	16 (33)			
MFA	1 (2)			
COLCH	5 (10)			
LEF	1 (2)			
TOCI	1 (2)			
First steroid-sparing agent; *n*/*N* (%)				
CYC	15 (31)	22.6 vs. 20/0.691	23.1 vs. 30/0.693	40 vs. 28.2/0.478
AZA	20 (41)	41.9 vs. 60/0.632	41 vs. 50/0.61	40 vs. 41/0.993
MMF	3 (6)			
COLC	3 (7)			
LEF	1 (2)			
None	7 (14)			
Steroid-sparing agent after cyclophosphamide; *n/N* (%)				
AZA	5/13 (38)	40 vs. 0/0.633	27.3 vs. 50/0.569	50 vs. 27.3/0.409
MMF	8/13 (62)	60 vs. 100/0.634	54.5 vs. 50/0.66	50 vs. 54.5/1.000
Steroid-sparing agent switch; *n/N* (%)				
AZA > MMF (adverse event)	4/42 (10)			
AZA > MMF (inadequate response)	1 (2)			
CYC > MMF (adverse event)	1 (2)			
CYC > AZA > TOCI (inadequate response for arthritis)	1 (2)			

Table 2. *Cont.*

	All of the Patients $N = 49$	Remission at 12 Months (+) vs. (−)/p-Value	VDI Score (≤1) vs. (>1)/p-Value	Unfavorable Renal Outcomes (+) vs. (−)/p-Value
Initial glucocorticoid dosage (prednisolone or equivalent MP); *n/N* (%)				
Pulse (≥250 mg/day)	26 (53.1)	48.4 vs. 80/0.342	48.7 vs. 70/0.296	70 vs. 48.7/0.22
1 mg/kg/day	8 (16.3)	19.4 vs. 0/0.64	17.9 vs. 10/0.477	10 vs. 17.9/0.541
0.5–1 mg/kg/day	7 (14.3)	9.7 vs. 0/0.633	12.8 vs. 20/0.624	20 vs. 12.8/0.565
≤0.5 mg/kg/day	8 (16.3)	19.4 vs. 0/0.561	15.4 vs. 0/0.32	0 vs. 15.4/0.187
Total glucocorticoid (prednisolone) exposure (gr); mean ± SD	3.1 ± 0.2	2.2 ± 1.3 vs. 3.5 ± 1.2 /***0.01***	3.0 ± 1.6 vs. 4.6 ± 1.6 /0.06	4.3 ± 1.8 vs. 2.8 ± 1.3 /***0.006***

CYC: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil; MFA: mycophenolic acid; COLC: colchicine; LEF: leflunomide; TOCI: tocilizumab; MP: methylprednisolone; VDI: vasculitis damage index; SD: standard deviation.

3.3. One-Year Renal Remission Rates and Factors Influencing Remission

A total of 36 patients reached the one-year follow-up point, and 86% of the patients were in remission at 12 months. The rate of NRP was significantly higher in patients who did not achieve renal remission at the end of the 12-month follow-up period (9.7% vs. 60%; $p = 0.02$). The one-year remission rates and the factors influencing remission are shown in Table 3.

Table 3. Factors associated with long-term renal remission.

	Renal Remission (+) at 12 Months $N = 31$	Renal Remission (−) at 12 Months $N = 5$	p-Value
Age; mean ± SD	48.6 ± 16	56.6 ± 19.8	0.322
Male; *n/N* (%)	17 (54.8)	2 (40)	0.651
Renal involvement; *n/N* (%)			
Nephrotic-range proteinuria	3 (9.7)	3(60)	***<0.02***
Non-nephrotic proteinuria	22 (71)	2 (40)	0.333
Isolated hematuria	4 (12.9)	0 (0)	0.398
Isolated proteinuria	2 (6.5)	0 (0)	0.559
Acute kidney injury	10 (32.3)	2 (40)	0.733
Other system involvement; *n/N* (%)			
Skin involvement	31 (100)	4 (80)	0.135
Joint involvement	10 (32.3)	1 (20)	0.515
Gastrointestinal involvement	7 (22.6)	0 (0)	0.554
Baseline laboratory findings; *n/N* (%)			
CRP (mg/L); median (IQR)	40.8 (7–116)	13.5 (2.1–22.8)	0.112
GFR; median (IQR)	102 (80–119)	93 (45–119)	0.742
Serum albumin, <3.5 gr/dL; *n/N* (%)	7 (22.6)	0 (0)	0.556
Serum IgA level; mean ± SD	3.6 ± 1.3	2.9 ± 1	0.513
SII; median (IQR)	975 (516–1585)	807 (473–1199)	0.478
BVAS; median (IQR)	12 (7–13)	12 (7–13.5)	0.732
Five-factor score, >1; *n/N* (%)	14 (45.2)	3 (60)	0.651
Initial glucocorticoid dosage (prednisolone), mg/day; median (IQR)	80 (60–1000)	1000 (500–1000)	0.09
Comorbid systemic disease; *n/N* (%)			
Hypertension	10 (32.1)	2 (40)	0.541
Type 2 diabetes mellitus	10 (32.2)	1 (20)	0.512
Comorbid rheumatic disease; *n/N* (%)			
FMF	3 (9.7)	0 (0)	0.631
AS	2 (6.5)	0 (0)	0.739
Predisposing factor; *n/N* (%)			
None	17 (54.8)	3 (40)	0.615
Infection	11 (35.5)	3 (60)	0.351
Drug	7 (22.6	0 (0)	0.312

CRP: C-reactive protein; IQR: interquartile range; GFR: glomerular filtration rate; SII: systemic immune–inflammation index; BVAS: Birmingham vasculitis activity score; FMF: familial Mediterranean fever; AS: ankylosing spondylitis; SD: standard deviation.

3.4. Overall Unfavorable Outcomes and Associated Factors

A total of 10 patients had unfavorable outcomes at the end of the follow-up period. The presence of NRP was an independent risk factor for unfavorable outcomes [OR: 17.18; 95% CI: 1.31–224.95; $p = 0.03$]. The unfavorable outcomes and the factors associated with them are shown in Table 4. The vasculitis damage index (VDI) was used to assess disease- and medication-related damage. A total of 20% of the patients had a high VDI score (>1) at the end of the follow-up period. Patients with high VDI scores had a significantly higher total glucocorticoid exposure than those without (2.8 ± 1.3 gr vs. 4.4 ± 1.8 gr; $p = 0.005$) (Table 2). A total of 16% of the patients developed an infection that required hospitalization during the follow-up period. There was no difference in glucocorticoid exposure or the glucocorticoid-tapering agents used between patients with and without an infection that required hospitalization. However, the patients who developed an infection requiring hospitalization had a higher rate of IgAVN-associated AKI (62.5% vs. 22%; $p = 0.02$), and these patients were significantly older (mean 46 ± 15,3 vs. 65 ± 13,3; $p = 0.002$) (Table 5). The mortality rate was 4%. End-stage renal disease (ESRD) and renal replacement therapy occurred in only one patient, and this patient died due to sepsis in the 4th month. Another patient died of a heart attack at 32 months; he was in remission with no unfavorable outcomes. During the entire follow-up period, relapsed disease occurred in three (6%) patients (Table 1).

Table 4. Factors associated with unfavorable outcomes and multivariate regression analysis.

	Unfavorable Outcomes (+) *N* = 10	**Unfavorable Outcomes (−) *N* = 39**	***p*-Value**	**Regression Analysis**	
				OR (95% CI)	***p*-Value**
Age, >60 years; *n*/*N* (%)	6 (60)	8 (20.5)	***0.01***	1.32 (0.02–73.32)	0.891
Male; *n*/*N* (%)	5 (50)	25 (64.1)	0.418		
Baseline laboratory					
CRP (mg/L); median (IQR)	22.8 (9.7–46.8)	40.8 (6.5–121)	0.444		
ESR (mm/h); mean ± SD	41.1 ± 30.7	43.3 ± 27.7	0.846		
GFR; median (IQR)	95 (70–115)	93 (80–110)	0.92		
Serum albumin (gr/dL); mean ± SD	3.9 ± 0.5	3.8 ± 0.6	0.591		
BVAS; median (IQR)	10 (6–13.2)	12 (9–15)	0.215		
Five-factor score, >2; *n*/*N* (%)	4 (40)	3 (7.7)	***0.02***	0.60 (0.23–15.97)	0.764
SII; median (IQR)	689 (335–1110)	978 (516–2135)	0.483		
Baseline renal condition; *n*/*N* (%)					
Crescent on biopsy (+)	4/4 (100)	10/16 (62.5)	0.266		
Proteinuria (>500 mg/day)	9 (90)	19 (48.7)	***0.03***	3.52 (0.33–37.14)	0.291
Acute kidney injury	2 (20)	4 (10.3)	0.581		
Nephrotic-range proteinuria (>3.5 gr/day)	6 (60)	2 (5.1)	***0.001***	***17.18 (1.31–224.95)***	***0.03***
Other system involvement; *n*/*N* (%)					
Skin	9 (90)	37 (94.9)	0.56		
Joint	3 (30)	13 (33)	0.84		
Gastrointestinal	2 (20)	9 (23.1)	0.83		
Renal remission; *n*/*N* (%)					
at 12 months	4/8 (50)	27/28 (96.4)	***0.005***	0.06 (0.02–2.53)	0.14

Table 4. *Cont.*

	Unfavorable Outcomes (+) N = 10	Unfavorable Outcomes (−) N = 39	*p*-Value	Regression Analysis	
				OR (95% CI)	*p*-Value
Glucocorticoid dosage, Pulse steroid (>250 mg/day/MP); *n/N* (%)	7 (70)	19 (48.7)	0.22		
Total steroid exposure (gr/PR); mean ± SD	4.3 ± 1.8	2.8 ± 1.3	***0.006***	2.49 (0.93–6.60)	0.06
First steroid-tapering agent; *n/N* (%)					
AZA	4 (40)	16 (41)	0.95		
CYC	4 (40)	11 (28.2)	0.47		
Comorbid systemic disease; *n/N* (%)					
Hypertension	4 (40)	11 (28.2)	0.47		
Type 2 diabetes mellitus	4 (40)	11 (28.2)	0.47		
Comorbid rheumatic disease; *n/N* (%)					
FMF	0 (0)	5 (12.8)	0.23		
AS	0 (0)	2 (5.1)	0.46		
Predisposing factor; *n/N* (%)					
None	2 (2)	18 (46.2)	0.16		
Infection	6 (60)	13 (33.3)	0.12		
Drug	1 (10)	11 (28.2)	0.23		

CRP: C-reactive protein; IQR: interquartile range; ESR: erythrocyte sedimentation rate; GFR: glomerular filtration rate; SII: systemic immune–inflammation index; BVAS: Birmingham vasculitis activity score; FMF: familial Mediterranean fever; AS: ankylosing spondylitis; AZA: azathioprine; CYC: cyclophosphamide; MP: methylprednisolone; PR: prednisolone; SD: standard deviation.

Table 5. Factors associated with infections that required hospitalization.

	Serious Infection (+) N = 8	Serious Infection (−) N = 41	*p*-Value
Age; mean ± SD	46 ± 15.3	65 ± 13.3	***0.002***
Gender; *n/N* (%)			
Male	5 (62)	25 (61)	0.931
Female	3 (38)	16 (39)	0.942
Comorbidities; *n/N* (%)			
Type 2 DM	4 (50)	11 (23)	0.072
FMF	1 (12.5)	4 (9.8)	0.601
AS	0 (0)	2 (4.9)	0.694
Total steroid exposure (gr); mean ± SD	3.6 ± 1.2	3.1 ± 1.7	0.382
First steroid-tapering agent used; *n/N* (%)			
CYC	3 (37)	12 (29)	0.68
AZA	2 (25)	18 (43.9)	0.444
MMF	2 (25)	1 (2.4)	0.062
Renal conditions during the follow-up period; *n/N* (%)			
NRP	3 (37.5)	5 (12.2)	0.113
AKI	5 (62.5)	9 (22)	***0.02***
CKD	2 (25)	2 (4.9)	0.125

SD: standard deviation; FMF: familial Mediterranean fever; AS: ankylosing spondylitis; CYC: cyclophosphamide; MMF: mycophenolate mofetil; NRP: nephrotic-range proteinuria; AKI: acute kidney injury; DM: diabetes mellitus; AZA: azathioprine; CKD: chronic kidney disease.

4. Discussion

It is generally accepted that renal involvement is more common and severe in adults with IgAV compared to children and is a major determinant of long-term morbidity and mortality [10]. The main management strategies of IgAVN are aimed at preventing the development of ESRD. In previous studies, the rate of ESRD in adult patients with IgAVN has been reported to be between 11% and 27% [16–19]. These ESRD rates seem to be comparable to those of ANCA-associated vasculitides (granulomatous polyangiitis and microscopic polyangiitis) and lupus nephritis [20,21]. In our study, only one (2%) patient developed ESRD. There may be several reasons for the lower rate of ESRD in this study. In previous studies, a significant proportion of patients (<40%) did not receive immunosuppressives other than glucocorticoids, whereas in this study, 87% of the patients received immunosuppressives in addition to the initial glucocorticoid treatment; the majority of previous studies had a retrospective design, whereas this study was prospective; patients were followed up closely at 3-month intervals and treatment changes were implemented promptly; and this study had a relatively shorter follow-up period (median of 22 months).

In cases of vasculitic renal involvement, it is crucial to define renal remission in clinical practice. However, there is not yet an internationally accepted definition of renal remission for IgAVN. Some previous studies have defined remission as the absence of proteinuria and hematuria with a stable GFR, while others have defined remission based on proteinuria alone. We believe that the dose of glucocorticoids used should be considered when defining renal remission, and we included the glucocorticoid dose in the definition of remission in this study. The remission rates were 86% at 12 months and 87% overall in this cohort. Previous studies have reported short-term remission rates of 10%-76.9% and long-term rates of 20%-80.8% [14,19,22,23]. Differences in the definition of remission, the lack of standardized treatment regimens, and genetic and geographical factors may be responsible for these different remission rates. It is clear that there is a need for internationally accepted, standardized remission definitions. Knowledge of the factors associated with remission rates and unfavorable renal outcomes may have implications for treatment and follow-up planning. In this study, NRP was a negative risk factor for achieving remission at 12 months. There is a paucity of studies that have examined the factors that influence long-term remission in IgAVN patients. However, a study published in 2019 by J Tan et al. revealed that IgAVN patients with nephrotic syndrome had lower remission and higher ESRD rates than others, which is similar to the findings of our study [24].

At the end of this study, 20% of the patients had unfavorable outcomes. In previous studies, an advanced age, the presence of hypertension, some histopathological findings (endocapillary proliferation, glomerular sclerosis and necrosis, and tubular atrophy and fibrosis), decreased GFR and proteinuria >1 g/day at presentation, and the presence of nephrotic syndrome were associated with unfavorable outcomes [18,24–27]. In our cohort, the rate of proteinuria >1 gr/day at presentation, the rate of NRP, and the five-factor score were significantly higher in the group of patients with unfavorable outcomes; in addition, the remission rates at 12 months were lower and the total glucocorticoid exposure was higher in this group. However, the multivariate regression analysis revealed only the presence of NRP as an independent risk factor for unfavorable outcomes. An elevated creatinine level and a low GFR at presentation have been highlighted as being associated with unfavorable outcomes in several previous studies [16,17,25]. In this study, there was no difference in unfavorable outcomes between patients with and without a low GFR at presentation; we believe this is related to the early and effective immunosuppressive treatment, given our high remission rates.

Looking at the treatment data in this study, all the patients received glucocorticoid therapy at different doses and for different durations, and 87% of the patients also received

immunosuppressive therapy. In fact, it is still unclear how to treat adult patients with IgAVN. There are no high-level evidence-based studies on the efficacy of oral or intravenous pulse glucocorticoid therapy in adult patients with IgAVN. Data on the benefit of glucocorticoid therapy in IgAVN come from studies in children or patients with IgA nephropathy [28–30]. In 1998, Niaudet P and Habib R reported the clinical and histopathological benefits of pulse methylprednisolone in a study conducted with 38 pediatric patients with crescentic glomerulonephritis and nephrotic syndrome, although there was no control group in the study [30]. In our study, 53% of the patients received intravenous pulse methylprednisolone (methylprednisolone, >250 mg/day). There was no significant difference between the pulse methylprednisolone and non-pulse groups in terms of the 12-month remission rates and the overall unfavorable outcomes. In this study, AZA was the most frequently preferred drug as the first-line glucocorticoid-sparing agent, followed by CYC and MMF. There are no studies revealing that AZA is effective in adult patients with IgAVN, although it is a frequently preferred drug for these patients. Limited data on the efficacy of AZA come from studies with a low level of evidence in pediatric patients [31,32]. Similarly, although the literature data on MMF are limited, two retrospective studies conducted in China have previously reported that MMF may be beneficial in adult patients with IgAVN [23,33]. In our cohort, 33% of the patients received MMF as the glucocorticoid-sparing agent. Although CYC is now a relatively less preferred drug in rheumatic diseases than in the past due to the risk of toxicity, it is recommended as a first-line drug because of its potency and rapid effect in severe life- or organ-threatening diseases (e.g., ANCA-associated vasculitis and lupus nephritis) [34,35]. The efficacy of CYC in adult patients with IGAVN has not been demonstrated in the limited number of previous studies [22,36]. However, the current KDIGO guidelines recommend the use of CYC in combination with steroids in the presence of rapidly progressive glomerulonephritis *(RPGN)* in patients with IgAVN [14]. In our cohort, 44% of the patients receiving CYC presented with AKI, 73% had crescent formation (<50%) on renal biopsies, the mean proteinuria level was 2.3 g/day, 25% had an unfavorable outcome, and 13% developed stage G3a CKD. These data suggest that clinicians may prefer CYC in cases with severe disease at presentation. There was no significant difference in the remission rates or unfavorable outcomes between the selected first-line glucocorticoid-sparing agent groups. Frankly, there are no specific guidelines for the treatment of adult IgAVN. In the current KDIGO guideline, IgAVN is included with IgAN to a limited extent. It is emphasized that these recommendations apply only to renal involvement and are largely based on data from studies of IgAN. However, the guideline recommends strict blood pressure control and lifestyle modification for at least 3 months with ACEis/ARBs (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) prior to steroid treatment for IgAN without RPGN, and the same recommendation is made for IgAVN. Despite the similarity in the histopathological findings, the clinical courses of these two diseases are very different. Even in the absence of RPGN, this recommendation worries rheumatologists. It is clear that more disease-specific studies are needed to formulate recommendations with high-level evidence for the treatment of IgAVN [14].

In systemic vasculitis, it is very important for clinicians to objectively determine disease- and treatment-related damage. There are no studies in the literature that have investigated disease/treatment-related damage in adult patients with IgAVN. However, Gazel U et al. published a study on the assessment of damage in patients with IgAV in 2020. In that study, the VDI score was used to perform a damage assessment; in total, 24.7% of the patients had at least one damage item, and the damage was related to the disease itself rather than the treatment [37]. In this study, the VDI was also used to perform a disease/treatment-related damage assessment. A total of 22% of the patients had at

least one damage item. The total glucocorticoid exposure was significantly higher in the high-damage score group than in the no-damage group. However, high damage scores were more related to the disease than to the treatment (64% vs. 36%).

In previous reports of adult IgAVN cohorts, serious infection rates have been reported to be between 2% and 4% [16,22,23]. In this study, during the follow-up period, 16% of our patients developed infections that required hospitalization. There was no difference between patients with and without serious infections in terms of the total glucocorticoid exposure and the glucocorticoid-tapering agents used. However, patients who developed serious infections were significantly older than those who did not, and the rate of AKI at presentation was significantly higher in this group. It is known that AKI creates an immunosuppressive status, and infections are important causes of mortality during the recovery period in patients with an AKI [38,39]. In a study published in 2016, Hong S et al. showed that the mortality was higher in patients with late-onset IgAV compared with early-onset patients and that infections were an important cause of mortality [40]. The higher rate of serious infections in this study compared to previous studies may be explained by the more frequent use of immunosuppressives and the more effective doses. Literature data on this issue are very limited and more detailed studies are needed. In previous studies, the relapse rate in patients with IgAVN has been reported to vary between 13% and 22.6% [23,33,40]. In this study, the relapse rate was 6%. Similarly to remission, a standardized definition for relapse has not been established to date. Differences in the definition of relapse and the treatments administered may explain the variable relapse rates. In our cohort, one patient died from sepsis and another patient died from a heart attack. The patient who died from sepsis was not in remission and was receiving renal replacement therapy. In the cohort analysis published by Pillebout E et al. in 2002, the mortality rate was 26% after 14.8 years of follow-up. This was a high rate, and the most common cause of mortality was cancer [17]. Subsequently, Coppo R et al. reported a mortality rate of 5.1% in a cohort with a follow-up of 5.5 years in 2006; Oh HJ et al. reported a rate of 2.2% in a cohort with a follow-up of 5.2 years in 2012; and Guan Y et al. reported a rate of 7.4% in a cohort with a follow-up of 8.5 years in 2023 [19,41,42]. The most common causes of death were cancer/cerebrovascular attack, unknown causes, and infections, respectively. It was striking that cancer was the leading cause of mortality and that disease-related complications were in the background. It is clear that more comprehensive studies are needed to determine the factors associated with mortality in patients with IgAVN.

Our study has some limitations. Only 55% of the patients included in the study had a renal biopsy, which may have influenced the clinicians' treatment preferences or the histopathological findings that affected the prognosis. The cohort consisted of a relatively small number of patients, resulting in wide confidence intervals for the parameters found to be significant in the regression analyses. Finally, there was no control group for the treatment groups.

5. Conclusions

These results suggest that contrary to popular belief, the renal prognosis of adults with IgVAN is not poor if they receive effective immunosuppressive therapy. The presence of NRP is associated with low remission rates, and it has predictive value for unfavorable outcomes. Patients with NRP should be followed-up more closely and treated more stringently. Effective immunosuppressive treatment and close follow-up can achieve high remission rates and significantly reduce the risk of ESRD in adults with IgAVN, but immunosuppressive therapy may also carry a high risk of infection, particularly in the elderly. It is clear that further prospective controlled trials are needed for the rational

management of adult patients with IgAVN. Future research should focus on the treatment of different subgroups (for the elderly, in cases of nephrotic disease, etc.).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/diagnostics15080957/s1, Table S1: Histopathological features of the patients. Dataset S1: Dataset form.

Author Contributions: Conceptualization: F.Y. and M.E.K.; methodology: F.Y. and B.İ.; formal analysis: Y.Ç.; investigation: F.Y.; resources: F.Y.; data curation: F.Y., Y.Ç., K.K., G.A., D.S.Ö., B.K., G.G.Ö. and R.D.; writing—original draft preparation: F.Y.; writing—review and editing: C.B.; supervision: C.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved in 9 January 2022 by the ethics committee (Decision number: KAEK/2022.11.361) of Başakşehir Çam and Sakura City Hospital, İstanbul, Turkey.

Informed Consent Statement: Informed consent was obtained from all the subjects involved in this study.

Data Availability Statement: The data can be provided by the authors upon request, with the removal of identifiable information and the anonymization of dates.

Conflicts of Interest: The authors declare no conflicts of interest.

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diagnostics

MDPI

Case Report

Hepatic Vascular Involvement in Adenosine Deaminase 2 Deficiency (DADA2): Case Reports and Literature Review †

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Abstract

Background and Clinical Significance: Deficiency of Adenosine Deaminase 2 (DADA2) is a rare monogenic vasculopathy characterised by systemic inflammatory and immunodeficiency features. Although neurological and haematological manifestations are well-documented, hepatic vascular involvement remains underappreciated. This report aims to describe the clinical and imaging characteristics of hepatic vascular involvement in a patient with DADA2 and to illustrate the evolution of hepatic lesions during long-term Etanercept therapy. In addition, we provide a synthesis of the available evidence on hepatic manifestations in DADA2, emphasising vascular pathology, clinical presentation, and therapeutic implications. **Case Presentation:** We describe a girl with early-onset DADA2 presenting with recurrent systemic inflammation, hypogammaglobulinaemia, vasculopathy, and two childhood strokes, followed by the development of multiple FNH-like hepatic nodules on CEUS and MRI with persistently elevated GGT. Genetic testing confirmed biallelic ADA2 mutations, and treatment with Etanercept led to sustained clinical stabilisation and marked regression of liver lesions over a nine-year follow-up period. Her older sister, carrying the same mutations, showed a milder phenotype without hepatic involvement but experienced a mesenteric vascular event. **Conclusions**: Large regenerative nodules with an FNH-like appearance on CEUS or MRI have not been previously reported in this setting. In our patient, Etanercept therapy produced a favourable hepatic response, reflected by a significant reduction in both the number and size of the lesions. Our case contributes to the understanding of liver disease in DADA2 and the influence of imaging and treatment on the hepatic manifestations of the condition.

Keywords: deficiency of adenosine deaminase 2; hepatic vascular involvement; nodular regenerative hyperplasia; FNH-like lesions; portal hypertension; vasculitis; immunodeficiency

1. Introduction

Deficiency of Adenosine Deaminase 2 (DADA2) is a monogenic autoinflammatory and immunodeficiency disorder first described in 2014 [1]. Caused by biallelic mutations in the

ADA2 gene (*CECR1*), DADA2 is characterised by systemic vasculopathy, recurrent fever, immunodeficiency, cytopenias, and variable organ involvement [1]. While neurological, haematological, and rheumatological manifestations have been extensively reported, hepatic involvement remains less well-characterised [2,3]. Nevertheless, emerging evidence suggests that hepatic vascular manifestations—including nodular regenerative hyperplasia, hepatoportal sclerosis, portal hypertension, and Budd–Chiari syndrome [4,5]—are an underrecognized but significant component of the DADA2 phenotype.

Meyts and Aksentijevich (2018) [2] and Lee et al. (2022) [3] provided comprehensive reviews of the clinical spectrum of DADA2, highlighting multi-organ vasculopathy but only briefly mentioning hepatic manifestations. More systematic phenotypic surveys, such as those by Barron et al. (2021) [4] and Maccora et al. (2023) [5], have explicitly documented hepatic involvement, reporting hepatomegaly, elevated liver enzymes, and biopsy findings of vascular pathology.

The vasculopathy associated with this rare monogenic disorder primarily affects small- and medium-sized arteries. Biallelic loss-of-function mutations in the ADA2 gene cause immune dysregulation, leading to a skewed macrophage polarisation towards a pro-inflammatory M1 phenotype, endothelial dysfunction, and increased TNF-α production. This results in inflammation of the vessel walls, necrosis, and subsequent vascular occlusion or aneurysm formation [2,3].

Histological data from cohorts and case series reveal a recurring pattern of vascular injury in the liver (compromised endothelial integrity, endothelial cellular activation and inflammation) [1]. Barron et al. (2021) [4] reported that 12% of patients developed portal hypertension, with biopsy findings including nodular regenerative hyperplasia (NRH), hepatoportal sclerosis, and portal vasculopathy. Springer et al. (2018) [6] similarly identified NRH as a key lesion, implicating small-vessel injury as a central pathogenic mechanism. Zhou et al. (2014) [1] included patients with liver biopsy evidence of vascular inflammation in their seminal description of DADA2, providing early evidence of hepatic involvement.

Nodular regenerative hyperplasia (NRH) denotes a diffuse transformation of the hepatic parenchyma into multiple small regenerative nodules, characterised by the absence of fibrosis. It involves the entire liver and can lead to non-cirrhotic portal hypertension. This condition probably stems from intrahepatic microvascular injury and hypoperfusion, which cause hepatocyte injury and the formation of regenerative nodules. Histologically, it is characterised by numerous small regenerative nodules separated by compressed hepatic plates, with no fibrous septa [7,8].

In NRH, regenerative nodules typically measure 1–3 mm in diameter, although larger lesions—up to 1–2 cm—may also occur. These have been referred to as large regenerative nodules or multiacinar regenerative nodules, defined histologically as regenerative nodules containing more than one portal tract [9,10]. Some of these larger nodules exhibit imaging characteristics similar to focal nodular hyperplasia (FNH) and are therefore described as FNH-like lesions [11]. According to current literature, there is no clear consensus on whether these lesions represent a variant of large regenerative nodules (LRN) or a distinct pathological entity [11]. FNH-like lesions have been described in children in association with a variety of liver conditions that alter hepatic perfusion and increase arterial inflow, including Budd–Chiari syndrome [11], congestive hepatopathy, Fontan-associated liver disease [12], sinusoidal obstruction syndrome after chemotherapy or hematopoietic stem cell transplantation [13], autoimmune hepatitis [11,14], cavernous transformation of the portal vein, hereditary hemorrhagic telangiectasia, and common variable immunodeficiency [11].

To date, no cases of focal nodular hyperplasia-like (FNH-like) hepatic lesions have been explicitly reported in patients with DADA2.

Mechanistically, hepatic manifestations seem to reflect the systemic vasculopathy linked to DADA2. Endothelial dysfunction, TNF-driven vascular inflammation, and defective perivascular repair mechanisms have been described (Lee et al. 2022) [3]. The liver, with its dual blood supply and dense sinusoidal network, may be particularly vulnerable to microvascular injury, leading to reactive or regenerative lesions and non-cirrhotic portal hypertension.

Literature evidence is extremely sparse on Budd–Chiari syndrome (BCS) associated with DADA2, suggesting it is a rare or underreported condition.

Clinically, hepatic involvement in DADA2 ranges from asymptomatic enzyme abnormalities to overt complications of non-cirrhotic portal hypertension and end-stage liver disease. However, elevated liver enzymes and hepatosplenomegaly are the most common clinical signs of liver-related disease [1,15,16]. Barron et al. (2021) [4] observed that liver fibrosis was detectable by transient elastography in approximately 25% of cases, while 7 of 56 patients developed portal hypertension with clinical consequences such as splenomegaly and varices. Colangelo et al. (2023) [17] described a striking case of Budd–Chiari syndrome, demonstrating that hepatic venous outflow obstruction can also occur. Case series from Iran (Ashari et al. 2023) [18] and other international cohorts have reported hepatomegaly, elevated transaminases, and hepatosplenomegaly in subsets of patients.

The diagnosis of NRH is often difficult because its histopathologic features may be interpreted variably, and most patients lack specific symptoms or laboratory abnormalities [14]. It may, however, be accompanied by slightly elevated ALP and gamma-glutamyltransferase levels, with a gradual increase over the years leading to chronic cholestasis, non-cirrhotic portal hypertension, or cirrhosis [11].

This article aims to synthesise current evidence on hepatic vascular involvement in DADA2, delineate key patterns, and discuss clinical implications, while adding a novel observation to the hepatic phenotype of the disease: large regenerative nodules of focal nodular hyperplasia appearance (FNH-like) in one patient and a favourable evolution of these lesions under anti-TNF therapy.

2. Case Presentation

2.1. Case 1

The first case involved a girl born to non-consanguineous parents and with no significant pathology in the family.

At 1.66 years of age, she suddenly presented with a high fever, a nonspecific maculopapular rash, arthralgia, and myalgia, accompanied by elevated levels of acute phase reactants and a rapid response to steroids. One year later, these symptoms recurred. A skin biopsy revealed interstitial granulomatous dermatitis associated with vasculopathy.

At the age of 3, she began experiencing recurrent cranial nerve palsies and livedo reticularis, followed by two stroke events at age 4—one ischemic and the other hemorrhagic. Magnetic resonance angiography revealed no signs of cerebral vasculitis, and a brain biopsy performed during the surgical procedure for the hemorrhagic stroke showed only extravasation of erythrocytes and fibrin deposition around small vessels without significant inflammation. The antibody profile was negative, including antinuclear antibodies, antineutrophil cytoplasmic antibodies, autoantibodies associated with autoimmune hepatitis, and antiphospholipid antibodies. Additionally, clotting tests were within the normal range.

Hypogammaglobulinemia with global immunoglobulin deficiency was present from the onset of the disease and persisted over time. She could not be classified as having common variable immunodeficiency (CVID) because her total serum IgG levels were not

consistently below 500 mg/dL. As part of a research study, she was also found to have a complete C4B deficiency.

At the age of 5, she developed moderate thrombocytopenia that persisted for the following 3 years.

At 5.5 years of age, ultrasound revealed multiple diffuse hyperechoic hepatic lesions measuring 1–2 cm and mild splenomegaly. On contrast-enhanced ultrasound (CEUS), the lesions exhibited arterial-phase hyperenhancement with centrifugal filling and became isoenhancing during the portal and late phases (Figure 1). These features were interpreted as consistent with large regenerative nodules of focal nodular hyperplasia-like appearance (FNH-like). At this stage, serum GGT levels were elevated and remained persistently high, peaking at 120 U/L. Serum transaminases (AST and ALT) were only slightly elevated, with ALT sometimes remaining within the normal range.

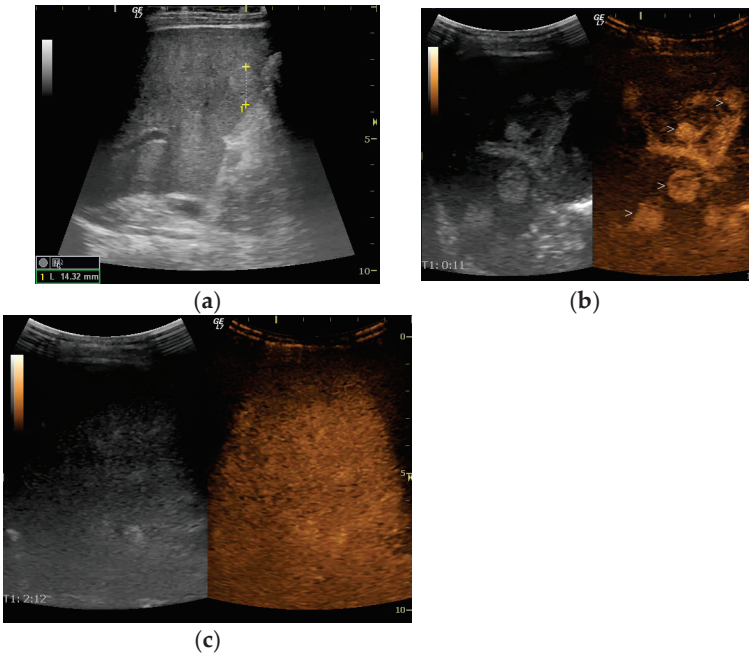

Figure 1. Initial ultrasound (US) of the liver before treatment. (**a**) Grey-scale US showing a hyperechoic nodule in the right lobe; (**b**) Contrast-enhanced ultrasound (CEUS). Arterial phase. Multiple round hyperenhancing nodules in the right lobe (marked with the symbol '>' on the image); (**c**) CEUS in parenchymal phase. The nodules are isoenhanced and no longer detectable.

MRI showed multiple hyperenhancing focal lesions visible in the arterial phase, disseminated throughout the entire hepatic parenchyma; most were isointense on T2w and native T1w images, iso- or hyperintense in the late phase, with no washout. The lesions were relatively similar in size (10–25 mm) and imaging features (Figure 2).

A liver biopsy was not performed at that time due to the increased risk of bleeding given our patient's thrombocytopenia, the absence of severe liver damage or other risk factors for primary liver malignancies and typical radiologic features of FNH-like nodules.

During the first two years of her condition, only high doses of corticosteroids were effective in controlling the disease manifestations. Treatments such as methotrexate, azathioprine, cyclosporine, and cyclophosphamide proved ineffective. In contrast, mycophenolate mofetil (MMF) combined with high monthly doses of intravenous immunoglobulin led to prompt and sustained improvements in clinical symptoms and acute-phase reactants, allowing for a gradual reduction in steroid dosage. With MMF treatment, no recurrences were observed; however, the FNH-like lesions showed slow progression.

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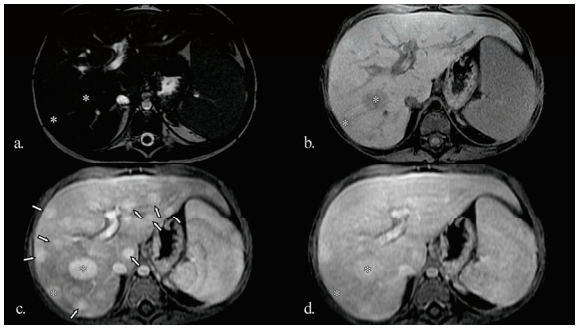
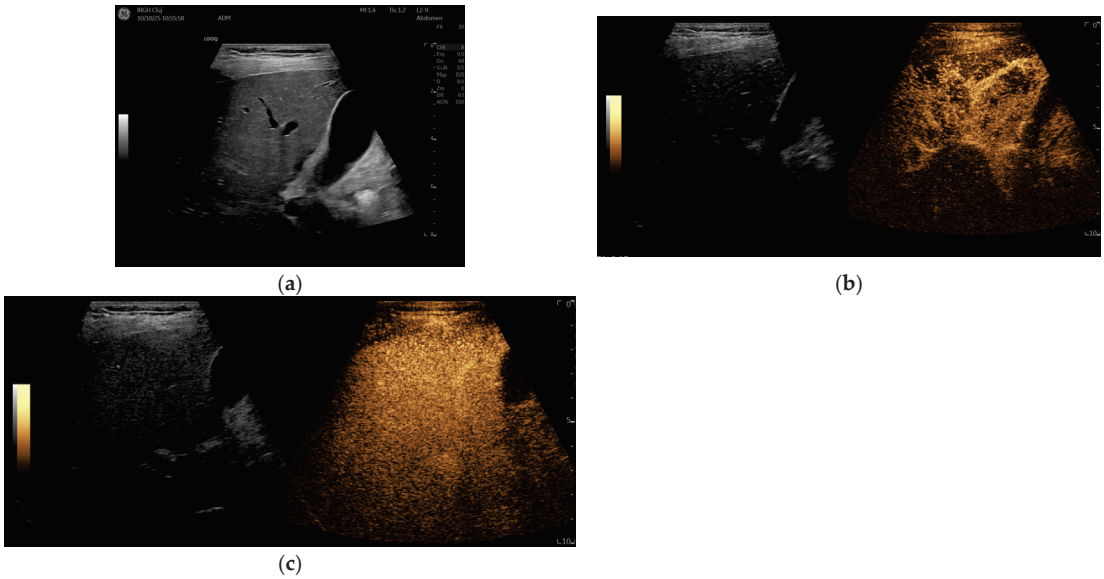


Figure 2. Initial MRI examination of the liver. (**a**) Native T2-weighted; (**b**) Native fat-saturated T1-weighted; Gd-enhanced fat-saturated T1-weighted in the arterial (**c**) and late (**d**) phases. Multiple hyperenhancing focal lesions are visible in the arterial phase (arrows, asterisks), most are isointense on T2w and native T1w images, iso- or hyperintense in the late phase, with no washout. The lesions are relatively similar in size (10 to 25 mm) and imaging features. Two of the lesions (asterisks) are slightly hyperintense on T2w and hypointense on native T1w, while still enhancing after Gd injection.

At the age of 8, genetic testing revealed two homozygous pathogenic mutations in the ADA2 gene (*p.G326R* and *p.V458D*). Plasma ADA2 enzyme activity was notably low, measured at 3 mU/mL/h. The patient was commenced on Etanercept, which effectively controlled systemic inflammation, thrombocytopenia, and vascular symptoms. Over the following 9 years, no neurological events occurred. She is hemiparetic due to the previous stroke, and some disease features persist, including hypogammaglobulinemia and livedo reticularis.

Remarkably, under anti-TNF treatment, there has been a significant improvement in liver lesions, as evidenced by reductions in both their size and number on repeated liver imaging (Figures 3 and 4), along with normalisation of GGT levels in subsequent years. Improvement was evident after just one year of treatment and continued to progress until the patient reached 17 years of age. Splenomegaly persisted without evidence of portal hypertension, and liver stiffness on elastography decreased slightly over time (6.1 kPa before Etanercept and 5.6 kPa after treatment).



(**a**) (**b**)

(**c**)

Figure 3. Ultrasound (US) evaluation after 9 years of Etanercept treatment. (**a**) B Mode US shows no evident liver nodules; (**b**) Contrast-enhanced ultrasound (CEUS) arterial phase shows an inhomogeneous pseudonodular enhancement of the right lobe; (**c**) CEUS in parenchymal phase—no hypoenhanced nodules are seen.

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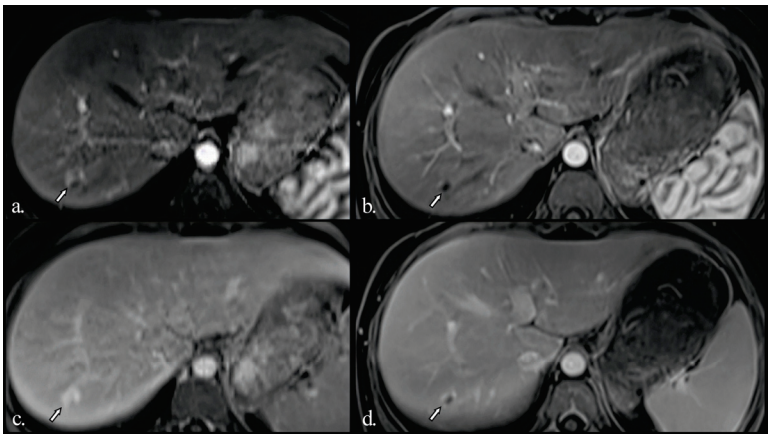

Figure 4. Subsequent MRI examinations after 5 years (**a**,**c**) and 9 years (**b**,**d**) of Etanercept treatment since the initial assessment. Gd-enhanced fat-saturated T1-weighted images in the arterial (**a**,**b**) and late (**c**,**d**) phases. Only one lesion (arrow) remains visible, showing hyperenhancement in the periphery and a central scar with progressive, incomplete filling in the late phases. The lesion has shrunk in the last examination.

The timeline (Figure 5) shows the progression of disease manifestations, liver involvement, and treatment response in patient 1.

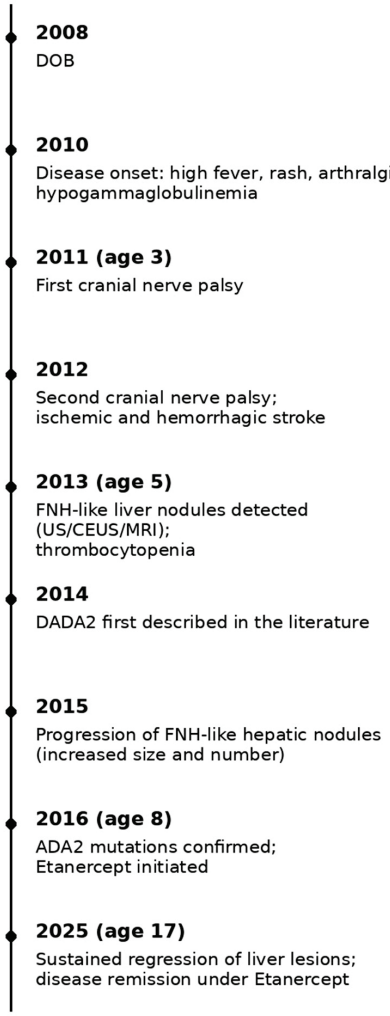

Figure 5. Concise timeline of disease progression, liver involvement, and treatment response in Patient 1 with DADA2.

2.2. Case 2

The older sister of the patient described above, who shares the same homozygous pathogenic mutations in the ADA2 gene, exhibited a later onset of clinical symptoms (at 6.5 years old), including persistent fever, myalgia, livedo reticularis, vascular purpura, painful subcutaneous nodules, systemic arterial hypertension, recurrent abdominal pain, and a highly persistent inflammatory response. In her case, the immunodeficiency phenotype appeared milder, with slightly reduced IgM levels and normal IgG and IgA levels. She did not show any hepatic vascular involvement of the disease, nor did she develop neurological symptoms. However, at 7.5 years of age, she experienced a massive intestinal bleed, preceded by acute abdominal pain, considered a vascular complication affecting the mesenteric vessels. The source of the bleeding was not identified on endoscopic and imaging studies. At the last assessment, during ongoing Etanercept treatment, patient 2 was in persistent clinical remission with no new complications.

3. Discussion

The literature indicates that hepatic vascular involvement is a significant yet often overlooked aspect of DADA2. While neurological and haematological symptoms are predominant, up to one-third of patients may exhibit biochemical, radiological, or histopathological signs of liver disease. The most consistent observation across reports is nodular regenerative hyperplasia, indicating noncirrhotic portal hypertension due to small vessel vasculopathy. Cases of Budd–Chiari syndrome highlight that hepatic venous outflow obstruction can also occur, extending the spectrum of hepatic features.

No prior reports have documented focal nodular hyperplasia-like (FNH-like) lesions in DADA2, highlighting the novelty of this observation within the disease's hepatic spectrum.

The underestimation of liver involvement probably arises from two factors: firstly, subtle or subclinical hepatic disease can be missed without systematic screening; secondly, the multisystem impact of DADA2 may overshadow hepatic symptoms in clinical practice. Nevertheless, the clinical significance is considerable. Portal hypertension carries risks such as variceal bleeding, hypersplenism, and reduced quality of life. Moreover, progressive liver disease may persist despite TNF inhibition, raising questions about the timing of treatment and the possible role of hematopoietic stem cell transplantation in refractory cases.

Comparative analysis with other systemic vasculopathies shows that hepatic involvement in DADA2 is unique in its frequent presentation as non-cirrhotic portal hypertension, rather than typical inflammatory hepatitis. This emphasises the vascular, rather than parenchymal, nature of hepatic injury in DADA2.

Nodular regenerative hyperplasia of the liver occurs in patients with the immunodeficiency phenotype of DADA2, as well as in those with hypogammaglobulinaemia disorders, particularly common variable immunodeficiency (CVID). NRH is the characteristic hepatic lesion in CVID, and relevant parallels with DADA2 have been drawn regarding this liver complication [8,14]. This relationship is also observed in our siblings. Only the one with significant hypogammaglobulinemia developed large regenerative nodules of focal nodular hyperplasia-like appearance (FNH-like), even though they share the same homozygous pathogenic mutations in the ADA2 gene.

Structural changes related to NRH can be detected on imaging studies such as ultrasound, CT or MRI; however, the radiologic findings are often nonspecific, and a definitive diagnosis typically requires clinical correlation and histopathologic confirmation [7,19,20]. FNH-like lesions, in contrast, exhibit more distinctive and characteristic imaging features than smaller regenerative nodules, which sometimes allow a confident radiologic diagnosis when interpreted in the proper clinical context [11,13].

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Grey-scale ultrasound detection of NRH is challenging, particularly for an inexperienced sonographer, because nodules are usually small and commonly isoechoic, and they affect the entire hepatic parenchyma diffusely. Moreover, in our patient, many larger nodules were identified with CEUS, highlighting its additional value in evaluating such cases.

Contrast-enhanced ultrasound has been sporadically explored for evaluating NRH. Evidence is limited to isolated case reports [21]. Due to the diffuse and micronodular nature of NRH, the technique lacks sensitivity and specificity. CEUS may occasionally reveal non-specific or misleading enhancement patterns, so its findings should always be interpreted in conjunction with clinical data, cross-sectional imaging, and histopathological confirmation. Currently, no validated CEUS criteria are available for the identification of NRH.

Larger hepatic lesions, such as those resembling focal nodular hyperplasia (FNH), can be more accurately characterised using CEUS. These lesions typically exhibit intense centrifugal arterial-phase enhancement, followed by isoechoic enhancement during the portal venous and delayed phases [22]. The development of advanced CEUS techniques, together with higher-resolution contrast agents and emerging microbubble or molecular contrast media, is expected to improve the detection and characterisation of microvascular alterations seen in nodular regenerative hyperplasia (NRH).

In our patient, CEUS provided additional value in characterising the hepatic lesions. The presence of larger, hyperenhancing nodules with centrifugal arterial-phase filling and isoenhancement in the portal and late phases was consistent with FNH-like regenerative nodules. Depending on the clinical context, however, malignant lesions should be considered in the differential diagnosis.

Magnetic resonance imaging (MRI) supports the assessment of liver nodules. While more sensitive than ultrasound in detecting subtle parenchymal heterogeneity, MRI findings in NRH are often nonspecific, typically showing diffuse reticular or micronodular enhancement without a dominant mass or fibrous septa. These features help differentiate NRH from cirrhosis and focal nodular hyperplasia; however, histological confirmation remains crucial for an accurate diagnosis [7,20].

Conversely, larger or macro regenerative nodules (LRN) or FNH-like lesions show arterial hyperenhancement but no late-phase washout. They are typically similar in native and post-contrast features to FNH nodules, which are mostly found in adult women. Still, they are usually multiple, relatively homogeneous in size, and seem to have arterial flow overexpression as the leading cause. Usual MRI features of these nodules include: iso- to hypointensity on T2-weighted (T2w) images, iso- to hyperintensity natively on T1w images, no diffusion restriction, homogenous or "spoke-wheel" enhancement in the Gd-enhanced arterial phase, and no wash-out in the venous and late phase. A central scar with arterial hypoenhancement and late-phase enhancement can also be common [11,23]. The use of hepato-biliary contrast (i.e., Gadoxetic acid) will show either isoenhancement or hyperenhancement in the hepato-biliary phase, which can help distinguish from hepatocellular carcinoma or liver adenoma (where some wash-out is to be expected in the hepato-biliary phase) [11,13,24,25].

Considering current evidence, the most recent consensus recommends abdominal ultrasonography with Doppler as the primary imaging modality for evaluating the liver and spleen in DADA2. This approach reflects recognition that patients may develop noncirrhotic portal hypertension and vascular or inflammatory hepatic lesions, including focal nodular hyperplasia and nodular regenerative hyperplasia [26].

An MRI was also performed in our patient to provide a more detailed characterisation of the hepatic nodules. Multiple hyperenhancing focal lesions were identified during the arterial phase; most appeared isointense on T2-weighted and native T1-weighted images

and iso- to hyperintense in the late phase, without evidence of washout. The nodules were relatively uniform in size and imaging appearance. Typical native and post-contrast features consistent with FNH were present in most lesions, except for two nodules that were T1 hypointense and T2 hyperintense. This finding suggests some heterogeneity among large regenerative nodules that do not always conform to classical imaging patterns. Given that these nodules also regressed during follow-up under therapy, they are unlikely to represent a different pathology. The native T1 hypointensity and T2 hyperintensity most likely reflect increased water content within the lesions, without a specific underlying cause.

Although suggested by magnetic resonance imaging or ultrasound scan, diagnosis must be histologically confirmed [14]. Being an invasive procedure with an increased risk of bleeding in the context of our patient's thrombocytopenia and in the absence of severe liver damage, the liver biopsy was withheld in the first year after the diagnosis. After TNF inhibitors demonstrated effectiveness in reducing the number of nodules and their size, the procedure was no longer considered beneficial for the patient.

In the absence of histologic confirmation, alternative diagnoses were considered. Malignant hepatic nodules may complicate conditions associated with liver fibrosis (such as Budd–Chiari syndrome), but they are rare in autoimmune-related liver disease. Other benign entities, including hepatic hemangiomatosis or biliary hamartomas, were unlikely, as they would typically exhibit markedly hyperintense T2-weighted signals. The longitudinal evolution under Etanercept therapy, however, provides more substantial support for DADA2-related regenerative nodules.

Available data suggest that anti-TNF agents (Etanercept, Adalimumab, or Infliximab) significantly improve survival and overall disease control in DADA2, although their effect on hepatic involvement remains inconsistent. Data from the National Human Genome Research Institute shows that TNF inhibition decreases systemic inflammation and improves endothelial integrity in blood vessels, and may even reverse endothelial damage at the clinical, molecular, and histological levels [27].

While anti-TNF therapy has transformed the prognosis of DADA2 patients, its impact on hepatic manifestations remains uncertain. Some reports suggest stabilisation of liver disease with anti-TNF therapy, while others document progression of portal hypertension despite systemic disease control (Table 1) [4,6,28]. This raises the possibility that hepatic injury, once established, may be irreversible or only partially responsive to treatment.

Table 1. Anti-TNF therapy and hepatic outcomes in DADA2.

Study/ Source	Year	No. of Patients	Hepatic Manifestation(s)	Effect of Anti-TNF Therapy	Comments/Notes
Barron et al. [4]	2021	60	Portal hypertension, nodular regenerative hyperplasia, increased liver stiffness	Mixed outcomes: some stabilisation, others progression despite systemic disease control	Liver stiffness improved in a few cases; portal hypertension persisted or worsened in others
Springer et al. [6]	2018	2 adult siblings	NRH, end-stage liver disease	One patient improved systemically; another developed irreversible hepatic failure	Suggests established liver damage may be refractory to TNF inhibition
Ombrello et al. [28]	2015	24 (NIH cohort)	Hepatomegaly, vascular involvement	Reported stabilisation in some hepatic findings; no detailed long-term data	Early report supporting TNF blockade as mainstay, without liver-specific endpoints

Table 1. *Cont.*

Study/ Source	Year	No. of Patients	Hepatic Manifestation(s)	Effect of Anti-TNF Therapy	Comments/Notes
Lee et al. [26]	2023	Consensus/ review	Multisystem vasculopathy (hepatic manifestations included)	Effective for vasculitic and hematologic features; hepatic response uncertain	Highlights lack of controlled data on hepatic disease progression
Deuitch et al. [27]	2022	Mechanistic study	endothelial cell model	TNF inhibition restores endothelial function in vitro	Supports biological plausibility, but no clinical hepatic outcomes reported

One reported DADA2 patient exhibited clinical symptoms from early childhood, including primary vasculopathy, hypogammaglobulinaemia, a history of stroke, and liver disease [6]. He was diagnosed in his 40s and began Etanercept, which proved effective in controlling the disease activity. However, he died 18 months after his initial DADA2 diagnosis and one year after starting Etanercept, due to complications related to end-stage liver disease (nodular regenerative hyperplasia of the liver with portal hypertension and varices). In this case, the NHGRI group observed intact endothelial layers in postmortem brain and lung biopsies, suggesting that anti-TNF therapy was effective in those vascular territories. However, it does not demonstrate a definitive clinical effect on portal hypertension [27]. Overall, this case demonstrates the importance of early diagnosis and treatment to minimise organ damage and prevent life-threatening complications in patients with DADA2.

While a recent consensus on the evaluation and management of DADA2 patients emphasises the benefit of anti-TNF therapy for vascular/neurologic disease, the authors state that evidence for efficacy against non-vascular manifestations (including hepatic disease) is more limited [26].

In our patient, the FNH-like lesions showed an early positive response after starting Etanercept, with a noticeable decrease in both the size and number of nodules. This improvement was maintained, as imaging performed nine years into continuous anti-TNF therapy showed substantial regression of the hepatic nodules. To our knowledge, this is the first documented case of FNH-like liver lesions in DADA2 that show long-term improvement with anti-TNF treatment.

Available data—mostly from small cohorts and case reports—underscore the need for prospective, liver-focused monitoring of DADA2 patients receiving TNF inhibitors.

4. Conclusions

Hepatic vascular involvement represents a clinically significant yet frequently underrecognised component of the DADA2 phenotype. Diffuse nodular liver infiltration—consistently reported as regenerative nodular hyperplasia—has been described in some patients with the immunodeficiency phenotype of DADA2, underscoring the need for systematic liver evaluation. NRH-type involvement should be considered in individuals with abnormal liver function tests and features of portal hypertension, with biopsy required for confirmation.

Large regenerative nodules with an FNH-like appearance on CEUS or MRI have not previously been documented in this setting. In our patient, Etanercept therapy produced a favourable hepatic response, reflected by a significant reduction in both the number and size of the lesions. Our case contributes to the understanding of liver disease in DADA2 and the influence of imaging and treatment on the hepatic manifestations of the condition.

https://doi.org/10.3390/diagnostics16020189

Author Contributions: M.S. developed the manuscript and contributed to the clinical evaluation, diagnostic work-up, and treatment management of the patients. Z.S. provided US and CEUS monitoring of our patient and offered expertise with imaging considerations. L.D. contributed to long-term follow-up and took over patient care after the transition to adult services. M.A.S. and O.F. contributed to the acquisition and analysis of the magnetic resonance images. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable, being a descriptive, not an interventional case report.

Informed Consent Statement: Written informed consent has been obtained from the patients for publication of this paper.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Acknowledgments: We thank all contributors involved in the diagnosis, imaging evaluation, and therapeutic management of these patients. This article is a revised and expanded version of a conference paper [29], which was presented as a poster at the 23rd Paediatric Rheumatology European Society Congress, Genoa, Italy, 28 September–1 October 2016.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

DADA2	Deficiency of adenosine deaminase 2
FNH	Focal nodular hyperplasia
CEUS	Contrast-enhanced ultrasound
US	Ultrasound
MRI	Magnetic resonance imaging
TNF	Tumour Necrosis Factor
GGT	Gamma-glutamyl transpeptidase
NRH	Nodular regenerative hyperplasia

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ISBN 978-3-7258-7501-6