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Case Report

A rare case of infliximab induced myeloperoxidase-cytoplasmic-antineutrophil cytoplasmic autoantibody positive cutaneous vasculitis

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ABSTRACT

Drug-induced cutaneous vasculitis is a known autoimmune complication of tumor necrosis factor (TNF) inhibitors with many instances resulting in the production of newly formed antibodies. We report a 21-year-old female with a past medical history of Crohn's disease controlled with infliximab who presented to dermatology with a purpuric rash and crusted plaques of her distal lower extremities. Biopsy of a lesion revealed perivascular lymphocytes, neutrophils and eosinophils, vessel wall damage, and dermal eosinophils consistent with a drug-induced vasculitis. Follow up labs assessing for antibodies revealed unusual findings of an elevated cytoplasmic-antineutrophil cytoplasmic autoantibody (C-ANCA) titer and myeloperoxidase (MPO) antibody level making this patient MPO-C-ANCA positive. The patient's lesions were treated with both oral and topical steroids, colchicine, and transition of her infliximab to ustekinumab with subsequent improvement of her lesions and normalization of antibody titers.

Keywords: TNF inhibitors, Cutaneous vasculitis, C-ANCA, MPO antibody

INTRODUCTION

Tumor necrosis factor (TNF) inhibitors are used to manage a variety of autoimmune and inflammatory diseases. Despite their efficacy in treating these diseases, reports have demonstrated subsequent formation of drug induced autoimmune complications as a result.[1,2] Cutaneous vasculitis is a common manifestation of TNF inhibitor use and can be characterized by palpable purpura, ulcerated lesions, erythematous macules, and blisters.[2,3] Literature reports have also noted the induction of newly formed antibodies as a result of TNF inhibitor therapy, with the most cited being double stranded DNA (dsDNA) and antinuclear antibody (ANA).[4,5]

CASE REPORT

A 21-year-old female with past medical history of Crohn's disease controlled with infliximab 100 mg infused at 5 mg/kg every 8 weeks presented in February 2021 with a rash on her lower extremities. Presenting eruption was October 2020, initially treated by her primary care provider with mupirocin ointment. On presentation to dermatology APP in February 2021, a purpuric eruption was noted with crusted plaques, superficial ulceration and post inflammatory hyperpigmentation (Figure 1A). The patient denied any new medications, no illicit drug use, including cocaine, or other systemic symptoms. The patient was instructed to

apply topical triamcinolone twice daily until follow-up and to contact the clinic for worsening symptoms.

When the patient returned in March, the rash was still present and had become painful (Figure 1B). A 4 mm punch biopsy of an entire red crusted macule was taken on the right lateral ankle at this time. Histopathological findings revealed superficial to deep dense dermal perivascular mixed inflammatory cell infiltrates including lymphocytes, neutrophils and rare eosinophils. Vessel wall damage with fibrinoid necrosis and neutrophilic inflammatory cell debris were observed, consistent with a vasculitis process. Most of the involved vessels were small capillaries with rare medium-sized arterioles. No granulomatous component seen. The presence of scattered eosinophils in the inflammatory cell infiltrates raised a possibility of drug-related etiology (Figure 2).

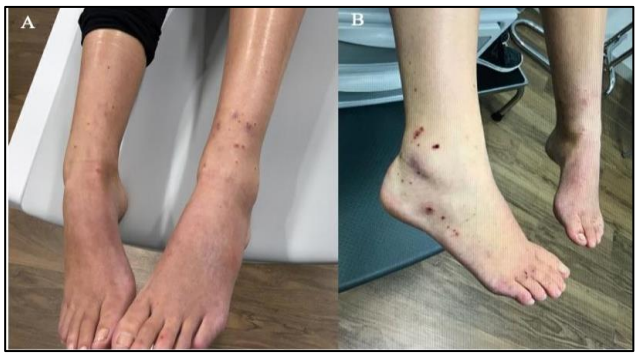

Figure 1 (A and B): Clinical images of patient's lower extremities at presentation to clinic in February 2021 as well as progression of lesions after initial encounter and at time of biopsy.

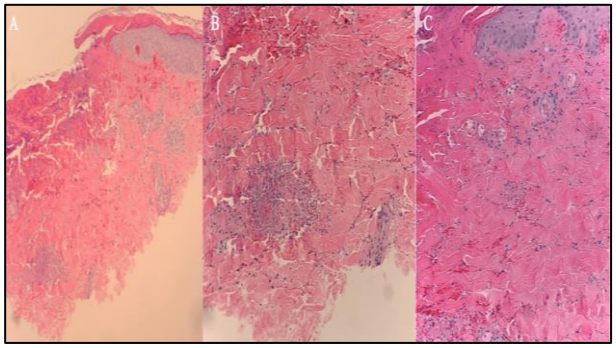

Figure 2 (A-C): Histopathological features showed epidermal ulceration with dense neutrophilic fibrin deposition, superficial to deep dermal perivascular lymphocytes, neutrophils and rare eosinophils, focal intravascular hyalinized material with vessel wall damage and rare neutrophilic inflammatory cell infiltrate hematoxylin and eosin, x100, hematoxylin and eosin, x200 and hematoxylin and eosin, x400.

Laboratory studies were remarkable for an anti-MPO antibody level of 10.5 (0-9.0 U/ml), C-ANCA titer 1:640 (<1:20 titer), CRP 11 (0-10 mg/l), and urinalysis with trace blood. Anti-PR-3 antibody was <3.5 (<3.5 U/ml) and P-ANCA was <1:20 (<1:20 titer). Given the positive C-ANCA titer, granulomatosis with polyangiitis was a diagnosis of concern and the patient was referred to rheumatology and nephrology for further evaluation. Further rheumatologic and renal testing was largely unrevealing. With all triggers for leukocytoclastic vasculitis (LCV) ruled out, infliximab-induced vasculitis appeared to be a likely etiology. The patient was started on prednisone 60 mg daily and clobetasol 0.05% ointment twice a day.

Two-week follow-up showed healing of ulcerations and she was deemed to be clinically stable (Figure 3). The patient was continued on clobetasol ointment and oral steroids were slowly tapered. Four weeks later, the rash worsened and the patient's steroid taper was increased. She was instructed to apply clobetasol under occlusion dressings at night. Colchicine 0.6 mg twice a day was also added to her regimen. Her infliximab was discontinued May 13, 2021, with her last dose being approximately 8 weeks prior in March.

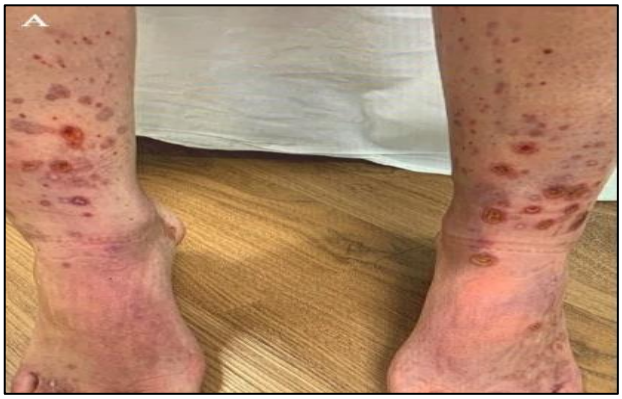

Figure 3: Clinical image of bilateral lower extremities at follow up in May 2021.

In June, the patient still suffered from multiple erosions on the lower extremities. Her steroid taper was continued as was colchicine. Unna wraps with clobetasol occlusion were added to her regimen, with transition to daily compression hose. Stelara 90 mg/ml was prescribed on June 14, 2021 for the management of her Crohn's disease. Laboratory studies three months after last infliximab dose revealed decreased C-ANCA antibody titer <1:20 (<1:20 AU/ml) and anti-MPO of 24 (0-19 AU/ml indicates negative result, 20-25 AU/ml is equivocal).

Gradual improvement of the lesions was noted at a follow up appointment in July (Figure 4). The patient was instructed to use compression stockings four times a week. A month later, she returned with new erosions and her medication regimen was adjusted to clobetasol and colchicine three times a day. She was also given a 70 mg injection of triamcinolone. Follow up in September showed marked improvement and quiescence of the

lesions with multiple areas of post inflammatory hyperpigmentation. The patient was reduced to colchicine 1 mg daily. Given the long-term stability of her disease and remarkable improvement (Figure 5), she was released from our care.

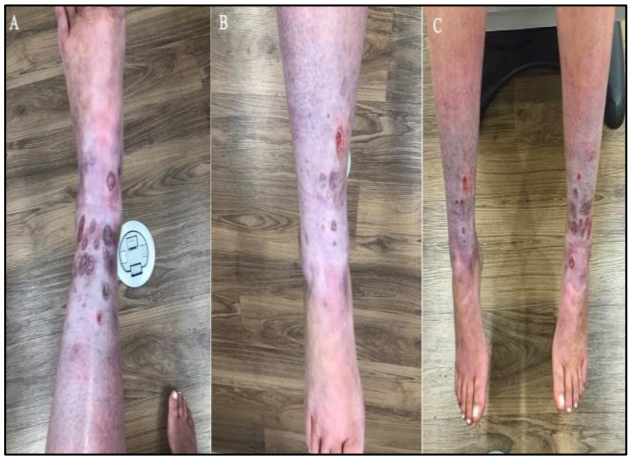

Figure 4 (A-C): Clinical images of patient's lower extremities in clinic in July 2021, left lower extremity, right lower extremity, bilateral lower extremities.

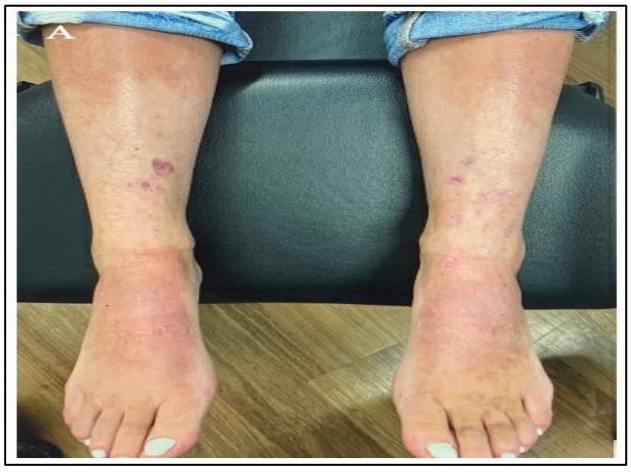

Figure 5: Clinical follow up in March 2022.

DISCUSSION

In this case, the authors present a rare instance of infliximab-induced MPO-C-ANCA positive cutaneous vasculitis. TNF inhibitors, such as Infliximab, are a known cause of drug-induced cutaneous vasculitis; however, there have been no reports to the authors' knowledge of MPO-C-ANCA positive cutaneous vasculitis. Antineutrophil cytoplasmic antibodies (ANCA) are classic markers used to identify types of ANCA-associated vasculitis. They are classified as either cytoplasmic (C-ANCA) or perinuclear/nuclear (P-ANCA).[6] Additionally, these antibodies are typically directed against specific antibodies: C-ANCA against proteinase-3 (PR3) and P-ANCA against MPO.[6] In this case, however, the patient had elevated titers of C-ANCA and MPO, a quite unusual finding, although sparsely documented in the literature and proven to be a possibility.[7] Case reports by Koratoala et al and Lim et al present patients with MPO-C-ANCA necrotizing and crescentic glomerulonephritis and eosinophilic granulomatosis with polyangiitis, respectively.[8,9] However, none of these patients had any cutaneous manifestations, making this report a first of its kind. In most cases of drug-induced cutaneous vasculitis, patients responded to systemic steroids and cessation of the TNF inhibitor. One case series reported an average time to resolution of approximately 7 months.[2] Although cutaneous vasculitis is a known autoimmune complication of TNF inhibitors, it is important for providers to recognize this diagnosis and to be aware that atypical antibody panels are possible

CONCLUSION

In conclusion, this case highlights the importance of recognizing drug-induced cutaneous vasculitis as a complication of biologic agents. More importantly, it draws attention to the rare possibility of MPO-C-ANCA positivity. Little is known regarding the systemic effects this antibody combination may have. Fortunately for this patient, her disease was limited to her skin. Chart review did reveal persistent hematuria on urine analysis with unremarkable renal function tests and an acute visit with otorhinolaryngology was remarkable for ulcerative lesions of the intranasal septum resulting in frequent nosebleeds; however, no further workup was completed by either specialist. Given the paucity of this phenomenon, it makes a multi-specialist approach more appropriate to ensure any current or future complications are addressed.

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