A rare case study regarding the effects of granulomatosis with polyangiitis (GPA/Wegener's) on the lower extremity

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Abstract:
Systemic vasculitides (SV) include an array of inflammatory vascular disorders of varied origins. In certain stages the illnesses and injuries sustained from a particular SV may mimic unrelated vascular disorders such as those caused by organic PVDs (i.e., diabetes, smoking, coagulopathies). Of the small- to medium-vessel variety SVs, three dominant disorders exist: Granulomatosis with polyangiitis (GPA/Wegener's), Churg-Strauss Syndrome (CSS), and Microscopic Polyangiitis (MPA). Although serologically sub-differentiated, these are similar disorders because they are all typically Antineutrophil Cytoplasmic Antibody (ANCA) positive. We present a 52-year old female who was Proteinase3-Antineutrophil Cytoplasmic Antibody (PR3-ANCA) positive for GPA. She developed black, necrotic erosions and bullae of her finger tips, toes, and legs which could have been related directly to her other co-morbidities. She was treated in our facility uneventfully with immunosuppressants and palliative wound care. Importantly, the patient experiencing an active vasculitic attack requires a multidisciplinary approach, which may include a surgeon’s opinion. However, outside of an infection or an underlying malignancy, surgical approaches of the lower extremities should be limited, at least until the patient is stable and optimized for reconstruction.

Key words: Bullae, Erosions, Granulomatosis with Polyangiitis (GPA/Wegener's), MPO-ANCA, PR3-ANCA, Vasculitis

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INTRODUCTION
GPA/Wegener's is a small- to medium-sized vessel vasculitis that may affect the lungs, kidneys, and skin of the extremities.1 Serologically, it is typically PR3-ANCA positive as opposed to other vasculitides which are positive for Myeloperoxidase-Antineutrophil Cytoplasmic Antibody (MPO-ANCA). This rare disease affects approximately 3 out of every 100,000 people, affecting men and women equally. GPA can occur at any age, but most often between the ages of 40 and 65. It is rare in children. MPO-ANCA associated vasculitis is more frequent in Japan, whereas PR3-ANCA associated vasculitis is more common in Europe and USA.9,10 Other ANCA positive vasculitides include CSS and MPA. With GPA, tissue biopsies-via direct immunofluorescence-commonly reveal neutrophilic transmural inflammation of the vessel walls associated with fibrinoid necrosis, termed leukocytoclastic vasculitis (LCV). Histogenic patterns in the lungs may reveal inflammatory or fibrotic pulmonary disease with macronodular necrosis.

CASE STUDY
We present a 52-year old Caucasian female who was admitted through the emergency room. She had necrotic distal phalanges of digits 4 and 5 on each hand and foot that were accompanied by multiple painful hemorrhagic
bullae of the feet and vasculitic erosions of the legs *(Figures 1, 2, and 3)*. The patient described a four-month history of extremity rashes and lesions, with dyspnea worsening in the last week. Complicating her presentation was diabetes mellitus, a long-term smoking history, and bipolar disorder. Blood tests revealed abnormal C (cytoplasmic) and PR3-ANCA levels with a normal MPO-ANCA. Nasal cultures grew a few colonies of mycobacterium avium, a known etiology of GPA. Clinically, she remained asymptomatic, and the culture was noted for observation. After the initial consultation, an indepth chart review, and a discussion with her rheumatologist, we learned that lung biopsy samples were taken several months earlier on a previous admission, supporting the diagnosis GPA. Microhematuria was not identified.

Her pain was treated with palliative topical and oral analgesic agents. Her vasculitis was treated with standard systemic glucocorticoid and Cytoxan (i.e., cyclophosphamide) combination therapy. The upper and lower extremity wounds were not addressed surgically. The attending podiatrist thought that debridement would cause unnecessary pain with increased wound morbidity and a poor outcome. The wounds were
dressed with dry sterile gauze on a daily basis to maintain peri-wound cleanliness and integrity. Her bullae progressively resorbed, and the necrotic digits began to re-epithelialize along well demarcated margins. She was discharged to a rehabilitation center for continued weight bearing therapy, wound care, and vasculitis management.

DISCUSSION

The patient presented with multiple co-morbidities, each of which could have been considered an etiology in contributing to her painful erosions and bullae. In isolation, her erosions may have been attributed to diabetic dermopathy or pyoderma gangrenosum. Her necrotic digits (Figures 4 and 5) may have been attributed to long-term smoking and arteriosclerosis. Collectively however, she presented with historical, clinical, and serologic findings consistent with a vasculitic condition, specifically GPA. Common characteristics of GPA include: granulomatous inflammation (not eosinophilia predominant as in CSS), necrotizing vasculitis affecting small- to medium-sized vessels (including focal and segmental pauci immune necrotizing glomerulonephritis), facial (saddle nose deformity), and pulmonary involvement. GPA, MPA, and CSS distinguish from other systemic small vessel vasculitides by the absence of immune deposits. MPA is distinguished from GPA and CSS by the absence of granuloma formation and the presence of a necrotizing vasculitis.

ANCA positivity alone, in the absence of appropriate clinical or pathologic findings, should not be used to substantiate a diagnosis of GPA, MPA, or CSS. Serologically, approximately 82% to 94% of patients with either GPA or MPA are ANCA positive, depending on the severity of the disease. GPA is primarily associated with PR3-ANCA, while MPA is primarily associated with MPO-ANCA. However, 20% of patients with GPA or MPA have the alternative ANCA, and at least 10% of patients are ANCA negative. The majority of patients with renal-limited vasculitis are ANCA-positive, with 75% to 80% having MPO-ANCA.\(^1\)
Malignancies mimicking small vessel vasculitides and infections should be ruled out. In one particular case, lymphoma was misdiagnosed as GPA. The presence of glomerulonephritis may have complicated matters, as this is less prevalent in lymphoma compared to SV. Early diagnosis in all of the above cases is necessary, since end organ failure and mortality are high. Untreated, GPA carries a 1-year mortality of up to 80% and a 2-year rate of 90%. Mean follow-up of 27 months showed relapse rates of 57% despite therapy.

Increasing evidence that accelerated atherosclerosis may occur in SV implies an increased risk of cardiovascular disease. The incidence of thromboembolic events in GPA is as high as in patients with previous idiopathic venous thromboembolism. Increasing endothelial progenitor cell (EPC) levels have been shown to reduce vascular inflammation, thus decreasing platelet aggregation and inhibiting thrombus formation. Prophylactic use of statins may increase EPC levels. This would be especially important during disease activity because 81% of thromboembolic events take place in individuals with active vasculitis. Simple cost-effective bedside tests, such as ABIs, have proven effective in early detection of this cardiovascular progression.

The patient lacked cardinal signs of infection such as pyrexia, sustained increased white blood count, evidence of cardiac vegetations, pneumonia, or generalized sepsis. Her digits presented as painful hemorrhagic bullae with necrotic margins, not as micro abscesses nor erythematous macules associated with Janeway lesions or Osler’s nodes. Violaceous lesions may have preceded the development of the necrotic bullae. In general, the risk of infection should not be minimized, as it is the most frequent cause of death. These infections often present themselves as pneumonia and/or sepsis. Common pathogens include fungi (such as aspergillus), gram-positive bacteria (including MRSA), acid-fast bacteria, and cytomegalovirus. Granulomatous hypophysitis causing central diabetes insipidus is an unusual presenting feature of vasculitis. The patient presented with diabetes, and it is unknown whether the ANCA associated vasculitis (AAV) precluded her diabetes.

The standard of care for severe GPA includes an induction phase with cyclophosphamide combined with high doses of glucocorticoids, followed by maintenance therapy with either methotrexate or azathioprine. A limited disease may be controlled with methotrexate or azathioprine. Combination therapy with cyclophosphamide and high-dose corticosteroid induces improvement in >90% of patients with GPA and complete remission in 75% of patients. Additional successful reports on the effects of rituximab exist. Using this agent is based on its ability to deplete B cells, which are important players in the pathogenesis of GPA. As mentioned earlier death usually stems from infection. Therefore, this class of medications, used to fight infections, needs to be monitored carefully. Corticosteroids inhibit not only antigen processing by macrophages and antigen presentation by T cells, but also interleukin 1 production and receptor expression, cellular/humoral immunity, and neutrophil function, which exerts potent anti-inflammatory and immunosuppressive effects. On the other hand, cyclosporine inhibits interleukin 2 production and receptor expression, inhibiting cellular immunity. Azathioprine and cyclophosphamide are metabolic antagonists, and they have myelosuppressive effects on cellular and humoral immunity, sometimes causing neutropenia.
CONCLUSION

Although GPA is an unusual podiatric presentation, its immunosuppressive nature and effect on the lower extremities mimics other small- to medium- sized peripheral vascular related diseases. Therefore, local wound care should not include aggressive debridement techniques in the absence of occult infection or malignancy. Instead, a communicative team approach should be employed to protect and re-establish the patient’s indwelling perfusion.

GPA can be confidently diagnosed; however, serologic tests specifically involving a PR3- and MPO-ANCA immunoassay must always be viewed in the context of the clinical picture.8,13

Correlation must be made of the history, clinical exam, lung biopsies, other histological findings, and radiographs. Once the diagnosis is confirmed, care must be taken to reverse the active state of the disease and maintain care without over suppressing the immune system into a state of sepsis. Renal studies and blood values should be regularly monitored for glomerulonephritis. Patients, and their support groups at home, need to be educated in avoiding risk factors such as exposure to antigens, smoking, substance abuse, poor hygiene, and non-protective clothing. An interdisciplinary medical team approach would be beneficial to aid in prevention as well as in the active or maintenance disease phases. Team members should include representation from primary care, rheumatology, nephrology, pulmonology, dentistry, and wound care. Other specialists such as ear, nose, and throat; vascular; cardiology; and podiatry may be required for more focused management.

References


