Toxin-Induced Autoimmune Hepatitis Caused by Raw Cashew Nuts

James F. Crismale, MD1, Ashley Stueck, MD2, and Meena Bansal, MD1

1Division of Liver Diseases, Icahn School of Medicine at Mount Sinai, New York, NY
2Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY

ABSTRACT
A 64-year-old man with no past medical history presented with abnormally elevated liver enzymes 1 year after developing a diffuse rash thought to be related to eating large quantities of raw cashew nuts. Liver biopsy was performed, which revealed features concerning for drug- or toxin-induced autoimmune hepatitis. The patient began treatment with azathioprine and prednisone, and liver enzymes normalized. We describe a unique case of a toxin-induced autoimmune hepatitis precipitated not by a drug or dietary supplement but by a food product.

INTRODUCTION
Idiosyncratic drug-induced liver injury (DILI) is rare but carries with it significant morbidity and mortality.1 Drug-induced autoimmune hepatitis (DIAIH) is a variant of DILI that may account for 6%-22% of cases and is most commonly seen after exposure to minocycline or nitrofurantoin.2-4 There are also rare case reports linking consumption of particular food products to the development of AIH.5,6

CASE REPORT
A 64-year-old man with no comorbidities presented with persistently elevated liver enzymes. One year prior to presentation, he developed a diffuse rash after eating large quantities of raw cashews (8 ounces nightly for 1 month). The rash was pruritic and consisted of confluent erythematous patches that developed first on his buttocks, then spread to his back and extremities. He denied jaundice or abdominal pain at that time, and his liver enzymes were normal, with alanine and aspartate aminotransferases both below 20 IU/L. A dermatologist diagnosed him with symmetrical drug-related intertriginous and flexural exanthema (“baboon syndrome”) and started the patient on a 2-week course of prednisone 60 mg daily, after which the rash improved.

Three months after the steroids were discontinued, bloodwork revealed elevated transaminases, with a serum alanine aminotransferase of 247 IU/L and aspartate aminotransferase of 155 IU/L. Alkaline phosphatase, γ-glutamyl transferase, and bilirubin levels were within normal limits. Extensive review of his history revealed no other new drug or dietary supplement exposures. Viral hepatitis serologies, quantitative immunoglobulins, and autoimmune markers including antinuclear, anti-smooth muscle, anti-liver/kidney microsomal, and anti-soluble liver antigen antibodies were all within normal limits. Skin prick allergy testing revealed no hypersensitivity to cashews or other nuts. Ultrasound of the liver was unremarkable, and transient elastography demonstrated normal liver stiffness. Magnetic resonance imaging of the liver revealed no steatosis, iron deposition, or evidence of cirrhosis. Over the next year of observation, his transaminases decreased from their initial peak but never fully normalized.
The temporal correlation of the initial peak in liver enzymes, the timing of cashew ingestion, and the appearance of the rash suggested a possible immune-mediated phenomenon, despite negative autoimmune markers. To make a definitive diagnosis, the patient underwent liver biopsy. Histopathological review revealed mild mixed portal inflammation including lymphocytes, eosinophils, and some plasma cells, along with mild interface hepatitis (Figure 1). Frequent centrilobular hepatocyte necrosis and dropout with bridging necrosis was noted, with ceroid-containing macrophages seen in areas of inflammation and dropout (Figure 2). These features were concerning for AIH, likely precipitated by a drug or toxin. Consequently, the patient was started on daily azathioprine 50 mg and prednisone 20 mg. Four weeks later, aspartate and alanine aminotransferases trended down from 89 and 126 IU/L, respectively, to 38 and 29 IU/L, respectively. After 16 weeks of treatment, the patient’s transaminases normalized, and prednisone was tapered. Assuming sustained biochemical response, the steroids will be tapered off completely and azathioprine continued for maintenance. A trial of withdrawal of immunosuppression may be attempted pending histological resolution on repeat biopsy.

DISCUSSION

The patient’s biopsy findings, in conjunction with the timing of exposure to raw cashews, and his favorable response to immunosuppression, is consistent with DIAIH. Raw cashews contain anacardic acid, a component of cashew nut oil that is highly allergenic and chemically similar to uroshiol, the allergen in poison ivy. Reactions ranging from rash to anaphylaxis can occur when the nut is improperly roasted and residual cashew nut oil remains.7,8 Due to passage of cashew nut oil in the stool, the rash typically begins in a symmetrical fashion on the buttocks, then extends to the groin and other flexural areas.9 The rash is known colloquially as baboon syndrome, as its initial distribution mimics the ischial callosities seen in baboons.10

In this case, the anacardic acid of the cashew nut produced AIH via a DIAIH-like mechanism. Typically, DIAIH presents similarly to other forms of AIH and accounts for approximately 6%-22% of DILI cases.2-4 The clinical course, including time to onset and response to withdrawal of the drug, may help distinguish DIAIH from classic DILI. Patients may present with nonspecific symptoms including fatigue, abdominal pain, and jaundice. The pattern of liver enzyme abnormalities is typically hepatocellular, with transaminases elevated out of proportion to other liver tests, including alkaline phosphatase, γ-glutamyl transferase, and bilirubin. Further, there may be a greater latency of onset between exposure and the development of abnormal liver tests and/or symptoms in DIAIH as compared to DILI.4,9 Finally, the patient should meet the simplified diagnostic criteria for AIH, which is a prospectively validated clinical scoring system that assigns a probability for the diagnosis of AIH based on the presence of autoantibodies, immunoglobulin G, and compatible liver histology.12

While pathology is helpful, the distinction between idiopathic AIH, DILI, and DIAIH on biopsy may be challenging due to a lack of definitive pathognomonic features.13 Ceroid-laden macrophages and cannalicular cholestasis are suggestive of DILI,4,14 whereas liver biopsy in AIH demonstrates interface hepatitis, lymphoplasmacytic portal infiltrates, and rosette formation.15 These features may overlap in DIAIH.14 Finally, while advanced fibrosis and cirrhosis is uncommon in DIAIH, it...
is seen in approximately 21% of patients with idiopathic AIH at the time of diagnosis.\textsuperscript{15}

Beyond withdrawal of the offending agent, treatment with immunosuppression may be warranted in DIAIH if liver tests do not normalize within 3 months. Response to immunosuppression either with steroids alone or with steroids plus azathioprine is excellent. Many patients with DIAIH do not require prolonged immunosuppression, whereas over 70% of patients with idiopathic AIH have recurrence of disease after withdrawal of therapy.\textsuperscript{4,11}

DISCLOSURES

Author contributions: JF Crismale drafted and edited the manuscript. A. Stueck provided and interpreted the pathology images. M. Bansal supervised and wrote the case report and is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received January 23, 2016; Accepted March 31, 2016

REFERENCES

1. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148(7):1340-52.e7.

2. Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol. 2009;50(3):511-7.

3. Kuzu UB, Öztas E, Turhan N, et al. Clinical and histological features of idiosyncratic liver injury: Dilemma in diagnosis of autoimmune hepatitis. Hepatol Res. 2010;40(4):320-21.

4. Björnsson E, Talwalkar J, Treerprasertsuk S, et al. Drug-induced autoimmune hepatitis: Clinical characteristics and prognosis. Hepatology. 2010;51(1):2040-8.