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Polyangiitis Overlap Syndrome with Granulomatosis and Systemic Sclerosis: Diagnostic Challenge

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Abstract

Overlap syndrome describes the coexistence of two or more systemic autoimmune diseases in the same patient, which is common in rheumatology. However, the concurrent appearance of vasculitis associated with antineutrophil cytoplasmic antibodies and systemic sclerosis is rare, occurring in 2.5-9% of cases. This paper presents the case of a 78-year-old patient with granulomatosis with polyangiitis (GPA) and systemic sclerosis, whose diagnosis was established following the ACR/EULAR 2022 criteria for ANCA-associated vasculitis (AAV) and the ACR/EULAR 2013 criteria for systemic sclerosis (SS). This case highlights the diagnostic complexity associated with the combination of both diseases. The explanation for this coexistence includes exposure to common risk factors and a reduced immune tolerance to ANCA antigens.

Keywords: Antineutrophil CYTOPLASMIC antibody; Antineutrophil cytoplasmic antibody-associated vasculitis; systemic sclerosis; Granulomatosis with polyangiitis; Overlap syndrome; Sclerodactyly; Saddle nose; Palpable purpura; Periungual ulcers.

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare occurrence with systemic sclerosis (SS), presenting in 2.5-9% of cases [1,2]. In a study published in 2024, 20% of patients were reclassified as having overlap syndrome (OS) of SS and AAV (SS-AAV-OS), with only 4.7% corresponding to granulomatosis with polyangiitis (GPA) [3]. Despite its low frequency, its knowledge and diagnosis are important due to the variations it may imply in treatment.

Clinical Case

A 78-year-old female patient who began experiencing recurrent sinusitis, serosanguinous crusts in the nose, and otalgia 2 years prior, was treated by an otolaryngologist with antibiotics. Subsequently, she developed palpable purpura and edema in the lower extremities, which led to referral to the rheumatology department. Upon further questioning, the patient reported dyspnea (MMRC grade 2), difficulty swallowing solids, and hoarseness.

Upon examination, the patient had a saddle nose, sclerodactyly, periungual ulcers, palpable purpura in the lower extremities, ++ edema, and scaly necrosis areas predominantly in the talar region, internal and external malleoli, and dorsum of both feet. Anti-cellular antibodies with a centromeric pattern (1:2560) and antiproteinase 3 (C-ANCA) antibodies at 131.62 U/ml were requested, meeting the ACR/EULAR 2022 criteria for AAV and the ACR/EULAR 2013 criteria for SS (see Figure 1).

Discussion

The association of vasculitis with other connective tissue diseases is significant. In the study by Guibert et al. [4], patients with SS and AAV had a higher relapse rate (non-renal, 25% vs. 7.7%, p = 0.037) and were more likely to experience a venous thrombotic event (31.2% vs. 10%, p = 0.021) compared to those with vasculitis alone.

Possible explanations for this association include exposure to common risk factors and reduced immune tolerance to ANCA antigens, which are present in up to 35% of SS patients (with bactericidal permeability-increasing protein [BPI] and cathepsin G being the main ones) despite this, only a minority will develop the disease [5,6]. BPI, a constituent of azurophilic granules in neutrophils with activity against various Gram-negative bacteria, is closely related to chronic respiratory tract infections. It is believed that the presence of interstitial lung disease in SS increases the risk of pulmonary infections and may play a role in inducing anti-BPI antibodies. BPI inhibits angiogenesis by inducing endothelial cell apoptosis, and anti-BPI antibodies could inhibit its antiproliferative effect on the vascular endothelium, thereby promoting angiogenesis, though its role is not yet fully understood, and in vitro studies are needed to confirm this.

A) Periungual ulcers and sclerodactyly. B) Palpable purpura in the lower extremity. C) Necrotic areas on the foot. D) Saddle nose.

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Our case differs from others reported in the literature, as the most common scenario is that patients with SS develop vasculitis [1,4-6]. In our patient, the clinical presentation began with vasculitis, and no renal involvement was found at that time, which aligns with the findings of Masiak et al [7] where patients with vasculitis and autoimmune diseases had less renal involvement (45.0% vs. 70.9%, p = 0.001), although this overlap was not reported in that study. This case also underscores the need for a multidisciplinary approach with timely referral to a rheumatologist to prevent complications.

Conclusion

This case highlights the importance of recognizing overlap syndrome between granulomatosis with polyangiitis and systemic sclerosis, a rare combination that requires specialized diagnostic and therapeutic management.

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