

Minocycline-induced Polyarteritis Nodosa-Like Vasculitis

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KEY WORDS: polyarteritis nodosa (PAN), minocycline, anti-neutrophil cytoplasmic antibody (ANCA), acne vulgaris

IMAJ 2014; 16: 322–323

Polyarteritis nodosa is a necrotizing vasculitis that typically affects medium-sized arteries. Most cases are idiopathic, although PAN has been associated with hepatitis B and C virus infections, human immunodeficiency virus, vaccinations and malignancy. PAN affects adult males more frequently, and symptoms result from the involvement of the skin, kidneys, heart, and nervous system. Systemic symptoms are frequent and include fever, fatigue, loss of appetite, weight loss, and myalgia and arthralgia [1].

Minocycline is a tetracycline derivative antibiotic commonly used to treat acne vulgaris. It has been associated with autoimmune disorders such as drug-related lupus, autoimmune hepatitis, cutaneous PAN, and anti-neutrophil cytoplasmic antibody-associated vasculitis [2]. Reports of minocycline-induced renal PAN are rare.

We report the case of a 19 year old male who was treated with minocycline for acne vulgaris and presented with recent onset of fever, weight loss, myalgias, and acute kidney injury.

PATIENT DESCRIPTION

A 19 year old male presented with fever that a week previously reached 39°C, weight loss of 8 kg, and myalgia and polyarthralgia a few months before presentation. Acute orchitis was diagnosed 1 month earlier and he was treated with antibiotics for 2 weeks.

PAN = polyarteritis nodosa

He was a healthy soldier and recalled no recent travel, environmental exposures, or family history of recent intercurrent diseases. His medical history included dust mite allergy and acne vulgaris treated with minocycline (100 mg twice a day) for the previous 3 years.

On physical examination, the patient appeared cachectic. His temperature was 36.5°C and blood pressure was normal. Diffuse arthralgias and myalgias were present, without signs of arthritis. The rest of the examination was unremarkable. Laboratory tests showed high serum creatinine 1.5 mg/dl, urea 43 mg/dl, aspartate aminotransferase 78 U/L, alanine aminotransferase 45 U/L, C-reactive protein 5.97 mg/dl, sodium 137 mEq/L, potassium 4.6 mEq/L. Urine dipstick showed protein trace, while microscopic evaluation did not show any red or white blood cells or casts. Chest X-ray and kidney ultrasound were normal. Immunological survey showed a positive antinuclear antibody at a titer of 1:40, but double-stranded DNA antibody was negative.

Perinuclear anti-neutrophilic cytoplasmic antibodies were positive at a titer of 1:80, with myeloperoxidase antibody titers of 7.26 U/ml (normal 0–5.0 U/ml). Additional serology, including hepatitis B and C, anti-streptolysin and rheumatoid factor, were negative; C3 and C4 were within normal limits.

In the setting of minocycline use, the combination of systemic symptoms, orchitis and acute kidney injury strongly suggest the diagnosis of drug-related PAN. Shortly after discontinuation of minocycline the patient's symptoms rapidly resolved. The fever and arthralgias disappeared within a few days with recovery of renal function. He was released from hospital 5 days after admission and referred

to the Rheumatology Outpatient Clinic for follow-up. He presented 1 month later with erythema nodosum-like lesions in both legs. Etodolac 600 mg/day was started. At the 2 month follow-up visit, he reported a significant amelioration of his symptoms. The cutaneous lesions had completely resolved, renal function recovered with a serum creatinine of 0.97 mg/dl, and liver enzymes normalized. p-ANCA and MPO antibodies were negative.

COMMENT

PAN is a rare, systemic necrotizing vasculitis that typically affects medium-sized arteries. However, occasionally, involvement of small-sized arteries has been described. The estimated prevalence ranges from 2 to 9 cases per million. Most cases occur between 30 and 49 years of age and the disease is more frequent in males (M/F ratio 2:1). Most reported cases are idiopathic but can occasionally be associated with hepatitis B or C, HIV, vaccinations, and malignancies. Patients typically present with non-specific symptoms including fever, weight loss, fatigue, myalgias and arthralgias. The organs classically involved are the skin, kidneys, gastrointestinal tract, central nervous system, and testes. Classification criteria for the diagnosis of PAN are presented in Table 1.

Minocycline is a tetracycline derivative antibiotic that exerts a bacteriostatic effect through bacterial protein synthesis. It is commonly used for the treatment of acne vulgaris. In the last two decades, several cases of minocycline-induced autoimmunity have been reported. Elkayam et al. [1] reviewed 82 cases and classified them

p-ANCA = perinuclear anti-neutrophilic cytoplasmic antibodies
MPO = myeloperoxidase
HIV = human immunodeficiency virus

Table 1. American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa

Criterion	Definition
Weight loss > 4 kg	Loss of 4 kg or more of body weight since illness began, not due to dieting or other factors
Livedo reticularis	Mottled reticular pattern over the skin of portions of the extremities or torso
Testicular pain or tenderness	Pain or tenderness of the testicles, not due to infection, trauma or other causes
Myalgias, weakness or leg tenderness	Diffuse myalgias (excluding shoulder and hip girdle) or weakness of muscles or tenderness of leg muscles
Mononeuropathy or polyneuropathy	Development of mononeuropathy, multiple mononeuropathies or polyneuropathy
Diastolic BP > 90 mmHg	Development of hypertension with diastolic BP higher than 90 mmHg
Elevated BUN or creatinine	Elevation of BUN > 40 mg/dl or creatinine > 1.5 mg/dl, not due to dehydration or obstruction
Hepatitis B virus	Presence of hepatitis B surface antigen or antibody in serum
Arteriographic abnormality	Arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes
Biopsy of small or medium-sized artery containing PMN	Histological changes showing the presence of granulocytes or granulocytes and mononuclear leucocytes in the artery wall

Courtesy of American College of Rheumatology

Classified as PAN if at least 3 of the 10 criteria are present

BP = blood pressure, BUN = blood urea nitrogen, PMN = polymorphonuclear neutrophils

into four groups: autoimmune hepatitis, drug-induced lupus, PAN-like vasculitis, and small vessel vasculitis.

In most cases, drug-induced vasculitis affects small vessels with a predilection for the skin. Drug-induced systemic vasculitis is rare and is characterized by positivity to p-ANCA and anti-MPO. The pathogenic role of myeloperoxidase in the drug metabolism and the creation of new haptens for autoantibodies have been reported [2]. Marzo-Ortega and colleagues [3] examined the association between minocycline therapy and ANCA positivity in 252 patients followed for acne. They found ANCA positivity in 5% of patients treated with minocycline. The most common pattern was p-ANCA (67%) with MPO positivity (87%).

Recently, Kermani et al. [4] reported nine patients with minocycline-induced PAN-like vasculitis. All patients were on longstanding minocycline therapy (median duration of 2 years). Four patients had isolated cutaneous disease and five presented with systemic symptoms, including fever, weight loss, arthralgia and myalgia (50–60%), central nervous system involvement (40%), renal disease (20%), and tes-

ticular pain (three of four men). In contrast to classical PAN, All patients were positive for p-ANCA, but specificity to MPO was observed in only two [4]. Diagnosis of PAN was confirmed by histopathology in six patients and by angiography in three. Minocycline was discontinued in all patients and resolution of symptoms occurred in all, including the six patients who required immunosuppressive treatment [4]. Reports of renal involvement in minocycline-induced PAN are rare. Kermani and co-authors described two patients who presented with hypertension and acute kidney injury. Kidney biopsy in one case showed well-demarcated regions of severe interstitial fibrosis and tubular atrophy coexisting with normal cortical parenchyma, suggesting large renal artery obstruction. The biopsy of the second patient showed signs of healed vasculitis, extensive glomerular ischemic changes with focal segmental glomerulosclerosis and large regions of interstitial fibrosis. Renal angiography in both patients showed the presence of microaneurysms of the second and third branches of the renal arteries [4].

Recently, Tabriziani et al. [5] reported a 21 year old woman with minocycline-induced renal PAN, who presented with sudden-onset hypertension, nephritic

range proteinuria and positive p-ANCA with specificity to MPO. Renal angiography revealed numerous microaneurysms in both kidneys. Blood pressure and proteinuria improved rapidly a few weeks after initiation of cyclophosphamide and prednisone.

The presenting symptoms and clinical picture of our patient strongly suggest the diagnosis of PAN. His young age, the absence of predisposing etiopathogenic factors, the presence of p-ANCA with specificity to MPO, and the rapid improvement after discontinuation of minocycline support the diagnosis of minocycline-induced PAN-like vasculitis. Based on the dramatic improvement after cessation of the drug, we decided not to perform invasive procedures such as kidney biopsy or renal angiography.

As described earlier, the involvement of myeloperoxidase in the minocycline metabolism induces the development of new haptens for autoantibody creation (anti-MPO and p-ANCA) and can be the potential mechanism in minocycline-induced PAN.

In summary, our case illustrates the potential role of minocycline, a widespread treatment for acne vulgaris, in the induction of autoimmune phenomena, and highlights the systemic presentation of minocycline-induced PAN.

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ANCA = anti-neutrophilic cytoplasmic antibodies