ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Doxycycline-Induced Autoimmune Hepatitis

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ABSTRACT

Doxycycline and minocycline are tetracyclines with the potential to cause hepatoxicity. Although autoimmune-like hepatitis from minocycline is well-described, doxycycline-induced autoimmune hepatitis (DIAH) has only been described once. We report a rare case of DIAH with elevated liver enzymes over 5 times the normal upper limit, elevated immunoglobulin G, and high titers of antismooth muscle antibody and antinuclear antibody. By stopping doxycycline, our patient's liver enzymes normalized and immunoglobulin G and autoantibody titers rapidly downtrended. As long-term doxycycline therapy becomes more prevalent to treat acne vulgaris and other skin conditions, DIAH may become more prevalent and recognized.

INTRODUCTION

Certain drugs can cause a type of liver injury that has features similar to autoimmune hepatitis, with elevated immunoglobulins, antinuclear antibodies, and antismooth muscle antibody. The liver biopsies in these cases are often indistinguishable from autoimmune hepatitis. This autoimmune-like injury is most commonly seen with minocycline and nitrofurantoin and can also be caused by hydralazine, methyldopa, atorvastatin, diclofenac, infliximab, and isoniazid.[1,2] It predominantly affects women in a hepatocellular pattern.[3] With discontinuation of the offending agent, mild to moderate forms of this drug-induced liver injury typically resolves in 1–3 months; severe forms with jaundice may require a short course of steroids. Unlike classic autoimmune hepatitis, drug-induced autoimmune-like hepatitis does not recur after steroids are discontinued, unless there is re-exposure to the offending agent.[4]

Although it shares a similar tetracycline structure to minocycline, doxycycline has been implicated in only 1 recently reported case of drug-associated autoimmune hepatitis; otherwise, this is not a known type of reaction with doxycycline.[5,6] We report the second case of doxycycline-induced autoimmune hepatitis.

CASE REPORT

A 50-year-old white woman with previously normal liver enzymes was referred to the Liver Clinic for abnormal liver enzymes noted on routine laboratory test results ordered by her primary physician. She was found to have the following: aspartate aminotransferase of 222 IU/L, alanine aminotransferase of 445 IU/L, total bilirubin of 0.7 mg/dL, alkaline phosphatase of 80 IU/L, albumin of 4.1 g/dL, and total protein of 8.1 g/dL. She was otherwise asymptomatic, without any abdominal pain/distention, confusion, nausea, vomiting, jaundice, fatigue, fever, or rash. Her history was notable for several decades of severe acne vulgaris of the face, neck, and back that required long courses of oral antibiotics. She had been taking doxycycline 50 mg orally daily for acne for the past 14 months. Otherwise, she did not consume alcohol and was not taking any other medications, including vitamins, herbal supplements, and over-the-counter medications. She had documented normal liver tests after 2 months of doxycycline therapy.

Regarding her long-standing history of acne, she had previously been exposed to courses of minocycline and doxycycline in the past 9 years. Her last exposure to doxycycline was 5 years ago at a higher dose (100 mg/d), which she took for a few months before she was switched to minocycline because of gastrointestinal upset and photosensitivity. She then received 4 years of minocycline 100 mg daily that was stopped 1 year before the current course of doxycycline.

In addition to her elevated liver enzymes and elevated globulin gap, she was found to have an international normalized ratio 1.2, elevated actin antibody of 65 units, antismooth muscle antibody titer 1:2,560, antinuclear antibody titer 1:2,560 (heterogeneous pattern),

ACG Case Rep J 2020;7:e00440. doi:10.14309/crj.0000000000000440. Published online: August 10, 2020

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immunoglobulin G 2,512 mg/dL, and elevated ferritin 301 ng/mL (transferrin saturation 36%). She had normal platelets (220×10^9/L; normal value $> 150 \times 10^9$/L) and normal eosinophils. She was previously immunized for hepatitis A and hepatitis B. Her other viral hepatitis workup was negative, and her ceruloplasmin and alpha-1 antitrypsin levels were normal.

The decision was made to undergo liver biopsy to further stage and confirm her autoimmune hepatitis. It was notable for predominantly lobular hepatitis with focal interface activity without iron deposits (Figure 1). Periodic acid-Schiff-diastase stain highlighted scattered lobular and portal ceroid-laden macrophages (Figure 2). No fibrosis on trichrome stain, which highlighted the areas of hepatocyte dropout (Figure 3). The combined clinicopathologic features and history favored autoimmune hepatitis-like drug reaction to doxycycline vs autoimmune hepatitis. After discontinuation of doxycycline, the patient's repeat liver tests were normal, and her antibody titers and immunoglobulin G improved significantly (Table 1).

DISCUSSION

Doxycycline and minocycline are the most commonly prescribed antibiotics by dermatologists. They are often used for several weeks to months for the treatment of acne and rosacea. Doxycycline use for acne was bolstered by a 2012 Cochrane analysis that did not demonstrate the superiority of minocycline to doxycycline, and although it has less risk of photosensitivity, oral minocycline is not approved for rosacea by the U.S. Food and Drug Administration.[7]

Doxycycline is known to rarely cause hepatotoxicity, typically within 1–2 weeks of therapy, in a mixed, hepatocellular, or cholestatic liver injury pattern.[6] The autoimmune-like hepatitis associated with minocycline was traditionally not believed to be associated with doxycycline. However, in this case, a patient took

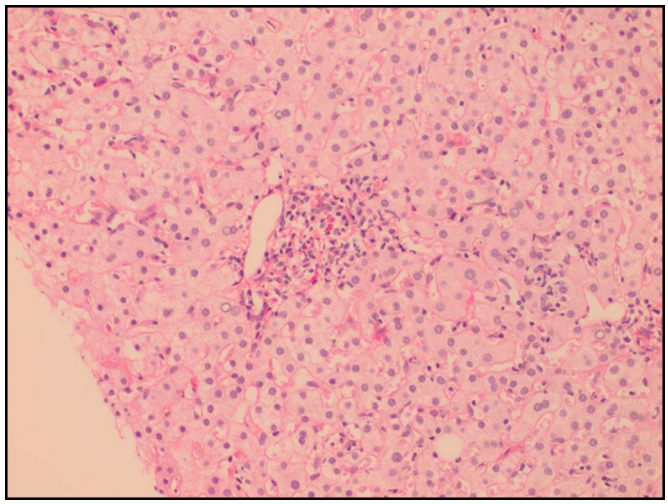

Figure 2. Periodic acid-Schiff-diastase stain highlights scattered lobular and portal ceroid-laden macrophages.

doxycycline 50 mg PO daily for 14 months for acne vulgaris and developed an autoimmune hepatitis reaction that resolved with withdrawal of doxycycline. Signs of hypersensitivity reaction (fever, rash, and eosinophilia) were not appreciated in this case. It is noteworthy that this patient had received previous courses doxycycline 5 years before this incident and had been on minocycline until 1 year before this more recent course of doxycycline. Owing to the structural similarity, previous exposure to minocycline may have predisposed this patient to immune-mediated liver injury, characterized by autoimmune reactions against liver cells.

Drug-induced autoimmune-like hepatitis is a diagnosis based on clinical judgment. We present the second case of doxycycline-induced autoimmune hepatitis. Unlike classic autoimmune hepatitis, this patient's liver enzymes normalized after approximately 1 month and 4 months after discontinuation of doxycycline without the intervention of corticosteroids. The patient's female sex is a risk factor for this drug-induced condition. The

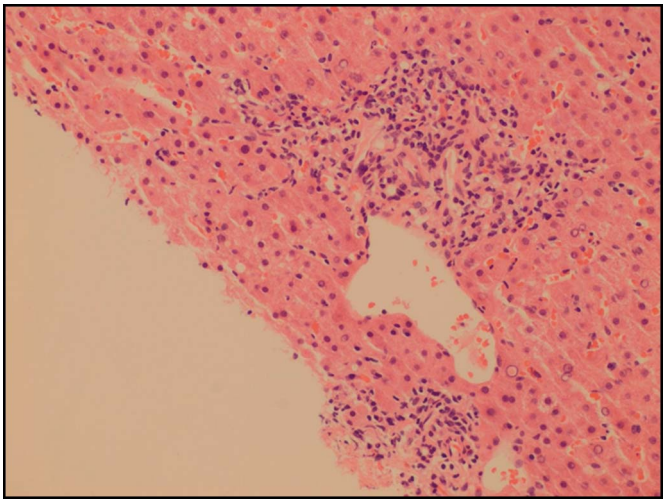

Figure 1. Mild, predominantly lobular lymphohistiocytic and lymphoplasmacytic inflammation with focal interface hepatitis.

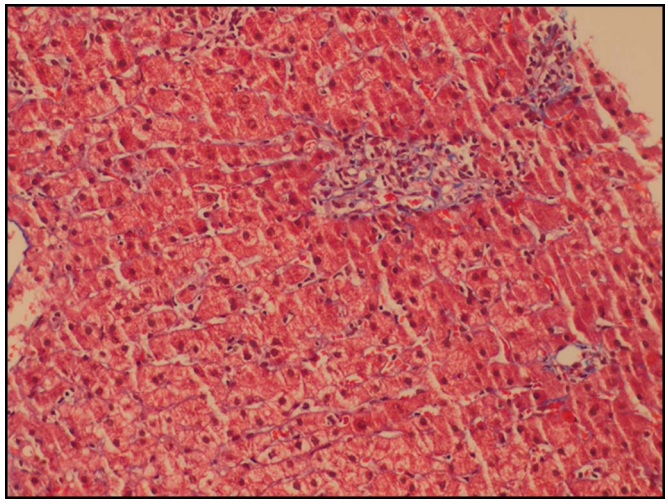

Figure 3. Trichrome special stain highlights areas of hepatocyte dropout; no definite fibrosis.

Table 1. Time course of doxycycline exposure and laboratory values

Time after starting doxycycline (mo)	Time after stopping (mo)	AST (IU/L)	ALT (IU/L)	AlkP (IU/L)	Bilirubin (mg/dL)	ANA	ASMA	IgG (mg/dL)
2		23	22	81	0.3			
14		222	445	80	0.7	1:2,560	1:2,560	2,512
	1	37	40	66	0.3			2,054
	4	25	21	67	0.5	1:1,280	1:320	1,733
Normal values		<42	<45	<104	<1.3	Non-reactive	<1:20	552–1,631

ALT, alanine aminotransferase; ANA, against nuclear antigen; ASMA, antismooth muscle antibody; AST, aspartate aminotransferase; IgG, immunoglobulin G.

insidious onset with long-term doxycycline use is similar to the experience with minocycline. Autoimmune-like hepatitis typically occurrs after at least 1 year of minocycline exposure, but a patient with previous exposure to minocycline could develop this syndrome as early as 10–60 days.[8] Given widespread and prolonged use of doxycycline in young patients for management of acne, it is important for clinicians to recognize the possible role of doxycycline in causing liver injury with autoimmune features and discontinue it promptly. Corticosteroid therapy can be avoided in patients without signs of liver failure who improve promptly after discontinuation of the implicated agent.

DISCLOSURE

Author contributions: JJ Pan wrote the manuscript and is the article guarantor. K. Promrat approved the final manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received March 21, 2020; Accepted May 21, 2020

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