CASE REPORT OPEN ACCESS

Granulomatosis with Polyangiitis (Wegener's Granulomatosis) Co-Existing with Antiphospholipid Syndrome – An Unusual Cutaneous Presentation

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is an autoimmune disease that causes inflammation of the small blood vessels and involves many organs, most commonly the upper and lower respiratory tracts and the kidneys. GPA can also affect other organs, such as the eyes, skin, and nervous system. Meanwhile, Antiphospholipid syndrome (APS) is known to cause arterial or venous thrombosis in various organ systems. We report the case of a 54-year-old Pakistani man diagnosed with granulomatosis with polyangiitis co-existing with antiphospholipid syndrome. He presented with unusual cutaneous manifestations, positive c-ANCA, antiphospholipid antibodies, and distinctive renal histopathological features that helped rule out other potential differentials. The patient ultimately received treatment with a high dose of prednisolone, monthly pulses of cyclophosphamide, and anticoagulation, leading to significant improvement in both clinical and laboratory findings. This case underscores the complexity of autoimmune diseases and the importance of comprehensive evaluation for accurate diagnosis and management.

Keywords: Gangrene, Wegener's Granulomatosis, Antiphospholipid Syndrome, Anti Neutrophil Cytoplasmic Antibodies, Antiphospholipid Antibodies.

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INTRODUCTION

Granulomatosis with polyangiitis is a type of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis in which immune cells infiltrate small blood vessels, forming inflammatory granulomas; GPA can affect multiple organs and can cause renal pauci-immune necrotizing vasculitis[1]. Antiphospholipid syndrome is an autoimmune condition more frequently observed in women than men, with a female-to-male ratio of around 3.5:1[2]. Here, we report a case of Granulomatosis with polyangiitis and Antiphospholipid syndrome presenting with unusual cutaneous features and distinctive renal histopathology. A good therapeutic response to anticoagulation, steroids, and cyclophosphamide solidified our diagnosis.

CASE PRESENTATION

A 54-year-old man, a chronic smoker, presented to the dermatology department of a tertiary care hospital with a 25-day history of blackish discoloration of all fingers of his right hand, some digits of the left hand, and the right foot. Additionally, the patient complained of fluid-filled, tense blisters on the dorsal aspect of bilateral feet and the right popliteal fossa. Further inquiry revealed oral ulcers, joint pain, undocumented fever, and generalized weakness.

On cutaneous examination, the patient exhibited edema and gangrene affecting all the digits of the right hand, tips of the index and middle fingers of the left hand, and, the third toe of the right foot. A necrotic plaque was also noted on the dorsal aspect of the right hand (Figure 1A-C). A small erosion with some crusting was noted on the right popliteal fossa (Figure 1D). Furthermore, multiple intact blisters were observed on the dorsal aspect of bilateral feet (Figure 1E). On peripheral vascular examination, the right-sided radial and brachial arteries were feeble.

Figure 1: (A) Gangrene involving all fingers of the right hand. (B) An annular necrotic plaque was noticed on the dorsal aspect of the right hand. (C) Gangrene on the pulp of the third toe of the right foot [white arrows]. (D) A small erosion is present on the right popliteal fossa [blue arrow]. (E) An edematous foot with intact blisters on the dorsum [red arrow].

Initial laboratory investigations revealed low hemoglobin of 9.7 g/dL (N:11.5-16 g/dL), raised C-reactive protein of 104.3 mg/L (N:<5 mg/L), creatinine of 1.6 mg/dL (N:0.7- 1.2 mg/dL), prolonged activated partial thromboplastin time of 33 s (N:21.1 s). Contrast-enhanced Computed-Tomography Angiogram of the right hand revealed a thrombus along the right brachiocephalic trunk and a partial peripheral thrombus along the 1st part of the subclavian artery.

Systemic lupus erythematosus was ruled out as anti-nuclear antibody (ANA), anti-double-stranded DNA, and anti-smith antibody were negative. However, the APS profile revealed an elevation of lupus anticoagulant, anticardiolipin IgM, and IgG.

Despite adequate hydration, there was a sudden rise in creatinine levels, reaching up to 3.9 mg/dL. The detailed urine analysis disclosed 3+ protein, 2+ blood cells, and 20-22 red blood cells. Recognizing the complexity, an urgent renal biopsy was done. The biopsy, encompassing up to 20 glomeruli, unveiled 15 with cellular crescents and 4 exhibiting fibro-cellular crescents, accompanied by fibrin in Bowman's space. Additionally, mild fibro-intimal thickening of arterial walls was observed (Figure 2A&B). Immunofluorescence microscopy revealed a completely negative panel, conclusively diagnosing pauci-immune crescentic glomerulonephritis.

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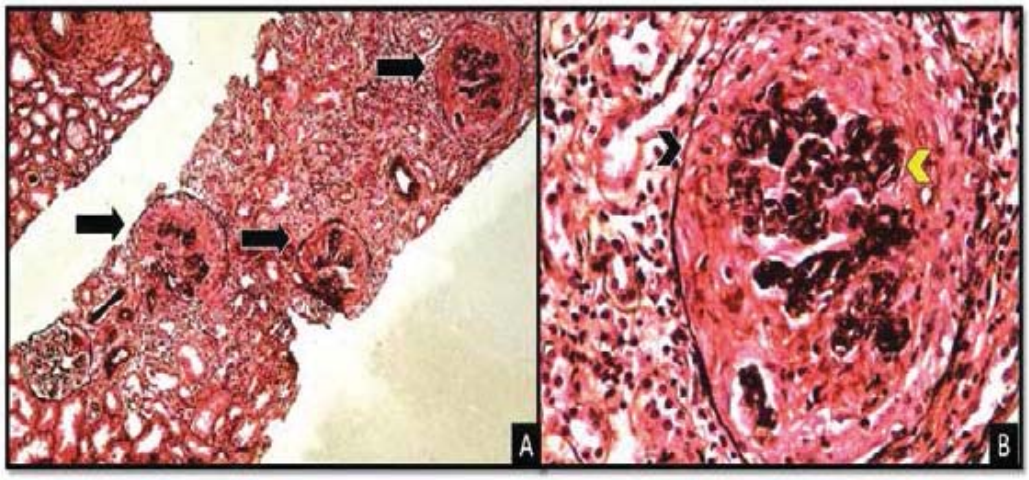

Figure 2: Renal histopathology. (A) At lower magnification, the methenamine silver stain reveals multiple crescents [black arrows]. (B) At higher magnification, a close-up view of the cellular crescent illustrates multiple layers of parietal epithelial cells [black arrowhead] compressing onto the glomerular tuft [yellow arrowhead].

Considering that these renal biopsy findings are commonly indicative of ANCA-associated vasculitis, additional laboratory investigations were pursued. Results revealed markedly elevated cytoplasmic antineutrophil cytoplasmic antibody (c-ANCA) levels while perinuclear antineutrophil cytoplasmic antibody (p-ANCA) and anti-glomerular basement antibody were negative.

Following extensive laboratory investigations and the renal biopsy, a conclusive diagnosis of c-ANCA-associated vasculitis, specifically Granulomatosis with polyangiitis co-existing with antiphospholipid syndrome, was established. An initial infusion of 1g/day methylprednisolone for 3 days, coupled with venous pulses of cyclophosphamide (single dose of 1g/month). Subsequently, the methylprednisolone 3-day regimen transitioned to oral administration of 1 mg/kg prednisolone. Anticoagulation therapy was also commenced.

During the one-month follow-up, serum creatinine demonstrated an improving trend, and urinalysis showed no signs of proteinuria or hematuria. A physical examination revealed the cessation of gangrene progression. Edema had subsided and no blisters were observed (Figure 3A-E). These positive developments indicate a favorable response to the treatment regimen.

Figure 3: (A-D) During one-month follow-up, dried-up gangrene with no further extension [white arrows]. (E) The swelling had subsided with no intact blisters leaving behind post-inflammatory hypopigmentation with some crusting [red arrow].

DISCUSSION

Granulomatosis with polyangiitis, also known as Wegener's granulomatosis, typically presents with non-specific symptoms such as fever, arthralgia, cough, and weight loss. Upper respiratory tract symptoms include sinusitis, nasal discharge, and nasal septal perforation with saddle nose deformity. Lower respiratory findings include pulmonary infiltrates, pulmonary nodules, and hemoptysis. The renal involvement often manifests abruptly, showcasing signs such as hematuria, proteinuria, and an increase in serum creatinine. The predominant renal condition is pauci-immune glomerulonephritis, wherein immunofluorescence reveals minimal to no staining for immunoglobulins. The prevalence of skin manifestations in GPA has been reported to range from 35% to 50%[3]. Varied cutaneous manifestations are observed, including palpable purpura, tender subcutaneous nodules, papules, vesicles, petechiae, ulcers, and pyoderma gangrenosum-like lesions. The occurrence of gangrene is considered rare[4].

Antiphospholipid syndrome is an autoimmune disorder characterized by vascular thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies. These antibodies include lupus anticoagulant, anti-cardiolipin antibodies, and anti–b2-glycoprotein I antibodies, which must be persistently elevated on two occasions at least 12 weeks apart to meet APS criterion[5].

Thrombosis stands as a crucial criterion in antiphospholipid syndrome and, although rare, can also manifest in granulomatosis with polyangiitis[6]. Nevertheless, the coexistence of antiphospholipid syndrome and granulomatosis with polyangiitis is scarcely reported in the literature. In a study by Juyoung Yoo et al., 18 out of 138 (13.0%) patients with ANCA-associated vasculitis demonstrated persistently elevated antiphospholipid antibodies, and these individuals were found to develop thrombosis more frequently than those without these antibodies[7]. Similarly, Sebastian et al., reported that among 176 GPA patients, 21 (12%) had positive anti-cardiolipin antibodies, with 3 out of 29 (10%) experiencing thrombosis[8].

Maassoumeh et al., report a similar presentation of granulomatosis with polyangiitis in the presence of positive antiphospholipid antibodies. Unlike our patient who developed sudden deterioration in renal functions, this patient had no internal organ damage[9].

The mechanism of vasculitis in the presence of antiphospholipid antibodies is controversial. Interestingly, anti–b2-glycoprotein I antibody (b2-GP-I) adheres to the surface of endothelial cells and this complex may get recognized by the b2-GP-I antibodies ultimately stimulating diverse biological effects, including upregulation of adhesion molecules and the production of proinflammatory cytokines. As a consequence, these antibodies may contribute to the pathophysiology of vasculitis, with APS-related thrombosis potentially initiating the pathology[10].

Upon reviewing the literature, it can be suggested that the simultaneous presence of both these entities is responsible for the development of thrombosis and ultimately digital gangrene in our patient. Our case report underscores the exceptionally rare co-existence of Wegener's granulomatosis with antiphospholipid syndrome, highlighting the importance of considering both these diagnoses when confronted with thrombosis and the rapid deterioration of renal function. Prompt evaluation is crucial for administering appropriate treatment and preventing irreversible or fatal organ damage.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PATIENT CONSENT

The patient's family has been informed regarding the study and written consent was taken.

AUTHOR'S CONTRIBUTION

All authors contributed equally to this case study.

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