

Fever, Eosinophilia, and Death: A Case of Minocycline Hypersensitivity

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Practice Points

- Minocycline has been associated with serious adverse effects including drug reaction with eosinophilia and systemic symptoms, which can be life-threatening.
- In cases of serious drug reactions, especially those with systemic symptoms, potentially offending medications should be immediately discontinued and systemic symptoms should be monitored.
- If rash or systemic symptoms from a drug reaction are persistent, further symptom-specific workup is warranted.

Minocycline (MCN) is a member of the tetracycline family that is commonly used to treat dermatologic conditions such as acne and perioral dermatitis; however, it also has been associated with a number of adverse effects, including drug reaction with eosinophilia and systemic symptoms (DRESS). We report the case of a 46-year-old woman who developed a rash, fever, and eosinophilia during treatment with MCN for perioral dermatitis. Although MCN was discontinued and the patient was administered oral corticosteroids for several months, she subsequently died from multiorgan failure with giant cell myocarditis (GCM) and eosinophilic myocarditis found on autopsy. This article highlights a rare consequence of hypersensitivity to a commonly used drug and illustrates the importance of rapid recognition and aggressive management of MCN-induced DRESS.

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Minocycline (MCN) is a semisynthetic, second-generation tetracycline with good skin penetration that is widely used to treat various dermatologic conditions¹; however, it also has been associated with several adverse effects, including

rare serious systemic reactions such as drug-induced lupus erythematosus, drug-induced hepatitis, and drug reaction with eosinophilia and systemic symptoms (DRESS).²

We report the case of a 46-year-old woman who developed a rash, fever, and eosinophilia from MCN for perioral dermatitis. Despite discontinuation of MCN and treatment with oral corticosteroids, she subsequently died of multiorgan failure, with giant cell myocarditis (GCM) and eosinophilic myocarditis found on autopsy.

Case Report

A 46-year-old woman developed fever (temperature, 39.5°C), arthralgia, and elevated liver function tests (LFTs) 3 weeks after starting MCN therapy for perioral dermatitis. Her medical history was otherwise unremarkable. Minocycline was discontinued within 3 days of onset of symptoms; however, 1 month later the patient continued to experience fevers and developed lymphadenopathy as well as a scaly erythematous eruption. She was subsequently hospitalized. On admission, she was found to have leukocytosis (4400/ μ L [reference range, 4300–10,000/ μ L]), eosinophilia (4100/ μ L [reference range, 0–700/ μ L]), and a peak creatinine level of 7600/ μ L (reference range, 700–1200/ μ L). Skin lesions were biopsied revealing leukocytoclastic vasculitis with eosinophils. She was started on methylprednisolone 40 mg daily. Acute renal failure was attributed to interstitial nephritis secondary to drug hypersensitivity with eosinophilia. During her hospitalization, the patient developed atrial fibrillation, which was pharmacologically converted. An echocardiogram showed no abnormalities. Further laboratory workup revealed a negative autoimmune panel with negative antinuclear, Smith,

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ribonucleoprotein, and Scl-70 antibodies and normal IgE levels.

The patient's rash, low-grade fever, and eosinophilia persisted following her discharge from the hospital despite a continued high dose of methylprednisolone daily (mean, 40 mg). Meanwhile, her renal function returned to normal within weeks after discharge. Three months after discharge she presented to our clinic with erythroderma (Figure 1) and intermittent low-grade subjective fevers. She was taking methylprednisolone 40 mg daily. Repeat biopsies of the rash showed interface dermatitis consistent with a hypersensitivity reaction (Figure 2). She had an eosinophil count of 1300/ μ L (reference range, 200–500/ μ L), normal LFTs, normal renal function, and another negative antinuclear antibody titer. A peripheral blood smear revealed absolute neutrophilia, eosinophilia, and mild thrombocytosis but normal cell morphologies.

Six months after her initial presentation, the patient was admitted to the hospital for chest tightness, shortness of breath, and malaise. Interestingly, her rash was not present on admission. Electrocardiograms showed an accelerated junctional rhythm and ST-segment abnormalities. A cardiac catheterization showed normal left ventricular and coronary arteriograms. An echocardiogram revealed normal left ventricular systolic function but a small pericardial effusion as well as septal hypokinesis. Computed tomography of the chest, abdomen, and pelvis showed no acute changes but was suggestive of hepatic venous reflux and possible right-sided heart failure. Laboratory studies demonstrated elevated LFTs as well as creatinine, brain natriuretic peptide, creatine kinase (CK), and CK-MB levels; however, the troponin I levels and CK-MB to CK ratio were normal. Two days after admission, an electrocardiogram showed continued conduction system abnormalities with sinus tachycardia, first degree atrioventricular block, and possible left bundle-branch block. The patient's clinical picture worsened over the next few days as she developed epigastric pain, wide complex tachycardia with left bundle-branch block, and shock, which required defibrillation, pressor support, and cardiopulmonary resuscitation. She subsequently developed metabolic acidosis and died 1 day later.

A postmortem examination revealed myocarditis with an infiltrate of lymphocytes, eosinophils, and multinucleated giant cells spanning the entire thickness of the myocardium. The final diagnosis was a marked eosinophilic myocarditis and GCM.

Comment

Although the most common adverse effects of MCN include nausea, vomiting, dizziness, and hyperpigmentation, our patient showed more severe signs of



Figure 1. Erythroderma following minocycline treatment (A). Keratotic plaques were present on the feet (B).

multiorgan failure and died 7 months after starting treatment with MCN for perioral dermatitis. Cardiac changes were the major abnormality found on autopsy and were consistent with GCM and eosinophilic myocarditis, both rare and potentially fatal entities.

Giant cell myocarditis is an uncommon disease that tends to affect young to middle-aged adults. As of 1997, the Multicenter Giant Cell Myocarditis Study Group Investigators logged 63 cases of GCM.³ The rate of death or cardiac transplant is 89% and the median survival is 5.5 months from onset of symptoms. Symptoms usually are related to conduction system

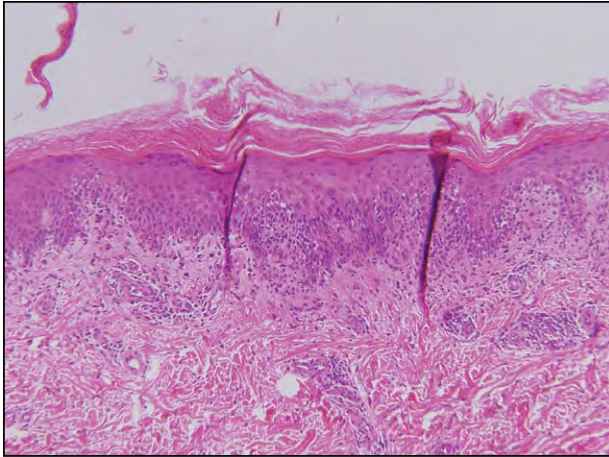


Figure 2. A skin biopsy revealed interface dermatitis (H&E, original magnification $\times 200$).

disease, tachyarrhythmias, or left ventricular dilation, and the diagnosis can be made from clinical symptoms and endomyocardial biopsy.⁴ Giant cell myocarditis usually is idiopathic, but approximately 20% of cases have been associated with autoimmune disorders, tumors, or infections.⁵ Four known cases of drug-induced GCM have been reported in the literature, with 1 case resulting from treatment with MCN.⁶ The patient was being treated with MCN for acne. Four weeks after starting the drug, she developed fever, hepatitis, and rash. Minocycline was discontinued, and the patient was started on daily prednisone. Three months later the patient was hospitalized with abdominal pain, fever, hypotension, and electrocardiogram evidence of conduction abnormalities. The hypotension was refractory to treatment and she subsequently died. An autopsy revealed GCM.⁶

Drug hypersensitivity-associated myocarditis, the other component of our patient's final diagnosis, typically is known as acute eosinophilic myocarditis, which is characterized by fever, rash, peripheral eosinophilia, and elevated hepatic enzymes, and often is associated with administration of tetracyclines, carbamazepine, or sulfonamides. The onset usually is from days to months after exposure to the offending drug, and cardiac abnormalities can range from ST-segment elevation to mild systolic dysfunction, myocardial wall thickening, or pericardial effusion.⁷ One known case of acute eosinophilic myocarditis following MCN treatment has been reported in the literature.⁸ In that case, a 15-year-old adolescent boy developed fever, pustular eruption, elevated hepatic enzymes, leukocytosis with eosinophilia, and enlarged lymph nodes 1 month after starting treatment with MCN. He responded to treatment with prednisone 1 mg/kg daily for 2 months but died 2 weeks after the prednisone was discontinued. Myocardial necrosis with eosinophilic infiltrate was found on autopsy.⁸

Although hypersensitivity myocarditis usually is self-limited and controlled with 1 mg/kg of prednisone, corticosteroid treatment usually is insufficient for treatment of GCM.⁹ There are data to suggest that patients with GCM should be treated with a combination of corticosteroids and cyclosporine, muromonab-CD3, or azathioprine.³⁻⁶ Symptomatic treatment with angiotensin-converting enzyme inhibitors, antiarrhythmics, or a pacemaker along with early placement on a cardiac transplant list also may be warranted.³

The list of adverse effects associated with MCN is long, but MCN-associated cardiac events are rarely reported in the literature. Common side effects of MCN include gastrointestinal tract upset, dizziness, and/or vertigo; more concerning but less common hypersensitivity reactions include DRESS, toxic or autoimmune hepatitis, drug-induced lupus, serum sickness-like reaction (SSLR), polyarteritis nodosa, pulmonary eosinophilia, interstitial pneumonia, and Sweet syndrome.^{2,10-13} Single or multiorgan dysfunction, DRESS, and SSLR usually manifest within 4 weeks of starting MCN therapy, whereas drug-induced lupus typically occurs 2 years after initiation of MCN.¹² Of note, there has been one report each of MCN-associated eosinophilic pericarditis and pericardial effusion in the literature.^{14,15}

These adverse reactions to treatment with MCN are important given its ubiquitous use in dermatology. Approximately 65% of prescriptions for MCN in the United States are written for the treatment of acne.¹⁶ The safety of MCN has been reviewed by several sources. A review of cases of hypersensitivity syndrome reaction, SSLR, single organ dysfunction, and drug-induced lupus in patients taking tetracycline, MCN, or doxycycline revealed that more patients with hypersensitivity syndrome reaction, SSLR, or drug-induced lupus were taking MCN.¹² Although doxycycline was prescribed 3 times more frequently than MCN in the United States from 1998 to 2003, the rate of adverse events (AEs) was calculated to be about 6-times higher for MCN.² Adverse events were tabulated from case reports and AE reports from clinical trials; AEs associated with doxycycline included gastrointestinal tract upset and skin reactions (eg, photosensitivity), and those associated with MCN included hyperpigmentation, hypersensitivity, lupuslike syndrome, central nervous system symptoms, and gastrointestinal tract effects. Overall, the incidence of AEs for both medications was rare, with event rates of 13 and 72 per million for doxycycline and MCN, respectively.²

Two particularly concerning MCN-associated AEs are autoimmunity and DRESS. Our patient did not show signs of autoimmunity, but the possibility of long-term autoimmune sequelae after MCN treatment was highlighted in a case report of a 15-year-old adolescent

girl who developed DRESS that manifested as fever, facial swelling, erythroderma, leukocytosis with eosinophilia, and elevated transaminitis. The patient developed autoimmune hyperthyroidism 7 weeks after MCN discontinuation and type 1 diabetes mellitus 7 months later.¹⁷ A case-control study of 29 patients in the United Kingdom found that current use of MCN conferred an 8.5-fold increase in the risk for developing lupuslike syndrome compared to a 1.7-fold increase with the other tetracyclines. The study also found increased prevalence in females and in patients taking 100 or more daily doses of MCN.¹⁶ The most common presentation of lupuslike syndrome tended to be arthralgia and/or arthritis, with constitutional symptoms of fever, weight loss, or malaise following prolonged exposure to MCN.^{1,11} Serology for antinuclear antibodies or antineutrophil cytoplasmic antibodies are positive in the majority of cases.¹ Although the majority of patients experience resolution soon after or within a year of MCN discontinuation, chronic MCN-induced autoimmunity has been reported in a subgroup of patients.¹

The pathogenesis of MCN-associated DRESS is unknown, though several theories have been proposed. Unlike the other tetracyclines, MCN metabolism may generate a reactive iminoquinone derivative, which may act as a hapten or bind to tissue macromolecules and cause cell damage.¹¹ Interestingly, patients with DRESS may have persistent levels of MCN in the skin or plasma, which may represent aberrant metabolism and accumulation of MCN.¹⁸

Conclusion

Based on our case and others reported in the literature, it is clear that MCN can have serious and potentially long-lasting adverse effects, including death. Although other tetracyclines are known to have a long list of possible side effects, MCN is most frequently associated with DRESS, lupuslike syndrome, and other severe reactions. It is important to consider the potential for these serious adverse reactions when prescribing MCN. We are not promoting cessation of MCN use. We do suggest, however, that an adverse reaction to minocycline, such as a prolonged rash with fever and eosinophilia, be treated quickly and aggressively. A thorough workup including complete blood cell count, metabolic panels (ie, hepatic and renal enzymes), and investigation of any additional symptoms should be performed. The offending medication should be withdrawn and aggressive treatment with corticosteroids and additional immunosuppressants may be warranted.

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