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Case Report

A Case of Paraneoplastic Anti-TIF1-γ Antibody-Positive Dermatomyositis Presenting with Generalized Edema and Associated with Aortic Aneurysm

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1. Introduction

Dermatomyositis (DM) is a rare autoimmune inflammatory disease characterized by pathognomonic skin findings, often accompanied by myositis beginning with proximal weakness. Limb edema is a rare finding in patients with DM that has been associated with severe disease [1].

Myositis-specific autoantibodies are over 90% specific to the diagnosis of autoimmune myositis and are associated with disease subtypes with characteristic patterns of clinical presentation and prognosis [2]. For example, in some cases, dermatomyositis presents as a paraneoplastic syndrome associated with underlying malignancy. A higher frequency of malignancy has been found in DM patients with anti-NXP-2 or anti-TIF1-γ antibodies than in DM patients without these antibodies [3]. Thus, if a patient is positive for these autoantibodies, it may warrant more extensive serologic and imaging evaluation for malignancy beyond that which is recommended in cases of DM without these myositis-specific antibodies.

While some patterns of phenotypic association with autoantibodies have been established, further efforts are warranted to uncover rare associations. Herein, we describe the case of a female patient with anti-TIF1-γ dermatomyositis who presented with edema of the face, arms, abdomen, and legs.

2. Case Report

A 69-year-old female presented to the dermatology clinic with complaints of an erythematous rash on the forehead, chest (Figure 1) arms, and hips that first appeared three months prior. She was initially treated with doxycycline for suspected Lyme disease by her primary care provider, but Lyme titers were negative. The patient then presented to the emergency room due to facial swelling (Figure 2) and was subsequently referred to dermatology and rheumatology. When she presented to the dermatology clinic, the rash was accompanied by sore, red cuticles; muscle weakness—-including a reported inability to walk upstairs, lower herself into bed, or lift her arms; and edema of the face, arms, abdomen, and legs. The patient also reported widespread soreness, subjective fevers, and occasional trouble swallowing. The patient was taking diphenhydramine at the time of appointment and had previously been treated in the past month with a short prednisone

taper for possible hives, but neither had alleviated her symptoms. At a follow-up visit three weeks later, the patient reported progressive dysphagia and a 12-pound weight gain.

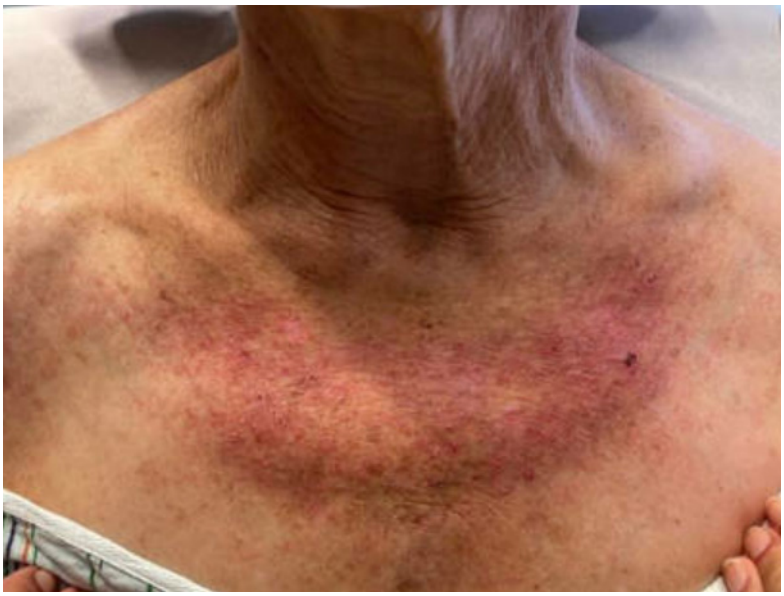

Figure 1. Shawl sign. Red violaceous poikilodermatous plaque with mottled hyperpigmentation and hypopigmentation along with areas of atrophy over the upper chest.

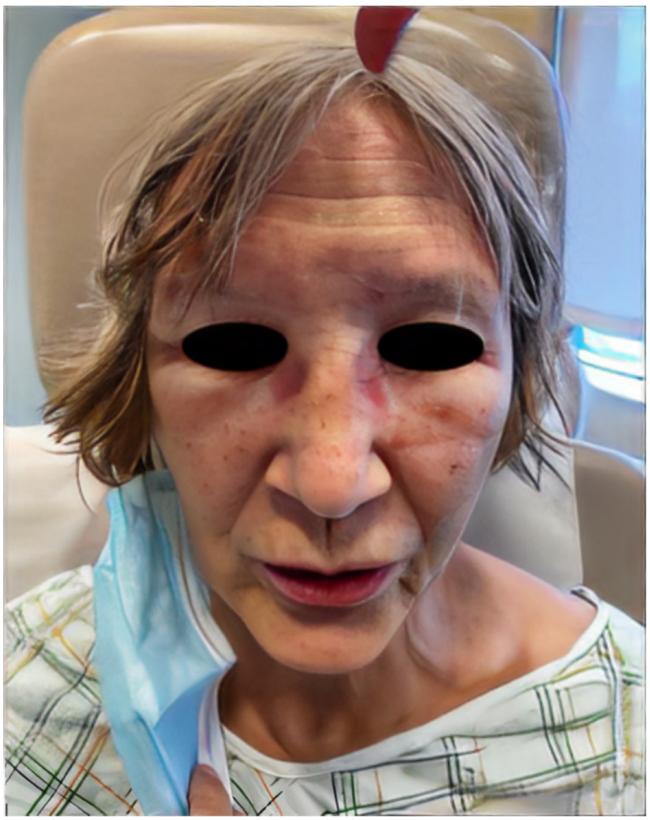

Figure 2. Facial edema. Facial swelling especially prominent around the eyes.

On exam, pink papules and plaques were observed on the scalp, upper chest, shoulders (Figure 1), thighs, and forehead. Pink papules were noted on the dorsal hand, and pink papules and slight edema were noted around the fingernails (Figure 3). Based on these findings, a diagnosis of dermatomyositis was suspected. A skin biopsy was performed

along with ordering CBC, CMP, ANA, ENA, CK, Aldolase, and a myositis panel. The patient was prescribed 60 mg prednisone daily for three weeks, which eliminated her facial swelling and ameliorated her erythematous rash. Additional workup included hepatitis serologies and HIV and tuberculosis screening to prepare for steroid-sparing immunosuppressive treatment. CA-125, CT abdomen pelvis, DEXA scan, mammogram, and PFTs were also ordered, and prophylactic treatment was started with Bactrim, calcium, and vitamin D.

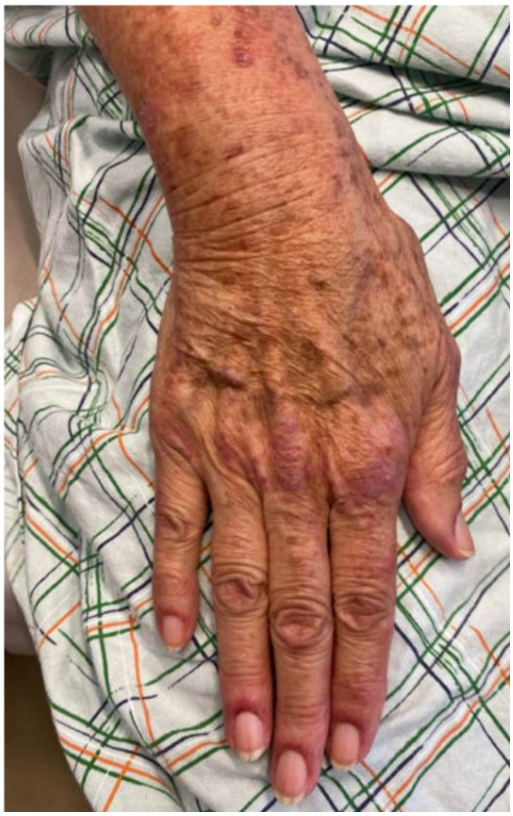

Figure 3. Gottron papules. Violaceous papules and plaques over metacarpophalangeal joints and around fingernails. Also noticeable is mild hand edema and edema in the wrist.

The skin biopsy revealed interface dermatitis consistent with dermatomyositis (Figure 4). Labs revealed elevated ANA (1:320 homogenous), CK (4480), and Aldolase (21.4), weak positive anti-TIF1-γ antibodies, low creatine and total proteins, and elevated AST and ALT. CA-125 was elevated at 117, and the patient was referred to gynecology. A CT of the abdomen and pelvis revealed a large complex cystic solid mass occupying the pelvis measuring 11 cm $\times$ 15 cm $\times$ 11 cm. Exploratory laparotomy and hysterectomy with bilateral salpingo-oophorectomy revealed stage IIIC high-grade carcinoma of the left ovary. An incidental finding on X-ray evaluation for dysphagia evaluation prompted a CTA chest, which showed a 4.7 cm ascending aortic aneurysm.

The patient completed chemotherapy with paclitaxel and carboplatin. During her treatment, she had one instance of hospital admission for neutropenic fever but recovered without complications. She was started on hydroxychloroquine 200 mg daily, and prednisone was slowly tapered until discontinuation as her symptoms resolved.

A six-month follow-up with cardiology noted that the post-resection CT abdomen and pelvis showed no evidence of abdominal aortic aneurysm. CTA and TTE measured a minimally changed 4.9 cm ascending aortic aneurysm and mild coronary artery calcification. Surgical evaluation was recommended when the diameter reaches 5 cm, with the eventual need for surgical intervention.

At her most recent visit, the patient was stable with normal CA-125 and low CK levels, and her only DM symptoms were periungual erythema and Gottron papules.

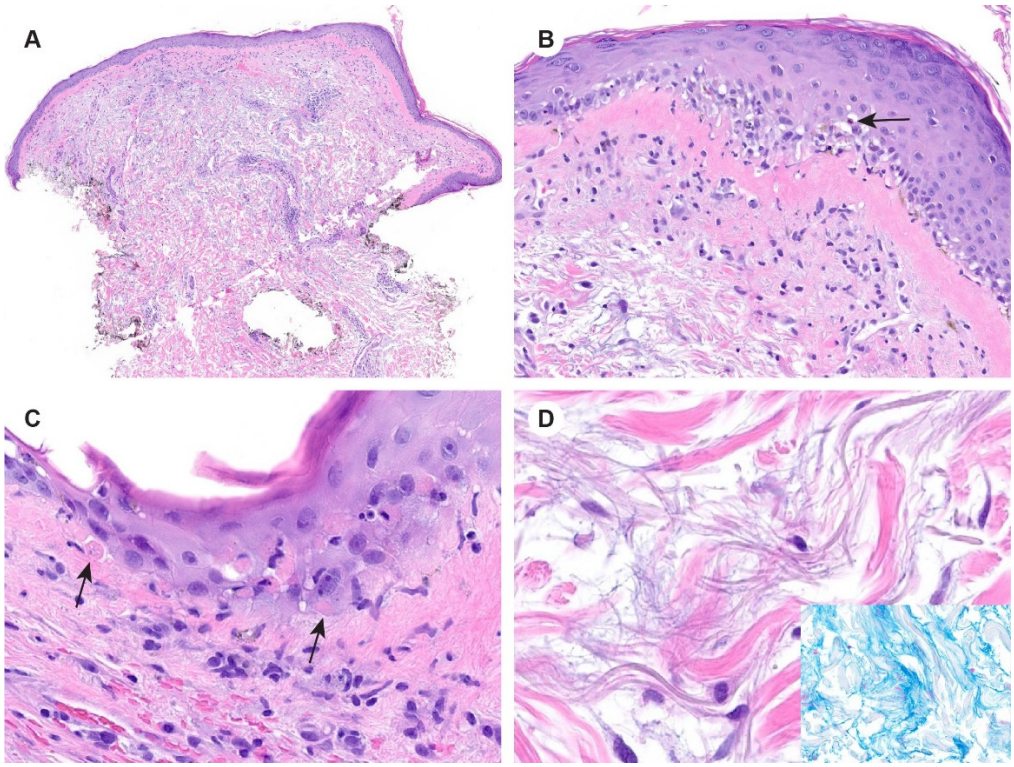

Figure 4. Punch biopsy from right upper chest. (**A**) On low magnification, there is mild epidermal atrophy and a sparse perivascular inflammatory infiltrate. (**B**) There is prominent vacuolar interface alteration with scattered dyskeratotic keratinocytes (arrow) and an underlying thickened basement membrane with occasional superficial dermal melanophages. (**C**) Colloid bodies (arrows) are present in the superficial papillary dermis. (**D**) There is extensive dermal mucin, as confirmed by a colloidal iron stain.

3. Discussion

A rare and severe manifestation of DM is the development of florid edema. Edematous DM has only been described in a few case reports [4], which were most commonly associated with a poor prognosis and higher mortality rates. For example, a study by Dunkley et al. revealed a 50% overall mortality rate in edematous DM patients, compared with a 5-year mortality rate of 10–20% in classic DM patients [5].

Differential diagnosis of this presentation includes hereditary or acquired angioedema, acute contact dermatitis, hypothyroidism, superior vena cava syndrome, or Drug Rash with Eosinophilia and Systemic Symptoms syndrome, amongst others [6]. A detailed history, physical exam, and laboratory studies, including myositis-specific antibodies, can help separate this rare DM phenotype from the above alike conditions. Additionally, paying close attention to the temporal pattern of edema is valuable in clinical practice. For example, angioedema typically exhibits a gradual onset and resolves spontaneously within approximately 72 h [6]. The edematous presentation of our patient, while bearing some resemblance to angioedema, was more widespread and presented in the context of stereotypical cutaneous findings of DM. Further, the concurrent resolution of edema after treatment of her erythematous rash was more suggestive of DM.

The mechanism behind edema in DM is unknown. Vasculopathy plays a central role in the pathogenesis of DM, including small vessel vasculitis as well as occlusive vasculopathy [7]. Therefore, generalized capillary leakage due to inflammatory damage of the vascular endothelium has been suggested as a potential etiology of third-spacing in edematous DM [8]. These pathologic findings are also seen in classic DM, which raises an interesting question as to why edema occurs in select DM patients. Milisenda et al. proposed that the widespread edema seen in DM could be related to the intensity of

vascular changes and ischemic microinfarction, which is consistent with the understanding of edema in DM as a possible indicator of disease severity [1,5].

Of interest is that our patient had an incidental finding of ascending aortic aneurysm despite the absence of established risk factors such as smoking history or hypertension. It is possible that vascular involvement in DM contributed to both the aortic aneurysm and the edematous phenotype of our patient's DM.

Insight into our patient's vascular and edematous findings may be gained by examining previous evidence supporting the progression and extension of vascular injury from small capillaries to large arteries as the disease process accumulates more immune and non-immune insults. To further illustrate this, histologic findings in early disease typically reflect a small vessel vasculitis with immune complex deposition in the muscle capillaries and endothelium of arterioles, resulting in vascular damage and subsequent hypoxic injury to muscle tissue [7,9]. This process is also believed to include complement activation and deposition of the membranolytic attack complex (MAC) on the capillary endothelium, leading to capillary damage [1]. Endothelial cell damage ensues, which leads to increased production of cytokines, cell adhesion molecules, and chemokine receptors [7]. The inflammatory milieu attracts mononuclear cell infiltration in the remodeling and reparative process that histologically results in intima and media degeneration and thickening not only in the capillaries but also in larger arterial vessels [7,10]. For example, there is preliminary evidence of endothelial cell dysfunction and atherosclerotic changes occurring in larger vessels such as carotid arteries in adults with a history of juvenile dermatomyositis (JDM) with subclinical cardiovascular disease [11]. Different forms of myocardial vessel findings, including hyalinized thickening, vessel narrowing, occlusion by fibrous thrombi, and vessel dilation, were observed in autopsies of DM patients [10]. These findings were accompanied by focal degenerative changes in muscle fibers, described as granular degeneration, loss of striation, vacuolization, and necrosis, with observations of fibrosis and occasional interstitial edema [10]. This is supported by studies demonstrating that patients with DM have an approximately twofold higher risk of myocardial infarction [12,13]. Interestingly, it has been suggested that a chronic inflammatory state resultant from small vessel vasculitis could lead to accelerated atherosclerosis in larger vessels, predisposing patients with autoinflammatory conditions to develop early-onset cardiovascular dysfunction [7,14].

In light of the above mechanistic pathogenesis, it is plausible to consider the pathogenic similarities between thoracic aortic aneurysm disorder and dissection (TAADs) and DM to explain the incidental finding of thoracic aortic aneurysm in our patient. TAAD is described as the medial degeneration of the aortic wall leading to the loss of elasticity and dilation, often in the presence of hypertensive injury [15]. In the current case, the chronic inflammatory state of DM could have led to degenerative and fibrotic changes in the aortic medial walls, resulting in a loss of elasticity and predisposing the patient to TAAD. Furthermore, a study examining the histopathology of thoracic aortic aneurysms found that medial degeneration is the predominant pattern, with atherosclerosis and inflammation as less common but important contributors to the development of chronic aortic thoracic disease [16]. While a pathologic link between TAAD and DM has yet to be fully established, the vascular inflammatory processes in DM described herein share elements of these histologic findings. Lending credibility to this hypothesis are findings reported by Pakpoor, where the authors revealed a two-fold increased risk of abdominal aortic aneurysms in DM patients [17]. One limitation of this observation in our patient is the lack of genetic testing for predisposition to TAAD. However, given her lack of family history of aneurysms or clinical signs of common conditions and syndromes related to TAAD (e.g., Ehlers–Danlos or Marfan syndrome), the vascular involvement of DM in the development of TAAD remains a possibility. However, more research is needed into the nature of vasculopathy in DM and the incidence of aortic aneurysms.

Several autoantibodies targeting both nuclear and cytoplasmic cellular components have revolutionized the diagnosis of DM and are shown to correlate with specific clinical manifestations and disease outcomes [18]. These antibodies can be categorized

into myositis-associated autoantibodies (MAAs) and myositis-specific autoantibodies (MSAs) [18].

Comorbidities and clinical course in DM are associated with the presence of certain MSAs [19]. For example, a higher frequency of malignancy has been found in DM patients with antibodies against nuclear matrix protein (anti-NXP-2) or anti-transcription intermediary factor 1γ (anti-TIF1-γ) antibodies than in DM patients with negative serotypes [20]. Anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive DM is frequently associated with rapidly progressive interstitial lung disease and high mortality rates [21]. Reports describing edematous DM have shown a common association with anti-NXP2 DM. Our case, however, is one of very few to indicate that edema can be a rare presentation of anti-TIF1-γ-positive DM. Our patient's diffuse edema, including striking upper extremity edema and severe muscle weakness, is consistent with the clinical presentation of other cases of anti-TIF1-γ edematous DM [22,23].

Other important findings of this report that warrant further exploration are the link between the TIF1-γ antibody, the malignancy found in our patient, and the vascular injury resulting in this edematous phenotype. Although rare, few reports have described the initial presentation of TIF1-γ antibody-positive DM patients with localized and generalized edema [22,23]. As mentioned earlier, anti-TIF1-γ is highly correlated with malignancy in DM and carries a temporal correlation of a cancer diagnosis approximately three years before or after the diagnosis of myositis [3,24,25]. The association is particularly strong for ovarian cancer, with a 17-fold risk increase and an overall prevalence of 13.3% in DM patients below 40 and 21.4% in older adults [26].

The clinical relevance of anti-TIF1-γ in DM is a topic of debate depending on the lens through which it is viewed, as either a marker of underlying malignancy or as a pathogenic agent contributing to the development or disease activity of DM. TIF1-γ has a diverse array of cellular regulatory functions, and of particular interest are its various roles as a tumor suppressor and promoter in several cancer types [24]. It has been proposed that TIF1-γ may act as a tumor autoantigen, given its regulatory role in tumorigenesis, and could trigger DM subsequent to the body's formation of TIF1-γ [24]. However, TIF1-γ antibodies have been co-observed in JDM and adult DM patients in the absence of malignancy, positioning another theory that TIF1-γ antibodies could arise as a late event of DM following muscle injury [27,28]. Two mechanisms could explain these observations: the overexpression of myositis-specific autoantigens in the setting of muscle inflammation and regeneration or the post-apoptotic modification of autoantigens that furthers autoimmune formation [29]. Further supporting both early- and late-onset TIF1-γ-related myositis are findings from a recent study using TIF1-γ-immunized mice models. The authors observed the development of experimental myositis and corresponding myofibril necrosis, CD8+ T cell infiltration with TIF1-γ specificity, and TIF1-γ IgG antibodies [30]. This indicates the potential role of anti-TIF1-γ in the disease process of DM beyond reflecting disease activity or underlying malignancy.

Paraneoplastic vasculitis is rarely described in the literature. This phenomenon could indeed provide an alternative theory that could rationalize most of the findings in our patients, including the edema, DM, and incidental thoracic aneurysm. For example, a report by O'Connell et al. in 2018 presented a case of aortitis preceding the diagnosis of colonic adenocarcinoma [31]. Interestingly, subsequent tumor excision corresponded to improvement in the degree of aortic inflammation and the ultimate resolution of symptoms. The underlying immune mechanisms are still not fully understood, especially given the rarity of these presentations. However, theories including cytokine imbalances, dysregulated antigenic presentation with persistent immune stimulation, and increased autoreactive CD8 and CD4 T cells have been postulated [32].

The outcome of DM may follow the course of malignant disease (a paraneoplastic course) or be independent of and unaffected by anti-tumor therapy [26]. Therefore, understanding the pathogenesis is of utmost importance to guide therapeutic decisions, particularly in light of a rare and complex presentation, as with our patient. For example,

a study by Milisenda et al. found that 16 of 19 patients with edematous DM required more aggressive therapies [1]. While the optimal treatment of this edematous phenotype remains unclear, the mainstay of therapy typically includes glucocorticoids, secondary to their anti-inflammatory and immunosuppressive properties. Additional immunosuppressive agents such as methotrexate and azathioprine are often used as a more aggressive attempt to control symptoms. Further, intravenous immunoglobulins improved outcomes in severe, life-threatening cases [1]. Newer biological agents, such as rituximab, are another escalating treatment option to consider. Results with these agents show great promise in refractory cases of dermatomyositis, though they have not yet been employed in DM with generalized subcutaneous edema as in our case [1]. Given the immunosuppressive nature of these selections, however, their use in a patient with an active cancer, as in the current case, should be weighed against the risk of compromising defensive immune mechanisms influencing the patient's response to antineoplastic therapies.

Adopting the surrogate hypothesis where the patient's symptoms and findings are secondary to her malignancy, treatment should be directed towards the root cause rather than the paraneoplastic presentation. After the diagnosis of DM and ovarian malignancy, the patient received a high-dose prednisone course and hysterectomy with bilateral salpingo-oophorectomy. Further, she received chemotherapy, a tapered prednisone course, and hydroxychloroquine. These treatments led to the resolution of her symptoms save for periungual erythema and Gottron papules on the right hand.

In this report, we describe a rare presentation of edematous DM in association with ovarian cancer, a thoracic aortic aneurysm, and anti-TIF1-γ positivity. Generalized edema is a severe presentation of DM that portends increased morbidity and mortality. Edematous DM can occur in association with paraneoplastic anti-TIF1-γ antibodies. The discovery of ovarian carcinoma in our patient is further evidence that patients with anti-TIF1-γ DM should be thoroughly evaluated for associated malignancy. In such cases, caution should be practiced to balance the benefits of aggressive immunosuppressive treatments required for the edematous phenotype with the risk of negatively impacting the efficacy of certain cancer treatments.

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