Medium-vessel vasculitis presenting as multiple leg ulcers after treatment with abatacept

Melia Hernandez Holt, MD,[a] Vincent Liu, MD,[a,b] and Janet Fairley, MD[a]
Iowa City, Iowa

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INTRODUCTION

Abatacept (Orencia) is a recombinant fusion protein of cytotoxic T-lymphocyte–associated antigen-4 and human immunoglobulin that inhibits T-cell activation and proliferation by binding to CD80 and CD86 on antigen-presenting cells and prevents binding to CD28 on T cells.[1] The drug is approved by the US Food and Drug Administration to treat adult rheumatoid arthritis, juvenile idiopathic arthritis, and, more recently, psoriatic arthritis.

Reported cutaneous reactions after treatment with abatacept, including rheumatoid vasculitis, cutaneous polyarteritis nodosa localized to the infusion site, pyoderma gangrenosum, erythema elevatum diutinum, psoriasis, and Sweet syndrome, have mostly been described in patients with rheumatoid arthritis.[2-5]

We present a patient who had small- and medium-vessel vasculitis presenting as numerous lower leg ulcers after treatment with abatacept for psoriasis and psoriatic arthritis.

Abbreviation used:

Th: T helper cell

CASE

A 42-year-old man with psoriasis and psoriatic arthritis who had been receiving methotrexate for the past 9 years, intermittent burst and tapers of prednisone, and abatacept for the past 3 months presented with 4 weeks of multiple leg ulcers. The ulcers began as small pink papules that gradually expanded and ulcerated. The ulcers were painful if touched but not while at rest. The patient underwent several scalpel debridements and received numerous antibiotics including doxycycline, vancomycin, levofloxacin, and clindamycin without improvement. Methotrexate and abatacept were discontinued soon after the onset of symptoms. On examination the patient was febrile but well appearing. Skin examination found approximately a dozen lower leg ulcerations with violaceous borders and surrounding erythema, ranging in size from 0.4 cm to 3 cm (Fig 1). The newest lesion on the right inner thigh showed a focal area of necrosis with surrounding induration and deep erythema (Fig 2). A biopsy of the newest lesion (Fig 2) found mixed acute and chronic inflammation throughout the dermis with fibrinoid necrosis of small and medium-sized blood vessels (Figs 3 and 4). No bacteria, fungi, or acid-fast organisms were detected on Gram, periodic acid–Schiff–diastase, and acid-fast bacillus stains, respectively. Tissue and blood cultures were negative. Chest radiograph and chest computed tomography showed no evidence of pulmonary disease. Laboratory workup including HIV, hepatitis B and C, QuantiFERON TB Gold, cryptococcal antigen, urine blastomycosis, urine histoplasmosis, bartonella henselae IgG/IgM, and bartonella quintana IgG/IgM were negative. Antinuclear antibody titer was elevated at 1:320 with a nuclear homogeneous staining pattern. Rheumatoid factor, complement (C3 and C4), serum protein electrophoresis, dsDNA antibody, Smith antibody, RNP antibody, SS-A/SS-B antibody, CCP antibody, antineutrophil cytoplasmic

From the Departments of Dermatology[a] and Pathology,[b] University of Iowa Hospitals and Clinics.
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Correspondence to: Melia Hernandez Holt, MD, University of Iowa Hospitals and Clinics, Department of Dermatology, 200 Hawkins Drive, 30000PFP, Iowa City, Iowa 52242. E-mail: melia-holt@uiowa.edu or meliadhernandez@gmail.com.

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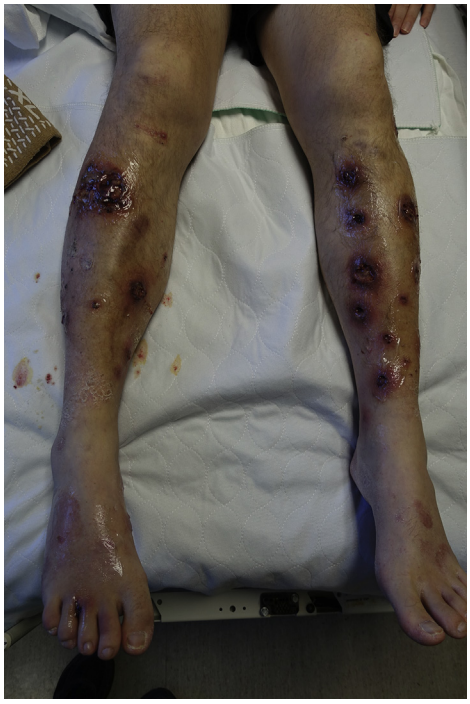

Fig 1. Lower legs. Multiple ulcerations with violaceous boarders and surrounding erythema.

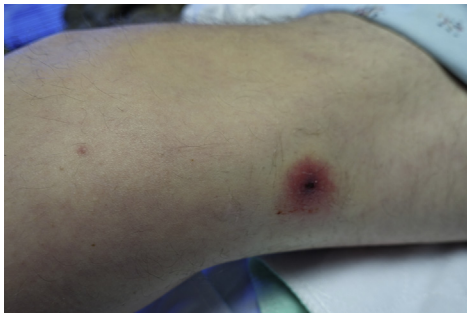

Fig 2. Right inner thigh. The newest lesion shows a focal area of necrosis with surrounding induration and deep erythema.

antibodies, and cryoglobulins were within normal limits. Erythrocyte sedimentation rate and C-reactive protein were elevated. A complete blood count found lymphocytosis with neutrophilia. Aspartate aminotransferase and alanine aminotransferase were elevated at 74 and 202 U/L, respectively, and trended downward. Blood urea nitrogen, creatinine, and urinalysis findings were within normal limits. Prednisone, 80 mg/d (1 mg/kg/d), was started with rapid improvement. Over the course of the next month, prednisone was tapered to 15 mg daily to maintain control of his arthritis. Apremilast (Otezla) was started for psoriatic arthritis 3 months after the initial presentation.

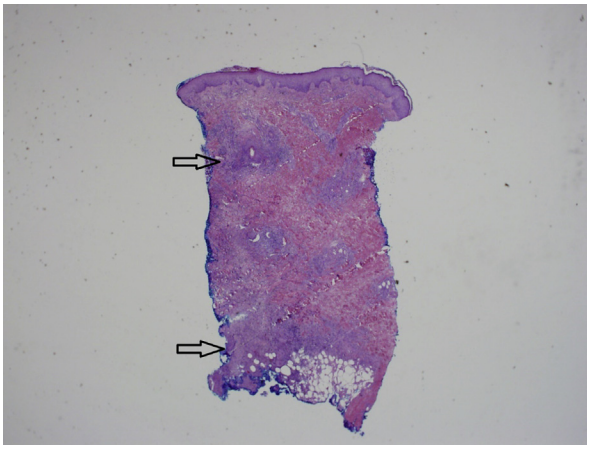

Fig 3. Punch biopsy of right inner thigh. A mildly spongiotic epidermis overlies an extensive mixed acute and chronic dermal inflammation. There are extensive, loose collections of neutrophils associated with necroinflammatory debris and admixed lymphocytes within the mid to reticular dermis with perivascular and periadnexal predilection (*arrows*). (Hematoxylin-eosin stain; original magnification: ×4.)

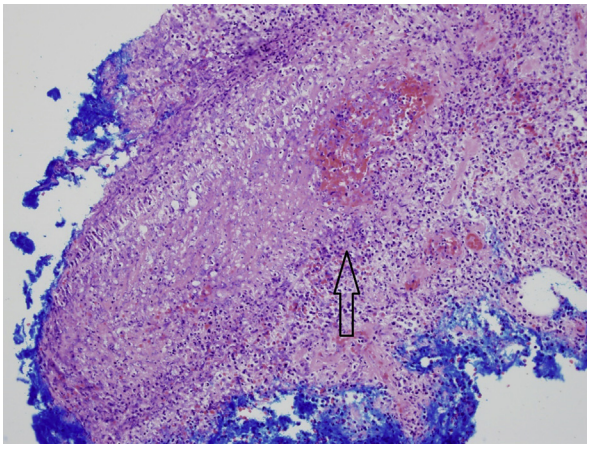

Fig 4. Punch biopsy of right inner thigh, H&E (20×). Fibrinoid necrosis of endothelial cells is seen with neutrophilic and karyorrhectic debris, involving a deep dermal medium-sized blood vessel (*arrow*). (Hematoxylin-eosin stain; original magnification: ×20.)

DISCUSSION

The exact cause of paradoxical reactions to biologic agents such as abatacept or tumor necrosis factor-α inhibitors is unknown. Proposed hypotheses include an imbalance in cytokine production, imbalance between effector and regulatory T cells, and an unopposed type 1 interferon production.[6,7] Abatacept inhibits T-cell activation by binding to CD80 and CD86 on antigen-presenting cells and can impact T helper cells (Th)1, Th2, and Th17 pathways.[8] Abatacept has been found to enhance

regulatory T-cell function but diminish the number of circulating regulatory T cells.[7]

This case illustrates an example of small- and medium-vessel vasculitis likely caused by abatacept administration for psoriatic arthritis. Abatacept was initiated 2 months before the onset of cutaneous symptoms, no other trigger was identified, and rapid clinical improvement was noted after discontinuation of the medication and prednisone administration. Prior reports of similar clinical and histologic findings, diagnosed as rheumatoid vasculitis and cutaneous polyarteritis nodosa, are probably caused by a similar process as presented in this case. Small- and medium-vessel vasculitis are likely the underlying mechanisms in each case, supporting the concept that this is a real phenomenon related to abatacept administration. In all cases of cutaneous vasculitis, it is crucial to evaluate for systemic manifestations of vasculitis such as glomerulonephritis. Even patients with drug-induced vasculitis are at risk for systemic manifestations. Recognition of uncommon paradoxical reactions to biologic agents, such as abatacept, is crucial for prompt diagnosis and treatment to reduce morbidity. Awareness that vasculitis represents a distinct complication of this class of medications is of particular importance to both the clinician and pathologist, as identification of vasculitis on skin biopsy can be challenging, requiring adequate sampling into subcutis, and frequently requiring multiple step sections.

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