CASE REPORT

THE PATIENT
17-year-old girl

SIGNS & SYMPTOMS
– Abdominal pain
– Lower-leg itching
– Dark urine & yellow eyes

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THE CASE

A 17-year-old White girl with no known past medical history presented to the emergency department (ED) with complaints of abdominal pain and pruritus. The abdominal pain had started 9 days prior and lasted for 3 days. One day after resolution, she developed bilateral lower extremity itching, which was not relieved with loratadine.

Review of systems included dark urine and yellow eyes noted for several days. The patient denied nausea, vomiting, diarrhea, constipation, fevers, chills, arthralgias, recent illness, travel, or sick contacts. Immunizations were up to date. The patient had no history of surgery or liver disease and no pertinent family history. Her current medications included ethinyl estradiol/norethindrone acetate for birth control and minocycline for acne vulgaris. She had been taking the latter medication for 2 years. No additional medications were noted, including vitamins, over-the-counter medications, or supplements. She denied smoking and alcohol or recreational drug use.

In the ED, the patient had normal vital signs. Physical exam findings included bilateral scleral icterus and scattered skin excoriations on the hands, arms, back of the neck, and feet. At the time of hospital admission, the patient's minocycline and birth control were held under the initial presumption that one or both might be contributing to her presentation.

Pertinent laboratory findings included aspartate transaminase (AST), 828 U/L (normal range, 2-40 U/L); alanine aminotransferase (ALT), 784 U/L (normal range, 3-30 U/L); lactic acid dehydrogenase, 520 U/L (normal range, 140-280 U/L); alkaline phosphatase, 119 U/L (normal range, 44-147 U/L); total bilirubin, 1.9 µmol/L (normal range, 2-18 µmol/L); and direct bilirubin, 1.3 µmol/L (normal range, 0-4 µmol/L). Baseline liver function test results (prior to admission) were unknown. Results of a coagulation panel, complete blood count, basic metabolic panel, amylase, lipase, urine toxicology, and urinalysis all were within normal limits.

Ultrasound of the abdomen revealed a normal abdomen, liver, pancreas, gallbladder, and common bile duct. This imaging study was negative for other obstructive pathologies.

THE DIAGNOSIS

During hospital admission, a noninvasive liver work-up was pursued by Gastroenterology. A hepatitis panel, Epstein-Barr virus testing, and levels of ceruloplasmin and acetaminophen were all found to be within normal limits, excluding additional causes of liver disease. Serum antinuclear antibody (ANA) testing was significantly positive, with a titer of 1:640 (range, < 1:20) and, as noted above, liver transaminases were severely elevated, leading to a presumptive diagnosis of drug-induced liver pathology.

During outpatient follow-up with Gastroenterology 2 days after discharge, the patient's liver transaminases and bilirubin continued to trend upward (to a maximum ALT of 871 U/L; AST, 1097 U/L; alkaline phosphatase, 122 U/L; and bilirubin, 2.9 µmol/L). Im-

munoglobulin G was 1342 mg/mL (normal range, 694-1618 mg/mL).

An ultrasound-guided liver biopsy was performed; it demonstrated lobular, portal, and periportal hepatitis with focal bridging necrosis, consistent with a diagnosis of autoimmune hepatitis. Mild-to-moderate focal cholestasis was demonstrated, consistent with cholestatic hepatitis.

DISCUSSION

Autoimmune hepatitis is characterized by inflammation of the liver, secondary to the presence of circulating antibodies or hypergammaglobulinemia. The pathogenesis is thought to involve a T-cell–mediated immune attack on the liver. Based on case reports, the use of minocycline is associated with risk for liver injury, although the incidence is rare.[1-4] Use of this medication may be associated with autoimmune disease in patients who are predisposed to autoimmune tendencies or who have genetic predeterminants.

Diagnosis is typically made based on abnormalities in aminotransferases (AST, ALT), elevation in serum immunoglobulins, and positive auto-antibody titers including ANA, smooth muscle antibodies, and anti-liver kidney microsomal type 1 antibodies. Although clinical presentations tend to differ, the confirmatory diagnosis is typically made histologically, with the presence of lobular and perivenular necro-inflammatory changes and plasma cell infiltration.[5]

Other infectious and metabolic causes of hepatitis should be excluded. Many medications and herbal agents have been noted to cause autoimmune hepatitis or similar syndromes that mimic the condition.

Medication history. Review of the case patient's medication list identified ethinyl estradiol/norethindrone acetate and minocycline as potential culprits. Ethinyl estradiol/norethindrone acetate is a low-dose combination oral contraceptive pill (OCP). Although earlier formulations of OCPs were associated with hepatobiliary complications, these adverse effects are noted to be rare in the absence of predisposing conditions.[6] In some cases, OCPs have been linked to cholestasis, chronic hepatocellular carcinoma, or hepatic adenomas, but studies have shown that these medications do not affect the course of acute liver failure.[7]

Minocycline is a second-generation tetracycline commonly used to treat acne vulgaris. Long-term treatment with minocycline has been associated with severe adverse effects, including autoimmune and hypersensitivity reactions.[8] Minocycline-associated hepatotoxicity can be due to a systemic hypersensitivity reaction, occurring within a few weeks of therapy initiation, whereas autoimmune hepatitis manifests after a year or more of exposure to the medication (as in this case). Patients may present acutely several months after starting the medication, with symptoms of jaundice, fatigue, and/or joint aches. The acute liver injury is typically self-limited and often resolves with cessation of the drug. However, patients may require corticosteroids and immunosuppressive therapy.

Which is it? Histologically, drug-induced autoimmune hepatitis is indistinguishable from idiopathic autoimmune hepatitis.[3] The estimated incidence of idiopathic autoimmune liver disease ranges from 0.7 to 2 out of 100,000 population.[9] A systematic review of the literature identified 65 reported cases of liver damage associated with minocycline specifically.[1]

In this case, given the patient's 2-year history of minocycline use, it is possible that she developed an acute presentation of autoimmune hepatitis. With drug-induced autoimmune liver injury, complete resolution occurs after withdrawal of the offending medication, and a response to corticosteroid therapy supports the diagnosis. Recurrence of signs or symptoms following corticosteroid cessation may indicate idiopathic autoimmune hepatitis as opposed to a drug-induced form.[2]

Our patient was started on steroid and immunomodulator therapy, with prednisone 40 mg/d and mycophenolate 250 mg bid. At follow-up with Gastroenterology, the patient's symptoms and liver function test results had improved significantly (AST, 27 U/L; ALT, 14 U/L; alkaline phosphatase, 51 U/L; and total bilirubin, 0.4 µmol/L). The patient

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was continued on a prednisone taper while simultaneously titrating mycophenolate. The ultimate plan of care included continuing mycophenolate for a total of 4 to 5 years.

THE TAKEAWAY

During evaluation of a patient with new-onset liver disease, it is important to inquire about prescription medications, drugs, vitamins, and herbal supplements as possible contributors to the disease process. This case highlights the importance of monitoring patients while on minocycline and of weighing the risks vs benefits of long-term therapy. It has been suggested that liver enzymes be tested before therapy initiation and about every 3 months during long-term antibiotic treatment.[4] Careful consideration and caution should be taken prior to the initiation of medications that have been linked to rare, but important, adverse reactions. JFP

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