Minocycline-induced Polyarteritis Nodosa-Like Vasculitis

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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 several months before presentation. Acute 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 tests. 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

PAN = polyarteritis nodosa
p-ANCA = perinuclear anti-neutrophil cytoplasmic antibody
MPO = myeloperoxidase
HIV = human immunodeficiency virus
between minocycline therapy and ANCA.

Recently, Kermani et al. [4] reported ANCA positivity in 252 patients followed for 5% of patients treated with minocycline. They found ANCA positivity in 252 patients followed for 21 year old woman with minocycline-related 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 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].

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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References

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

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

ANCA = anti-neutrophilic cytoplasmic antibodies

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 hapten for autoantibody creation (anti-MPO and p-ANCA) and can be the potential mechanism in minocyclin-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.