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Delayed diagnosis of cholestatic drug-induced liver injury treated with corticosteroid for adrenal insufficiency secondary to miliary tuberculosis

S.Y. LEE[1], A. SCHNEIER[2], T. SCHIANO[3], S.J. LIU[4], O.N. MACHADO[1]

[1]Department of Medicine, Elmhurst Hospital Center, Icahn School of Medicine at Mount Sinai, Elmhurst, IL, USA
[2]Department of Medicine, Mount Sinai Medical Center, Icahn School of Medicine at Mount Sinai, Elmhurst, IL, USA
[3]Division of Liver Diseases, Department of Medicine, Mount Sinai Medical Center, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[4]Department of Pathology, Elmhurst Hospital Center, Icahn School of Medicine at Mount Sinai, Elmhurst, IL, USA

Abstract. – Drug-induced liver injury (DILI) in a patient with multiple comorbidities is often challenging to diagnose because liver injury can be attributed to multiple disease processes. Delayed treatment of DILI could have fatal consequences and, therefore, understanding the features and risks of DILI is crucial.

We report a unique case of a patient who was admitted for severe sepsis of unknown etiology. This patient was later found to have miliary tuberculosis (TB) with associated adrenal insufficiency, complicated by acute cholestatic liver injury. Liver injury fully improved after initiation of corticosteroid for the treatment of adrenal insufficiency. The most likely pathophysiology of acute liver injury was DILI, given the clinical course of liver injury and the liver biopsy result of non-caseating granulomas. Although five different antibiotics including ciprofloxacin, metronidazole, vancomycin, imipenem/cilastatin, and cefepime were provided, the timing of liver injury and pharmacology of each drug imply that ciprofloxacin was the most likely antibiotic causing DILI, given the pharmacology of each antibiotics.

This case is unique because miliary TB was complicated by adrenal insufficiency and drug-induced cholestatic liver injury, but acute liver injury was fully reversed after corticosteroid treatment. This implies an immune-mediated etiology of DILI, especially ciprofloxacin-induced cholestatic liver injury.

DILI is challenging to diagnose in the setting of multiple comorbidities. Therefore, it is crucial that clinicians are to be aware of signs and symptoms of DILI, in that delayed diagnose and treatment may have fatal consequences.

Key Words:
Drug-induced liver injury, Miliary tuberculosis, Non-caseating granulomas, Ciprofloxacin-induced liver injury, Adrenal insufficiency.

Introduction

As the body's primary site of drug metabolism, the liver is prone to a variety of drug toxicities, including the condition known as drug-induced liver injury (DILI)[1]. DILI is defined by an elevation in liver enzyme levels including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (AP), while drug-induced liver dysfunction refers to an advanced disease defined by elevation of total and conjugated bilirubin levels and/or an abnormal synthesis of coagulation factors manifested as prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT)[1]. DILI can be designated as hepatocellular liver injury (ALT greater than two times the upper limit and/or ALT:AP ratio greater than 5), cholestatic liver injury (AP greater than two times the upper limit and/or the ALT:AP ratio less than 2), or mixed liver injury (ALT:AP ratio between 2 and 5)[2]. Understanding the features and risks of DILI is crucial especially when the implicated drug is commonly used, as missed diagnosis and delayed treatment of DILI could be fatal as specified by Hy's law[3,4].

Corresponding Author: Orlando N. Machado, MD; e-mail: orlando.machado@mssm.edu

Numerous medications have been reported to cause drug-induced liver injury, but the pathophysiology of liver injury by each medication is multifactorial and difficult to pinpoint: direct toxicity by a drug or its metabolite, genetic susceptibility, hypersensitivity reaction, and immune-mediated injury have been suggested mechanisms[5]. Consensus guideline for the treatment of DILI is therefore lacking due to the complex pathophysiology of the disease, and treatment of choice for DILI is to simply discontinue the medication. Corticosteroids, however, have been reported to be beneficial for DILI[6,7], especially when DILI is mediated by autoimmune antibodies or an immune-allergic reaction[7].

Here, we present a unique case of a patient who received five different antibiotics that developed cholestatic drug-induced liver injury. The diagnosis of immune-mediated DILI was delayed, but liver injury immediately improved upon the initiation of corticosteroid for the treatment of adrenal insufficiency secondary to military tuberculosis.

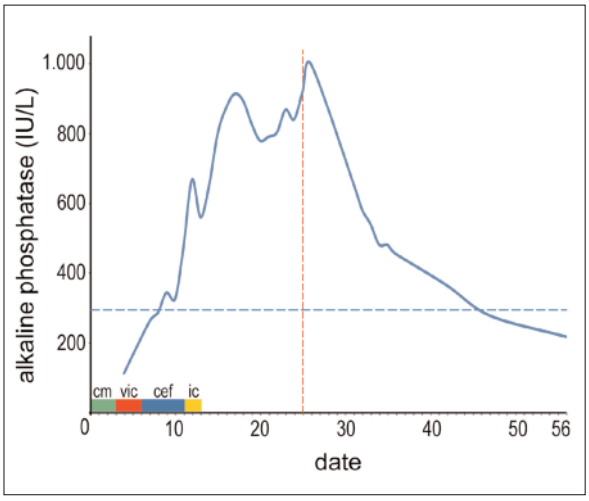

Figure 1. Daily trend of alkaline phosphatase (AP). Day 1 is the first day of ciprofloxacin and metronidazole. Liver injury is cholestatic when AP is greater than two times the upper limit, represented as blue horizontal dotted line. The date on which corticosteroid was given is represented as the red vertical line. Liver injury started on day 8. "cm" stands for ciprofloxacin and metronidazole (for 3 days); "vic," vancomycin and imipenem/cilastatin (for 3 days); "cef," cefepime (for 5 days); and "ic," imipenem/cilastatin (for 2 days).

Case Report

A 82 year-old woman who arrived from Uruguay three months prior presented with altered mental status and a pre-syncopal episode. She had a remote history of cholecystitis with cholecystectomy. Two days prior, the patient had been discharged from another hospital after prescribed ciprofloxacin and metronidazole for colitis diagnosed by abdominal computational tomography (CT). She took ciprofloxacin and metronidazole for 3 days in total. At admission, she was tachycardic, tachypneic, and hypotensive with a white blood cell count of 3.6 K/μL. She also had elevated AST (111 IU/L) and ALT (450 IU/L) with normal AP (111 IU/L) and hyponatremia to 125 mEq/L. She was treated with vancomycin and imipenem/cilastatin in addition to fluid resuscitation. She became hemodynamically stable after three days. At this time, vancomycin and imipenem/cilastatin were discontinued, and cefepime was started, given negative blood and urine cultures. However, though her AST and ALT trended downward to normal levels within the next 3 days, her AP began to increase (Figure 1). After five doses of cefepime, it was discontinued as a possible cause of liver injury. She was restarted on imipenem/cilastatin for two more days for a total of 10 days of antibiotic treatment, but her AP continued to rise. A search for common non-drug causes of acute liver injury was negative included hepatitis B and C serologies, autoimmune antibodies, ultrasound and magnetic resonance cholangiopancreatography (MRCP) for biliary obstruction, and there was a negative history of alcoholism. Transjugular liver biopsy revealed cholestasis and non-caseating granulomatous disease, suggest-

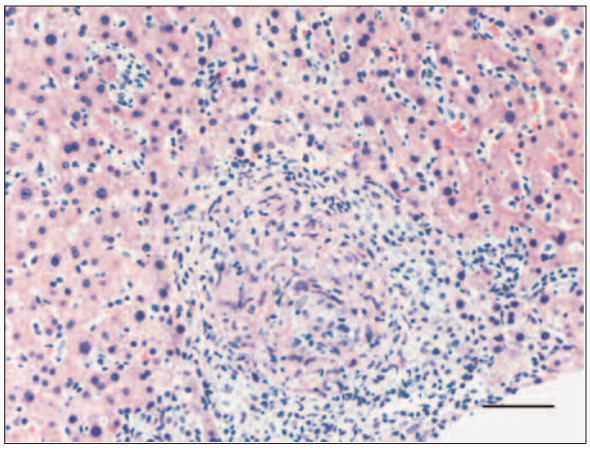

Figure 2. Liver biopsy of this patient, demonstrating a non-caseating epithelioid granuloma involving both portal tracts and lobules with evidence of cholestasis. Scale bar = 150 μm.

ing DILI or infection including tuberculosis (Figure 2). In the meantime, an adrenal corticosteroid stimulating hormone (ACTH) stimulation test was performed for persistent hyponatremia and fatigue, and this confirmed primary adrenal insufficiency (Addison's disease) for which corticosteroids were started. The AP peaked at 1,004 IU/L, and started to trend down two days after steroid was started. Chest CT revealed multiple subcentimeter central and peripherally located densities. A diagnosis of miliary tuberculosis (TB) with associated adrenal insufficiency was made, and the patient improved with isoniazid, rifampin, ethambutol, and pyrazinamide, as well as corticosteroids. A few weeks after discharge, induced sputum cultures grew mycobacterium tuberculosis confirming the diagnosis.

Discusssion

Miliary TB is known to cause both hepatocellular and cholestatic liver injury. This patient's non-caseating granuloma in the liver biopsy could be from miliary TB, DILI, or sarcoidosis, but sarcoidosis was not a likely diagnosis due to absence of significant sclerosis in granulomas. Her AP trended down two days after the initiation of corticosteroid for managing adrenal insufficiency although a diagnosis of DILI had not been made. The improvement in AP level occurred before the initiation of anti-TB medications, implying that the cholestatic liver injury was not secondary to TB, although the granuloma could be from both TB and DILI; we know of no reports of TB-induced liver injury improving after corticosteroid administration. Furthermore, liver injury can cause the adrenal insufficiency (hepatoadrenal syndrome)[8], but adrenal insufficiency (Addison's disease) is not known to cause the cholestatic liver injury besides a few reported cases of mildly elevated AST and ALT secondary to adrenal insufficiency[9]. Given patient's initial hyponatremia and fatigue, the patient most likely had adrenal insufficiency from TB before the diagnosis was made and, therefore, the acute cholestatic liver injury is not likely from adrenal insufficiency.

While a third generation cephalosporin such as ceftriaxone, which is largely excreted via the biliary system is known to cause cholestatic liver injury[10], the fourth generation cephalosporin cefepime, which is largely excreted via the urinary system (81.1-95.1%[11,12]) has not been previously associated with DILI. Less than 0.3% of imipenem/cilastatin was reported to be excreted in the biliary system[13] although one case of imipenem/cilastatin-induced cholestatic liver injury has been reported[14]. Although a small amount of vancomycin is known to be excreted in the biliary system[15], most of reported cases of vancomycin-associated liver injury were a part of larger hypersensitivity reactions including drug rash eosinophilia systemic symptoms (DRESS) syndrome. About 33% of metronidazole is reportedly excreted through the bile, but reported cases of metronidazole-induced liver injury followed the pattern of hepatocellular injury[16]. Ciprofloxacin is actively excreted through the biliary tract, and many case reports have been published on ciprofloxacin-induced cholestatic injury[17].

Danan et al[2] provide a consensus method for assessing the causal role of a drug in liver injury. Cholestatic DILI is "suggestive" when DILI starts 5 to 90 days after the initiation of an inciting drug, or when AP decreases > 50% from the peak within 180 days after its cessation. DILI is considered "compatible" with an inciting drug if the injury occurs < 5 or > 90 days after the initiation of the drug, or if the AP decreases < 50% within 180 days. In this case, DILI began > 5 days after initiation of ciprofloxacin and metronidazole ("suggestive"), but < 5 days after initiation of vancomycin, imipenem, and cefepime ("compatible"). The improvement occurred within 180 days of discontinuation of all five antibiotics ("suggestive"). Only ciprofloxacin and metronidazole are "suggestive" agents for cholestatic liver injury in terms of both the onset and cessation of medications, but metronidazole is known to cause hepatocellular liver injury.

This case is unique since DILI occurred in the setting of miliary TB and associated adrenal insufficiency that was treated with corticosteroid. Despite a delayed diagnosis of DILI, liver injury improved after initiation of corticosteroids. Infectious etiologies including miliary TB and virtually any medication can potentially cause liver injury. However, TB was an unlikely cause of the acute rise in AP for this patient because AP trended down before anti-TB medications were initiated. Furthermore, among the five antibiotics administered, ciprofloxacin is the most likely culprit given the timing of initial rise of AP with respect to administration of medication and the previously published associations between ciprofloxacin and cholestatic liver injury.

Conclusions

Given the improvement of liver injury after initiation of steroids, this case suggests an immune-mediated etiology of ciprofloxacin-induced cholestatic liver injury.

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Conflict of Interest Statement

There are no conflicts of interest regarding the publication of this article.

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