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Granulomatous Gastritis of Uncertain Aetiology in a Patient with Recurrent Serositis and Polyarthralgia

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Abstract

Granulomatous gastritis is a rare histopathological pattern of gastric mucosal inflammation associated with a broad spectrum of infectious, inflammatory, systemic, and medication-related conditions. We report the case of a 55-year-old female with a history of recurrent pleuritis, pericarditis, and polyarthralgia, initially accompanied by a right hilar soft tissue mass that regressed following corticosteroid therapy. Despite multiple immunosuppressive treatments and subsequent anakinra and canakinumab treatment, her symptoms persisted, and the underlying systemic disorder remained unresolved. During subsequent gastroduodenoscopy, gastric biopsies revealed moderate chronic, focally active gastritis with multifocal non-necrotizing granulomas in the antral lamina propria. The granulomas consisted of CD68-positive histiocytes, while investigations for infectious agents, including mycobacteria and fungi, yielded negative results. *Helicobacter pylori* immunohistochemistry was also negative in the antral specimen, although a separate corpus biopsy demonstrated *Helicobacter pylori*-associated gastritis. In view of the patient's systemic manifestations and histopathological findings, several potential aetiological factors were considered, including *Helicobacter pylori* infection and medication-induced granulomatous inflammation. However, systemic conditions such as sarcoidosis and Crohn's disease also warrant consideration and further exclusion. None of these potential causes could be definitively established based on the available clinical and histopathological findings. This case highlights the diagnostic complexity of granulomatous gastritis and emphasizes the importance of integrating histopathological findings with clinical, radiological, microbiological, and serological data. Granulomas are a histological finding rather than a definitive diagnosis; identifying their underlying cause requires a multidisciplinary approach, particularly when gastric pathology occurs in the setting of unexplained systemic inflammation.

Keywords: granulomatous gastritis; *Helicobacter pylori*; sarcoidosis; CD68

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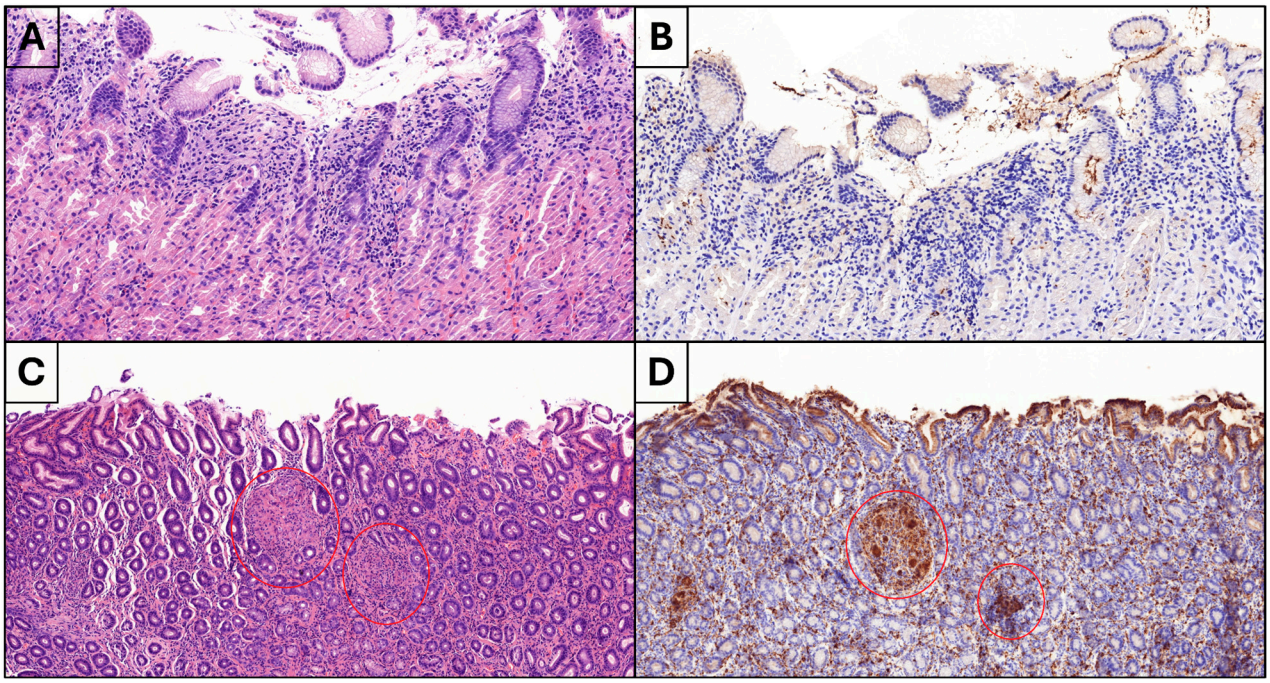


Figure 1. A 55-year-old woman presented with polyarthralgia and recurrent pleuritis and pericarditis in 2021. Chest CT revealed pleural and pericardial effusions and a right hilar soft tissue mass, which had not been biopsied and later became undetectable following methylprednisolone therapy. Despite subsequent treatment with methotrexate, leflunomide, azathioprine, and hydroxychloroquine, her joint symptoms persisted, accompanied by hair and weight loss. Systemic lupus erythematosus was excluded based on clinical and immunoserological findings (anti-ds-DNA antibody: 7.2 U/mL [ref: 0–20 U/mL]), while the differential diagnosis included adult-onset Still's disease and autoinflammatory serositis. Anakinra was discontinued after 2 weeks because of severe urticaria and ocular pruritus. Subsequent treatment included low-dose methylprednisolone, etoricoxib, topical methylprednisolone, and colchicine, followed by canakinumab. At follow-up in early 2023, inflammatory markers and pulmonary function were normal, except for eosinophilia (16.3%). Nasal congestion, persistent cough, hyposmia, and dyspnea subsequently developed. The patient continued to experience polyarthralgia and cutaneous pruritus, accompanied by a sensation of subcutaneous nodules. At follow-up in early 2023, inflammatory markers and pulmonary function were within normal limits, apart from peripheral eosinophilia (16.3%). By late 2023, the eosinophil percentage had decreased, and in the most recent laboratory investigations, both the absolute eosinophil count and percentage were within normal limits (0.32 G/L and 5.9%, respectively). IgG and IgA levels were within normal ranges (11.64 and 0.95 g/L, respectively), whereas IgM was slightly decreased (0.53 g/L; reference range: 0.60–3.70 g/L). Serum calcium was normal (2.55 mmol/L). Subsequent gastroduodenoscopy was performed in October 2026 to investigate possible coeliac disease, eosinophilic enteritis, and *Helicobacter pylori* infection, although tissue transglutaminase values were normal (<10 U/mL). At the time of biopsy the patient's medication list included canakinumab, metformin, Mounjaro, nebivolol, amlodipine, telmisartan, spironolactone, rilmenidine, colchicine, pantoprazole, montelukast, azelastin and fluticasone combination nasal spray, and vitamin D3. Endoscopic examination revealed no significant abnormalities, apart from mild biliary reflux. Histological examination of a randomly sampled corpus biopsy showed proton pump inhibitor (PPI)-related changes and severe chronic, superficial, active *Helicobacter pylori*-associated gastritis ((**A**)—HE, 10×), with strong immunohistochemical positivity (3+) ((**B**)—Helicobacter pylori, 10×). The antral specimen demonstrated foveolar hyperplasia, corkscrew-shaped glands, smooth muscle bundles extending into the lamina propria, and an increased lymphoplasmacytic infiltrate with inflammatory activity. *Helicobacter pylori* immunohistochemistry was negative. Additionally, multifocal non-necrotizing granulomas ((**C**)—HE, 20×) composed of CD68-positive histiocytes were identified within the lamina propria ((**D**)—CD68, 20×). No significant tissue eosinophilia was identified, and no infectious agents were detected by mycobacterial immunohistochemistry, Ziehl–Neelsen staining, or periodic acid–Schiff (PAS)–Alcian blue staining. The final

diagnosis included mild reactive changes, moderate chronic, focally active *Helicobacter pylori*-negative antral gastritis without atrophy or intestinal metaplasia, and granulomas. The patient is currently receiving *Helicobacter pylori* eradication therapy, with follow-up clinical evaluation planned after completion of the treatment. Granulomatous gastritis is a rare histopathological pattern of gastric mucosal inflammation rather than a distinct disease entity. It is characterized by chronic inflammation and the presence of organized aggregates of epithelioid histiocytes forming granulomas, which commonly express CD68. Its reported prevalence in gastric biopsies ranges from 0.03% to 0.35%, with the underlying aetiologies varying across patient populations. Common causes include infections, particularly tuberculosis and fungal infections, Crohn's disease, which is more frequently reported in younger men, and sarcoidosis, which has been described more commonly in adult women [1–4]. Accordingly, diagnosis requires comprehensive clinical, endoscopic, radiological, histopathological, microbiological, and serological correlation. When no underlying cause can be identified, the condition may be classified as idiopathic granulomatous gastritis, accounting for up to approximately 25% of reported cases [1,5]. Concurrent *Helicobacter pylori* infection should also be investigated, although its aetiological role in granuloma formation remains controversial. Granulomatous inflammation may occur in a small subset of patients with *Helicobacter pylori*-associated gastritis [3,4]. The differential diagnosis also encompasses foreign-body reactions, common variable immunodeficiency (CVID), reactions associated with adjacent malignancies, Whipple disease, syphilis, granulomatosis with polyangiitis, and medication-associated granulomatous inflammation [1,6,7]. Immune checkpoint inhibitors have been described to cause several patterns of gastric injury, one of which is characterized by lymphoid infiltration, cellular aggregates mixed with neutrophils and eosinophils, mimicking granulomatous gastritis [8]. Furthermore, granulomatous gastritis has been reported in association with non-steroidal anti-inflammatory drugs (NSAIDs), and mycophenolate mofetil [9,10]. The clinical presentation is generally nonspecific and depends largely on the underlying aetiology. Reported symptoms include epigastric pain, nausea, gastroesophageal reflux, vomiting, diarrhea, weight loss, and anemia, while gastric outlet obstruction is an uncommon complication [1,3,4,11–13]. Management is primarily directed at the underlying cause rather than the granulomatous inflammation itself. Treatment may involve immunosuppressive or biological therapies for Crohn's disease, corticosteroids for sarcoidosis, antituberculous therapy for tuberculosis, or *Helicobacter pylori* eradication when indicated. In the present case, the absence of detectable mycobacteria and fungi, negative serological investigations, and the patient's history of prolonged treatment with various immunomodulatory agents complicates the identification of the underlying cause. Furthermore, the initial detection of a right hilar soft tissue mass, which subsequently regressed following corticosteroid therapy, raises the possibility of a systemic granulomatous disorder. Given the history of peripheral eosinophilia, upper and lower respiratory symptoms, serositis, and arthralgia, eosinophilic granulomatosis with polyangiitis (EGPA) was also considered in the differential diagnosis. However, both anti-MPO and anti-PR3 antibodies were negative, and no significant tissue eosinophilia was identified in the gastric biopsies. These findings do not provide histopathological or serological support for EGPA, although the available data are insufficient to definitively exclude this diagnosis. Considering the patient's clinical history, demographic characteristics, and radiological findings, besides *Helicobacter pylori*-associated gastritis, sarcoidosis and medication-associated, more specifically according to literature data NSAID-induced granulomatous inflammation remain important differential diagnoses. However, neither aetiology could be definitively established based on the available evidence. This case underscores the importance of interpreting gastric granulomas in their broader clinical context and highlights that, in patients with unexplained systemic inflammatory manifestations, granulomatous gastritis may provide a valuable diagnostic clue to an underlying systemic or treatment-related process.

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Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and institutional policies, and ethical review and approval were waived because the study included only a single case and used only non-identifiable data.

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Abbreviations

The following abbreviations are used in this manuscript:

CD68	Cluster of differentiation 68
CT	Computed tomography
CVID	Common variable immunodeficiency syndrome
EGPA	Eosinophilic granulomatosis with polyangiitis
HE	Hematoxylin and eosin
IL-1	Interleukin-1
MPO	Myeloperoxidase
NSAIDs	Non-steroidal anti-inflammatory drugs
PAS	Periodic acid-Schiff
PPI	Proton-pump inhibitor
PR3	Proteinase 3
SLE	Systemic lupus erythematosus

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