Unexpected outcome (positive or negative) including adverse drug reactions

Minocycline-induced renal polyarteritis nodosa

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Summary

Minocycline is a bacteriostatic, long-acting, lipid-soluble tetracycline that is generally well tolerated, but has been associated with polyarteritis nodosa (PAN). This is a case report of a 21-year-old woman presented to her primary care physician with several months of fatigue, myalgias, weight loss and intermittent severe bi-temporal headaches without changes in vision. Her medications included an Ortho-Tri-Cyclen Lo and Minocycline, which she started 2 years prior for acne. On presentation, she was tachycardic and severely hypertensive. Initial laboratory evaluation showed hyponatraemia and hypokalaemia as well as elevation of inflammatory markers. Autoimmune work-up was positive for perinuclear antineutrophil cytoplasmic antibodies. Renal arteriogram was characteristic of PAN and along with her other symptoms, she fulfilled the necessary criteria of American College of Rheumatology for diagnosis of PAN. Minocycline as a possible causative agent was discontinued since it was reported to cause cutaneous PAN in the literature. Cyclophosphamide and prednisone were initiated for treatment of her vasculitis. Her symptoms and hypertension improved over the next several months. This is the first report of the minocycline-induced renal PAN.

BACKGROUND

Minocycline is a semi-synthetic derivative of tetracycline. It has bacteriostatic effect by inhibiting bacterial protein synthesis. It is long-acting and the most lipid-soluble of the tetracycline-class antibiotics. It is widely considered the most effective tetracycline derivative for the treatment of acne.¹

Minocycline is generally well tolerated; however, in 2009 the FDA added minocycline to its Adverse Event Reporting System, citing a potential link between the use of minocycline products and Drug Reaction with Eosinophilia and Systemic Symptoms syndrome.²

Polyarteritis nodosa (PAN), a necrotising vasculitis of medium-sized arteries, has been also linked to the use of minocycline; except for our report, this has been in relation to cutaneous lesions and vasculitic neuropathy.

The following is a case of minocycline-induced PAN with renal and mesenteric artery involvement. To the authors' best knowledge, this is the first case report of minocycline-induced PAN documenting visceral involvement.

CASE PRESENTATION

An athletic 21-year-old woman presented to her primary care physician with several months of worsening fatigue and myalgias that were now interfering with her college coursework. She had developed salt-craving, polyuria, easy bruising, dyspnoea on exertion, a 10 pound weight loss and pharyngitis. She experienced intermittent, severe bitemporal headaches without vision changes. Her medications were minocycline for acne and Ortho-Tri-Cyclen Lo. She did not use tobacco, alcohol, diet supplements or recreational drugs. She was referred to the emergency room and hospitalised.

On ER presentation, her BP was 177/121 mm Hg and HR was 111 beats/min, with no orthostatic changes. Cardiac, lung, abdominal and neurological exams were all normal. Extremity exam was without rash or skin lesions.

INVESTIGATIONS

Laboratory evaluation revealed serum sodium of 129 mmol/L, potassium 3.0 mmol/L, chloride 85 mmol/L, bicarbonate 32 mmol/L, creatinine of 0.9 mg/dL, and, urine protein/creatinine ratio of 3500 mg/g.

Urine microscopic evaluation did not show any red or white blood cells or casts. ECG was normal except for sinus tachycardia.

Studies to evaluate the hypertension and electrolyte abnormalities showed a plasma renin activity of 110 ng/mL/h, aldosterone 89 ng/mL, with an aldosterone: renin ratio of 0.6. A 24-h urinary fractionated metanephrines, catecholamines and 5-hydroxyindoleacetic acid were normal. A two-dimensional echocardiogram revealed a diminished ejection fraction of 40% without ventricular hypertrophy.

Urine electrolytes showed sodium 37 mmol/L, potassium 25.2 mmol/L, chloride 20 mmol/L, osmolality 300 mosm/kg with a serum osmolality of 280 mosm/kg with normal urine toxicology and diuretic screens. Proteinuria had improved to 1680 mg/24 h with improved BP control.

Imaging, including renal ultrasound with Doppler, computerised axial tomography with contrast of chest, abdomen and pelvis and positron emission tomography were normal excluding renal artery stenosis and a renin-secreting tumour.

Immunological studies showed an erythrocyte sedimentation rate of 85 mm/h and C-reactive protein of 4.3 mg/dL. Antinuclear antibody titer was 1:160 but double-stranded DNA antibody, extractable nuclear antigen antibodies and ribonucleoprotein antibody were negative. Perinuclear anti-neutrophil cytoplasmic antibodies (pANCA), specifically antimyeloperoxidase at 1.7 were present, and antiproteinase-3 was absent. In the setting of minocycline use, this picture along with the symptoms and hypertension suggested drug-induced PAN.

Figure 1 Renal arteriogram demonstrating many round subcentimeter microaneurysms.

An arteriogram was performed that revealed numerous subcentimeter microaneurysms in both kidneys (figure 1) and the superior mesenteric arterial vasculature, highly suggestive of PAN.

DIFFERENTIAL DIAGNOSIS

These radiological findings along with myalgia, diastolic hypertension and weight loss fulfilled 4 of the 10 criteria

Table 1 American College of Rheumatology 1990 criteria for the classification of Polyarteritis Nodosa

Classified as PAN if at least 3 of the 10 criteria are present:
1. Weight loss >4 kg: loss of >4 kg body weight since illness began, not related to dieting or other factors
2. Livedo reticularis: mottled reticular pattern over the skin of portions of the extremities or torso
3. Testicular pain/tenderness: pain or tenderness of the testicles, not due to infection, trauma or other causes
4. Myalgias, weakness or leg tenderness: diffuse myalgias (excluding shoulder or hip girdle) or weakness of muscles or tenderness of leg muscles
5. Mono- or polyneuropathy: development of mononeuropathy, multiple mononeuropathies or polyneuropathy
6. Diastolic BP >90 mm Hg: development of hypertension with the diastolic BP higher than 90 mm Hg
7. Elevated blood urea nitrogen (BUN) or creatinine: Elevation of BUN >40 mg/dl or creatinine >1.5 mg/dl, not due to dehydration or obstruction
8. Hepatitis B virus: presence of hepatitis B surface antigen or antibody in serum
9. Arteriographic abnormality: arteriogram showing aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia or other non-inflammatory causes
10. Biopsy of small or medium-sized artery containing polymorphonuclear cells: histological changes showing the presence of granulocytes or granulocytes and mononuclear leucocytes in the artery wall
Courtesy of American College of Rheumatology

of the American College of Rheumatology for diagnosis of PAN (table 1).

TREATMENT

Minocycline as the likely causative agent was discontinued. Because of significant visceral involvement including renal and cardiac abnormalities, cyclophosphamide and prednisone were initiated. Hypertension was controlled by using an ACE inhibitor.

OUTCOME AND FOLLOW-UP

Her symptoms rapidly improved, hypertension was well controlled and CRP and ESR returned to normal within 3 months after initiation of therapy; her left ventricular ejection fraction improved slightly to 45%. Measured proteinuria had improved to about 730 mg/g creatinine in 6 weeks and dipstick UA was normal at 6 months after diagnosis.

DISCUSSION

PAN is a systemic necrotising vasculitis that typically affects medium-sized muscular arteries, with occasional involvement of small muscular arteries. It usually involves multiple organs in a patchy distribution with areas of impressive necrosis and inflammation interspersed with unaffected vessels. It has a propensity for aneurysm formation, especially in the mesenteric circulation. Other target organs include the kidney, the peripheral nerves, heart and skin. Immune deposits are usually very minimal or absent. Antineutrophil cytoplasmic antibodies (ANCA) are typically negative, but patients with microscopic PAN may have ANCA directed against myeloperoxidase.^{3 4}

Patients with classic PAN can be any age, including children, but the peak onset is in the fifth or sixth decade. There is approximately a 2:1 male-to-female preponderance in most studies.⁵

Most cases of PAN are idiopathic although there are reports of PAN related to malignancies, infections, vaccinations and medications. These are considered secondary PAN. Important infectious causes of PAN include hepatitis B, hepatitis C and HIV-1. PAN following vaccination for influenza⁶ and hepatitis A⁷ has also been reported. It has been argued that some of these associations could be random events, or that PAN already was present before the exposure.⁵

Therapeutic agents from virtually every pharmacological class have been implicated in the development of drug-induced vasculitis. The exact pathogenic mechanisms involved remain to be elucidated, but cell-mediated and humoral immunity appear to play important roles.⁸ Among these agents, minocycline has been reported in many cases of PAN.

The presentation of minocycline-induced PAN can be abrupt, but is more typically a course of weeks to months of non-specific systemic symptoms including fever, weight loss, abdominal pain and arthralgias. Usually during this period, diagnosis is not clear and patients are often treated for other entities such as viral infections. Sudden events may occur which trigger a search for an alternative diagnosis, such as in this case the severe hypertension. This is usually a result of organ ischaemia, for example, ischaemia of the epineurium-causing mononeuritis multiplex, the loss of the function of multiple sensory and motor

nerves.^{9 10} The loss of function can be gradual but usually a sudden onset of motor nerve damage is the sentinel event.

Minocycline-induced PAN most commonly affects the arteries of dermis and panniculus and causes palpable subcutaneous nodules, purpura and even ulceration.^{4 11–15} Frequent sites are finger and ankles. In severe cases, it can even cause digital ischaemia. Splinter haemorrhage and livedo reticularis^{14 15} have also been reported.

This is the first report of minocycline-induced PAN affecting visceral arteries. While one previous report documented systemic PAN,¹⁰ abdominal aortography was negative in that patient. Our patient was also initially treated for a possible diagnosis of a viral infection with supportive therapy until she developed severe hypertension and hypokalaemia. Further work-up revealed high renin and aldosterone levels. With the hypothesis that PAN-related renal ischaemia was leading to activation of the renin-angiotensin system, an abdominal angiogram was done which showed aneurysm formation in both renal arteries and the superior mesenteric artery.

Mesenteric vasculitis, as in our case, usually causes dull abdominal pain which is often worsened by eating (intestinal angina). The combination of the malabsorption resulting from the ischaemia and avoiding oral intake because of intestinal angina are thought to cause weight loss. In severe cases, bowel ischaemia and even perforation can be seen.

Kidney involvement in PAN usually manifests only as hypertension, often with mild-to-moderate azotaemia.⁵ Incomplete luminal narrowing of the inflamed arteries leads to glomerular ischaemia but not inflammation or necrosis. The urinalysis can be normal or just show minimal proteinuria and perhaps modest haematuria, but red blood cell casts, which are indicative of a glomerular focus of inflammation, are usually absent.¹⁶ Rupture of renal arterial aneurysms can cause perirenal haematomas and severe pain. Renal infarctions may also develop in those with severe vasculitis causing sudden onset of flank pain associated with acute elevation of blood pressure. Interestingly, in idiopathic PAN, autopsy studies have shown that the kidneys are the most commonly involved organ.¹⁶

In summary, we are reporting a case that demonstrates that in addition to previously noted nerve and skin damage, minocycline-induced PAN can also cause significant visceral organ vasculitis, and should be considered a severe systemic disorder.

Learning points

- ▶ Minocycline can not only cause cutaneous polyarteritis nodosa (PAN) but can also cause PAN in the visceral organs.
- ▶ Always look for secondary causes of hypertension in young adults.
- ▶ Always review the list of the medication and search for adverse effects.
- ▶ Combination of hypertension and electrolyte abnormalities usually leads to a renal problem.

Competing interests None.

Patient consent Obtained.

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