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Case Report and Review of Minocycline-Induced Cutaneous Polyarteritis Nodosa

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Introduction

Minocycline is a semisynthetic derivative of tetracycline that exerts a bacteriostatic effect through inhibition of bacterial protein synthesis. Duration of therapy is usually short, but minocycline may be prescribed in adults on a long-term basis for the management of acne vulgaris or rheumatoid arthritis. The drug is generally well tolerated and the most common adverse drug reactions are photosensitivity and esophagitis. Rarely, severe allergic reactions have been observed, including Stevens-Johnson syndrome. Elkayam et al (1) reviewed several case reports of autoimmune syndromes associated with minocycline, including minocycline-induced systemic lupus erythematosus, minocycline-induced serum sickness, minocycline-induced autoimmune hepatitis, and minocycline-induced vasculitis. The following is a case report of minocycline-induced cutaneous polyarteritis nodosa (PAN). The common clinical features of this syndrome are identified, and criteria for diagnosis of minocycline-induced cutaneous PAN are proposed.

Case report

A 19-year-old woman presented with abrupt onset of a nodular rash on the lower extremities. Her medications included oral contraceptive pills and minocycline, 100 mg twice a day for the past 15 months for pustular acne. She was a college student and recalled no recent travel, illness, or exposures. There were no cardiac, pulmonary, gastrointestinal, musculoskeletal, or neurologic symptoms.

Examination revealed multiple violaceous, tender, subcutaneous nodular lesions ranging in diameter from 0.5 cm to 2 cm throughout her lower legs. The overlying skin was mildly warm but nontender. A brief steroid taper was prescribed and the skin lesions resolved for 1 week and then recurred with the new onset of bilateral ankle pain, stiffness, and swelling with preserved range of motion. The rest of her exam was unremarkable.

Perinuclear antineutrophilic cytoplasmic antibodies (pANCA) were positive at a titer of 1:256, with negative enzyme-linked immunosorbent assay to myeloperoxidase and proteinase-3 (see Table 1 for additional laboratory results). Purified protein derivative was negative and a chest radiograph was normal.

A skin biopsy revealed necrotizing vasculitis of the small vessels of the dermis and panniculus characterized by vascular wall neutrophilic infiltration, hyalinizing necrosis, and intravascular thrombi. Extensive lobular panniculitis exhibited lymphocytes and granuloma formation characterized by epitheloid giant cells (see Figures 1 and 2 for histology). Stains for mycobacterial and fungal organisms were negative.

The patient was diagnosed with minocycline-induced cutaneous PAN and treated with a 6-week taper of prednisone starting at 20 mg per day. Minocycline was discontinued, but the oral contraceptives were continued at her request. Clinically, she responded well to treatment with sustained resolution of the nodular skin lesions and ankle arthritis. Four months later, she remained well and her ANCA titer had decreased to 1:64 with a nonspecific pattern.

Discussion

This patient presented with features characteristic of minocycline-induced cutaneous PAN, showing a previously unappreciated granulomatous pathology. Although oral contraceptives can be associated with erythema nodosum, this case involved a cutaneous vasculitis, and she improved despite remaining on the oral contraceptives. The elevated antistreptolysin O titer probably reflected a nonspecific inflammatory response as noted by her elevated total IgG. She did not meet clinical criteria for rheumatic fever.

ANCA are useful serologies in the diagnosis of vasculitis (2). Classic ANCA, an antibody directed against proteinase-3, is a specific marker for Wegener's granulomatosis. Perinuclear ANCA is more heterogeneous, with antibodies to myeloperoxidase, lactoferrin, elastase, cathepsin G, or lysozyme. Classically, pANCA has been associated with Churg-Strauss vasculitis, microscopic polyangitis, and

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Table 1. Clinical data*

WBC, /mm^3	4,900
Hemoglobulin, gm/dl	11.2
Platelets, /mm^3	248,000
Metabolic panel	Normal
Urinalysis	Normal
ESR, mm/hour	52
CRP, mg/dl	1.1
ANA	1:40, speckled
pANCA	1:256 with negative ELISA to myeloperoxidase
Anticardiolipin IgG, U/ml†	19.9 U/ml
Repeat testing	<11
IgG, gm/dl	23.2 g/dl, elevated
IgM, gm/dl	3.73
IgA, gm/dl	0.76
Hepatitis B/C serologies	Negative

* WBC = white blood cell count; UA = ; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ANA = antinuclear antibodies; pANCA = perinuclear antineutrophil cytoplasmic antibody; ELISA = enzyme-linked immunosorbent assay.

pauciimmune necrotizing glomerulonephritis (3). Perinuclear ANCA can also be detected in several other inflammatory conditions, including rheumatoid arthritis, inflammatory bowel disease, lupus, and autoimmune hepatitis (4). Recently, there have been reports of pANCA associated with drug-induced autoimmune syndromes and vasculitis (5), including minocycline-induced lupus and vasculitis.

Idiopathic cutaneous PAN is a necrotizing vasculitis of small- and medium-sized arteries within the skin, without involvement of internal organs (6). Skin manifestations include subcutaneous nodules and livedo reticularis, usually involving the lower extremities. Additional manifestations may include fever, arthritis, peripheral neuropathy, and myalgias localized to the distribution of the skin findings (7). The presence of ANCA is found in <10% of classic or cutaneous PAN (8). In contrast, all current case reports of minocycline-induced CPAN identify the presence of pANCA serologies. The positive pANCA serology in this case supports our diagnosis of minocycline-induced cutaneous PAN and the association of the vasculitis with minocycline.

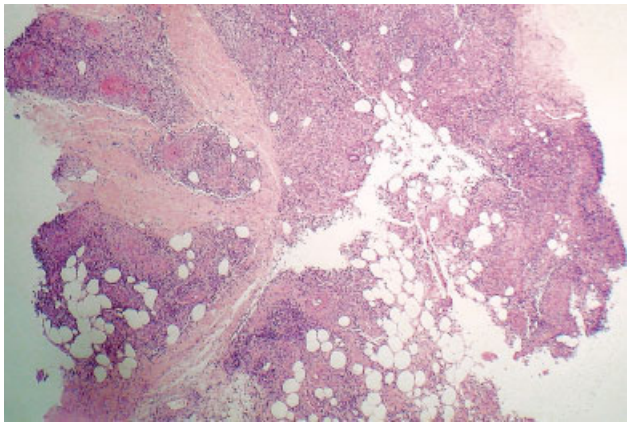

Figure 1. Skin biopsy with necrotizing granulomatous vasculitis characterized by infiltration of medium and small-sized arterial walls by neutrophils exhibiting leukocytoclasis. There is complete destruction of vessel walls with intraluminal thrombosis and deposition of fibrinoid material. Dense granulomatous perivascular infiltrate composed of lymphocytes, histocytes, plasma cells, and rare eosinophils surrounds damaged vessels in the middle and deep dermis and subcutis (4× magnification).

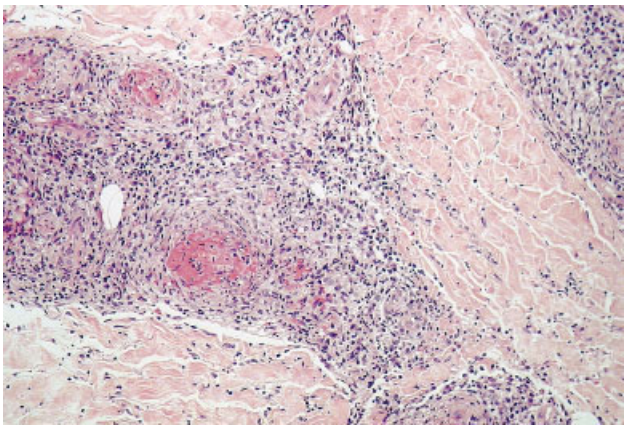

Figure 2. Dense perivascular granuloma composed of histiocytes, lymphocytes, plasma cells, and rare eosinophils surrounding a small blood vessel with intravascular thrombus, fibrinoid necrosis of the vessel wall, and multiple intramural neutrophils exhibiting leukocytoclasis (10× magnification**).**

Six prior cases of minocycline-induced cutaneous PAN have been reported (9–12). This case represents the seventh. All the reported cases described arthritis, livedo reticularis or subcutaneous nodules, histologic confirmation of vasculitis, and positive pANCA. Our case is unique in that the skin biopsy also revealed giant cells and granuloma formation within the panniculus.

Several different autoimmune syndromes associated with minocycline are described in the literature. Elkayam et al in 1996 (13) and 1998 (14) reported 2 case series of minocycline-induced autoimmune syndromes. The patients were noted to have frequent fever, arthritis, and livedo reticularis or subcutaneous nodules. The pANCA was positive, but histology was not reported. Although the patients were not diagnosed with cutaneous PAN, the clinical features are suggestive. Without skin histology, it is difficult to exclude a vasculitis. In 2000, Schlienger et al reported an extensive review of 57 reported cases of minocycline-induced lupus (15). The median exposure to minocycline prior to symptoms was 19 months. All patients had positive antinuclear antibodies (ANA) and joint complaints. Twelve patients developed skin manifestations including livedo reticularis, subcutaneous nodules, oral ulcers, and alopecia. The presence of livedo reticularis and subcutaneous nodules suggests the diagnosis of cutaneous PAN. Dunphy et al (16) reported a series of minocycline-induced lupus-like syndromes in 2000 that consisted of 14 patients taking minocycline for an average of 3.8 years. Each patient's serum was positive for ANCA with 11 of the 14 associated with pANCA. This study suggested that pANCA might be a marker for lupus-like syndrome in cases involving minocycline. The complexity of these cases underscores the importance of developing diagnostic criteria that include histology because vasculitis cannot be ruled out without a skin biopsy. Therefore, the true incidence of minocycline-induced cutaneous PAN is unknown.

Drug-induced lupus and cutaneous PAN share some similar features, but should be considered separate entities. Arthritis, fever, fatigue, and positive ANA are nonspecific and cannot distinguish between the 2 conditions. The presence of pANCA, livedo reticularis, nodular lesions, and vasculitis on skin biopsy support the diagnosis of cutaneous PAN.

Diagnosis of rare conditions typically is based on the experience of the treating physician. Creation of specific diagnostic criteria would allow for uniform reporting, diagnosis, and treatment. The authors thus propose the following diagnostic guidelines. Consider minocycline-induced cutaneous PAN if a patient presents with 6 of the 7 following criteria: 1) minocycline use for >12 months, 2) skin manifestations including livedo reticularis and/or subcutaneous nodules, 3) arthritis and/or myalgias and/or neuropathy in the distribution of the rash, 4) lack of systemic organ involvement, 5) skin biopsy with necrotizing vasculitis of small- and/or medium-sized vessels, 6) pANCA, and 7) improvement after discontinuation of minocycline. Systemic diseases and conditions that mimic vasculitis should always be excluded.

Awareness of this presumably rare condition is important because effective treatment involves simply discontinuation of the medication. Short courses of prednisone have been beneficial in reducing the duration of symptoms. Repeat exposure to minocycline is contraindicated. This report adds to the growing body of literature regarding drug-induced vasculitis.

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