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CASE REPORT | LIVER

Idiosyncratic Liver Injury Due to Levocetirizine

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ABSTRACT

Levocetirizine is an over-the-counter nonsedating antihistaminic agent commonly used to treat allergic diseases. Clinically significant acute liver injury has been very rarely associated with its use. Only 2 cases of acute liver injury associated with levocetirizine have been reported in the literature. We describe the case of a 67-year-old man who developed clinically significant acute hepatic injury after using levocetirizine. On the liver biopsy, there were histological findings of periportal inflammation and prominent cholestatic injury; such findings are consistent with those previously described in another similar case.

INTRODUCTION

Drug-induced liver injury (DILI) is among the most common causes of acute liver injury (ALI) and acute liver failure (ALF) in the United States.[1] Levocetirizine is an over-the-counter nonsedating antihistaminic agent commonly used to treat allergic diseases. To our knowledge, there are only 2 case reports of ALI associated with the use of levocetirizine.[2,3] The mechanism behind the process is not well understood.

CASE REPORT

A 67-year-old man with a medical history of osteoarthritis, allergic rhinitis, and dermatomyositis was referred to the hospital by his primary care physician because of a 2-week history of worsening jaundice and pruritus associated with elevated liver enzymes, as well as hyperchromic urine and hypocholic stool. One month before the beginning of the symptoms, routine laboratory tests revealed normal liver enzymes.

The patient had a remote history of tobacco use and reported drinking a glass of wine only on rare occasions. He denied using recreational drugs or herbal supplements and reported no recent travels. His medications were acetaminophen, esomeprazole, and levocetirizine, which he took as needed. He reported that he had previously been taking levocetirizine, but never for more than 2 consecutive days. However, 3 weeks before presentation, he took levocetirizine 5 mg daily for 11 consecutive days for symptoms of allergic rhinitis. He stopped the medication when he began noticing jaundice. The physical examination revealed scleral icterus, jaundice, and mild hepatomegaly without asterixis or other signs of hepatic encephalopathy. There were no palpable lymph nodes or tonsillar exudates.

Laboratory tests on admission revealed aspartate transaminase 1,170 IU/L, alanine transaminase 1,352 IU/L, alkaline phosphatase 130 IU/L, total bilirubin 19.5 mg/dL, direct bilirubin 15.4 mg/dL, albumin 2.1 g/dL, and international normalized ratio 1.6. Serological markers for human immunodeficiency virus, herpes simplex types 1 and 2, and hepatitis viruses A, B, C, D, and E were negative. Polymerase chain reaction test for varicella zoster, cytomegalovirus, human herpesvirus 6 types A and B, and hepatitis B and C viruses was negative. The Epstein-Barr virus antibody to viral capsid antigen was negative for the immunoglobulin M and positive for the immunoglobulin G. The Epstein-Barr virus real-time polymerase chain reaction was weakly positive (1,036 IU/mL; plasma log 3.02). This was deemed to be a weak reactivation of a past subclinical infection and not an acute infection. Ceruloplasmin, iron saturation, thyroid-stimulating hormone, and alpha-1-antitrypsin levels were within normal limits. Serum antimitochondrial

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antibody, anti-liver-kidney microsome antibody, and anti-soluble liver antigen antibody were negative. The antinuclear antibody was found to be positive (1:640, nucleolar pattern), but this was consistent with previous tests.

An abdominal ultrasound showed no evidence of cholelithiasis, biliary ductal obstruction, or hepatic parenchymal disease, and the Doppler study revealed patent hepatic veins. The abdominal magnetic resonance imaging with and without contrast showed evidence of periportal edema. Liver biopsy was performed with results indicative of acute DILI (Figure 1). Because of high clinical suspicion of acute DILI, the patient was started on prednisone 60 mg daily, and within 2 days, both the symptoms and the levels of transaminases enzymes improved dramatically (Figure 2).

DISCUSSION

Our case illustrates a highly probable association between ALI and the use of levocetirizine according to the Roussel Uclaf Causality Assessment Method based on a score of 9.[4] DILI can be classified according to the biochemical pattern of the liver enzymes abnormalities into hepatocellular, cholestatic, and a mixed pattern. A different classification based on the pathophysiological mechanisms of drug-related injury distinguishes an "intrinsic" from an "idiosyncratic" hepatotoxicity. Although the first has been proven to be dose dependent and predictable in human and animal models, the second one is rare, typically unrelated to the dose and has a variable latency of onset.[5] The mechanisms of idiosyncratic DILI are not completely understood and seem to be heterogeneous. Genetic and immunologic factors may play a role; it is possible that a deficiency of drug-metabolizing enzymes could trigger an abnormal immune response, and studies showed that specific human leukocyte antigen alleles could impact the severity and biochemical pattern of the liver injury in patients who developed an idiosyncratic DILI after the exposure to amoxicillin-clavulanate.[5,6] However, other mechanisms may be involved as well, including some that could be dose dependent.[7] Interestingly and in conformity with this observation, the patient in our case had been taking levocetirizine multiple times in the past, but always for very short periods and developed a clinically relevant liver injury only when he took it for 11 consecutive days.

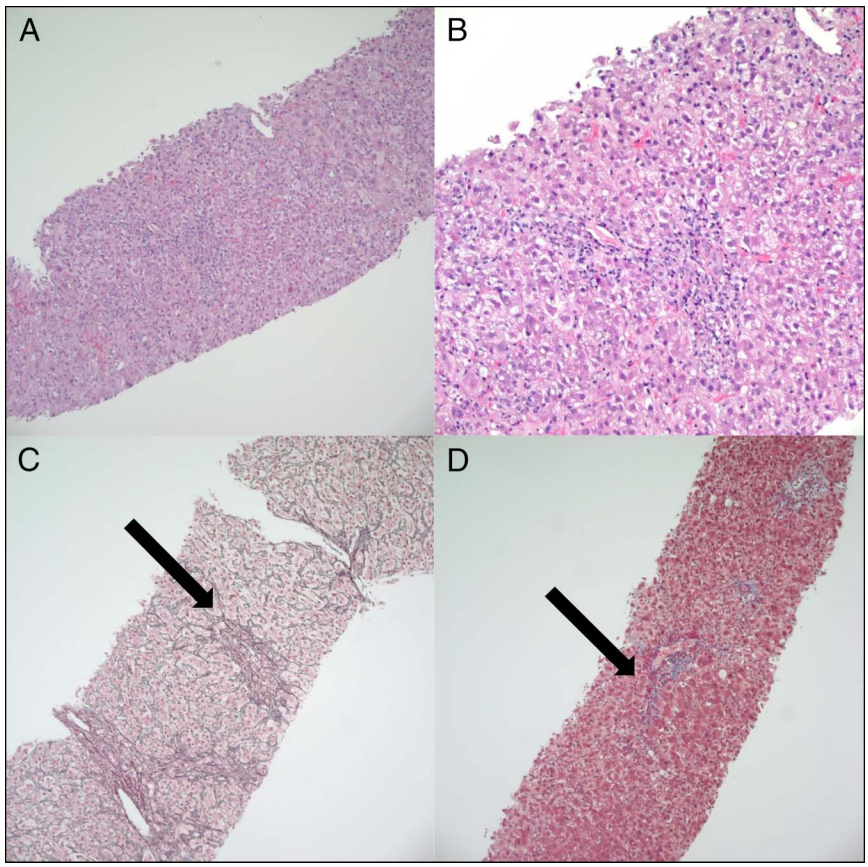

Figure 1. (A) Low-power view of hematoxylin and eosin (H&E) stain of liver biopsy showing evidence of portal inflammation. The lobular parenchyma shows multifocal inflammatory infiltrates and acidophil bodies. Neither hepatocyte rosettes nor severe necrosis are seen. (B) Mid-power view of H&E stain showing the periportal inflammation composed of lymphocytes, scattered plasma cells, eosinophils, and neutrophils. The lobular parenchyma shows mixed inflammatory infiltrates, but eosinophils are not prominent. Intrahepatic cholestasis and prominent cholestatic injury are seen as well. (C) Reticulin-stain showing intralobular and periportal collapse (arrow). (D) Trichrome stain showing mild increase in periportal fibrosis (arrow).

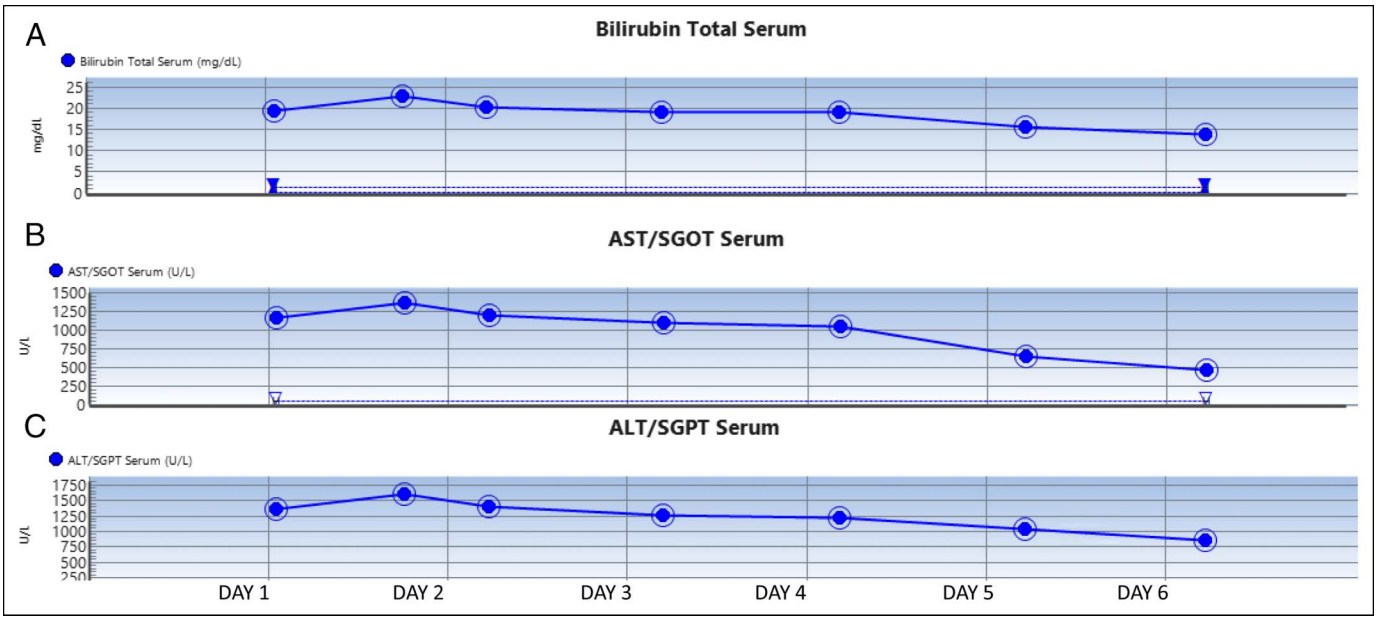

Figure 2. Trend of laboratory parameters during the hospital stay. (A) Total bilirubin levels. (B) Aspartate transaminase (AST) levels. (C) Alanine transaminase (ALT) levels.

Ultimately, the diagnosis of idiosyncratic DILI relies on the exclusion of other etiologies. After having ruled out other possible causes of ALI, we concluded that the most likely diagnosis was idiosyncratic levocetirizine-induced liver injury based on the timing of the administration of the drug and the documented improvement of clinical and laboratory parameters after the patient stopped taking it. The histological findings were found to be similar to another reported case of levocetirizine-induced liver injury, which further supports the diagnosis.[3] Currently, the mainstay of treatment is the prompt identification and discontinuation of the offending drug; there are no approved pharmacologic therapies for DILI and ALF.[8] Steroids have been proposed as potentially effective to hasten recovery or prevent the progression to ALF based on the current evidence available on the pathophysiology and the role played by immunological mechanisms in DILI: however, high-quality data to support this are lacking. Nevertheless, corticosteroids are commonly used in the treatment of DILI and ALF: data from the Drug-Induced Liver Injury Network show that they were used in the 82% of the patients who died or underwent liver transplantation and 36.6% of the patients alive with native liver at 6 months.[9]

A retrospective study by Hou et al in 70 patients with DILI showed that corticosteroid use was associated with shorter recovery time and fewer deaths or development of chronic liver disease.[10] Similar findings were observed in another retrospective study by Hu et al in patients with severe DILI.[11] Other anecdotal reports described clinical improvements with steroids in severe DILI.[12,13] Conversely, a retrospective study conducted by Pang et al did not show improvements in recovery time or resolution rate in 32 patients with acute DILI treated with steroids compared with the nonsteroid group, and other retrospective studies in patients with drug-induced ALF failed to show any benefit.[13–16] An approach proposed by Hu and Xie is to consider the use of corticosteroids in patients with severe DILI (defined by total biluribin level greater than 5 times the upper limits of normal, with or without an internal normalized ratio $\geq$1.5), while avoiding them in cases of ALF.[17] In such cases, the condition may be too critical, and there is no evidence that steroid use improves prognosis. Because in mild to moderate DILI, the risk of progression to ALF is considered to be low, the discontinuation of the drug is usually sufficient. Future high-quality controlled trials should further investigate the role of steroids in DILI to better define their possible clinical utility.

DISCLOSURES

Author contributions: G. Annunziata and M. Barbara analyzed the data and wrote the manuscript. I. Mayuko revised the manuscript. G. Annunziata is the article guarantor.

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