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Single Case

Levonorgestrel-Releasing Intrauterine Device-Related Acute Liver Injury

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Abstract
Oral contraceptives have long been associated with liver injury. However, very little attention is paid to the metabolic side effects of hormone-releasing intrauterine devices (IUDs). These devices are generally considered safe and commonly used. We report for the first time acute liver injury associated with a levonorgestrel-releasing IUD. Our patient did not have any comorbidities that could have caused or exacerbated liver injury. A detailed workup and liver biopsy remained negative for any other potential cause of liver injury. The patient's symptoms resolved with removal of the device. She remained symptom free on subsequent outpatient follow-ups.

Introduction

Drug-induced liver injury (DILI) has an annual incidence of 10–15 per 10,000–100,000 individuals [1]. It can occur from both prescription and over-the-counter medications. Over

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1,000 medications have been shown to cause DILI and the list is growing. DILI is also the most frequently cited reason for removal of medications from the market [2]. It is very common to miss DILI, especially when patients are on multiple medications. Also, some medications are not known to cause DILI and should be taken into account on the basis of suspicion. The clinical presentation can mimic any form of liver disease, including acute and chronic infectious hepatitis. Several risk factors, such as alcohol and acetaminophen consumption, can also potentiate the toxic affects of the drug. The threshold for DILI should be very low, and early recognition and prompt intervention is vital. The treatment is to stop the offending agent.

Case Presentation

We report a 24-year-old female with a medical history significant for hypertension and Henoch-Schönlein purpura as a child with no residual illness. The patient presented to the emergency room with complaints of dull epigastric pain radiating to the right hypochondrium for 1 week. The pain was gradually progressive and worsened with heavy meals and deep breath and was relieved after a warm bath or with ibuprofen. She had also had nausea and vomiting for the last 3–4 days but denied any fevers, chills, rash, or pruritus. She had no recent travel or exposure to sick contacts. Her past history included a recent pregnancy and delivery of a healthy baby girl 3 months prior to presentation. She had been taking labetalol 200 mg twice daily during her pregnancy for hypertension. No preeclampsia or eclampsia was reported. All her laboratory results had remained normal during pregnancy. A levonorgestrel intrauterine device (IUD) had been placed 1 month prior to presentation. Her only current medication was metoprolol, and she denied using any over-the-counter or herbal medications. She also denied any history of prior blood transfusions. No family history of liver disease or gastrointestinal malignancies was reported, She denied any use of alcohol, tobacco, or illicit drugs. On physical examination her vitals were normal. She had marked scleral icterus and jaundice.

Significant laboratory findings were total bilirubin 11.2 mg/dL, direct bilirubin 7.9 mg/dL, aspartate transaminase (AST) 1,712 U/L, alanine transaminase (ALT) 3,243 U/L, and alkaline phosphatase (AP) 166 U/L. CT of the abdomen showed cholelithiasis without evidence of cholecystitis. MRCP showed a contracted gallbladder with pericholecystic fluid and edematous changes. A detailed viral workup was negative for hepatitis A, B, C, and E, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and HIV. Autoimmune markers for serum ceruloplasmin, ferritin, hemochromatosis mutations H63D, C282Y, S65C, F-actin smooth muscle antibody, antimitochondrial antibody, alpha 1 anti-trypsin, anti-nuclear antibody, and liver kidney microsome 1 antibody were negative. Acetaminophen levels were normal.

Four days after admission, laboratory workup showed increasing transaminitis, i.e., AST 1,994 U/L (from 1,712), ALT 3,055 U/L (from 3,243), AP 185 U/L (from 166), and total bilirubin 18.6 mg/dL (from 11.2). Given all the preliminary workup having been negative and rising liver enzymes and hyperbilirubinemia, a liver biopsy was performed under US guidance. Liver biopsy showed panacinar hepatitis with mild hepatocellular cholestasis (Fig. 1, Fig. 2, Fig. 3). It was decided to remove the levonorgestrel IUD and follow her as an outpa-

tient. No other treatment or intervention was performed. Table 1 shows the liver function tests on days 10, 20, and 60 after discharge.

Discussion

Oral contraceptives frequently produce mild hepatocellular dysfunction. Three major categories of liver-related side effects are hepatic dysfunction, cholestatic jaundice, and benign hepatic tumors. The initial presentation may resemble obstructive hepatobiliary disorders or viral infections [3]. Cytolytic hepatitis related to levonorgestrel/ethinyl estradiol oral contraceptive use was suggested in two case reports [4, 5]. Other side effects reported with oral contraceptives include follicular nodular hyperplasia of the liver, peliosis hepatitis, cirrhosis, and malignant tumors of the liver [6–9]. The use of oral progestogens is contraindicated in patients with liver dysfunction or disease [10].

Levonorgestrel IUD use is contraindicated in patients with ongoing liver injury or tumors. We report for the first time acute liver injury related to a levonorgestrel-releasing IUD. Our diagnosis is based on temporal association with acute liver injury after placement of the levonorgestrel IUD and marked improvement of the liver enzymes after its removal in the absence of any other alternative etiology. All likely etiologies as suggested by liver biopsy were excluded. The patient started feeling better symptomatically over the next few weeks after IUD removal. She had no abdominal pain, her appetite was back, and icterus was much improved. Table 1 shows a significant downward trend in transaminase and bilirubin levels of over the next 2 months.

To our knowledge, there are no previously reported cases of levonorgestrel IUD-related liver injury. This case is important as it raises the issue of keeping in mind similar side effects and of being cautious with IUDs just as when using oral contraceptives. We hope that after publication of this case, other colleagues will also report similar findings.

Statement of Ethics

Informed consent was obtained from the patient for publication of this article. This paper is a case report on a rare condition and did not involve research on human or animal subjects. The work was approved by the Texas Tech University Health Sciences Center Department of General Internal Medicine.

Disclosure Statement

There are no financial disclosures for this paper and no funding was received related to it. None of the authors have any conflicts of interests. The paper and images are original works done for this case.

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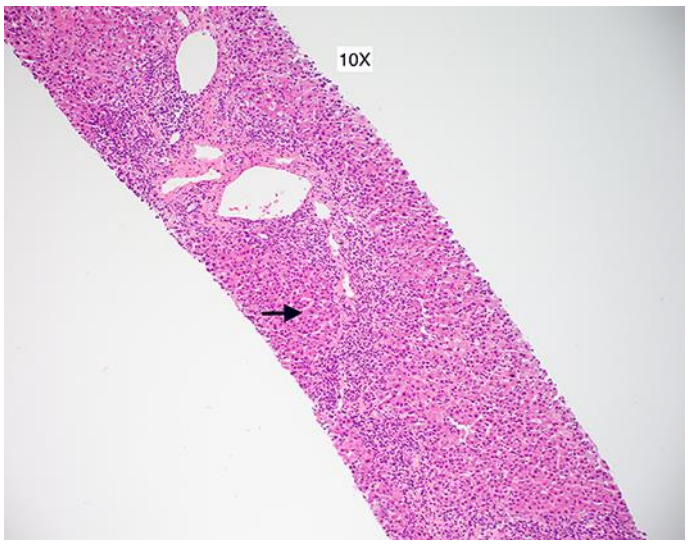

Fig. 1. Histology from the liver biopsy showing panacinar hepatitis. The arrow shows intrahepatic globules.

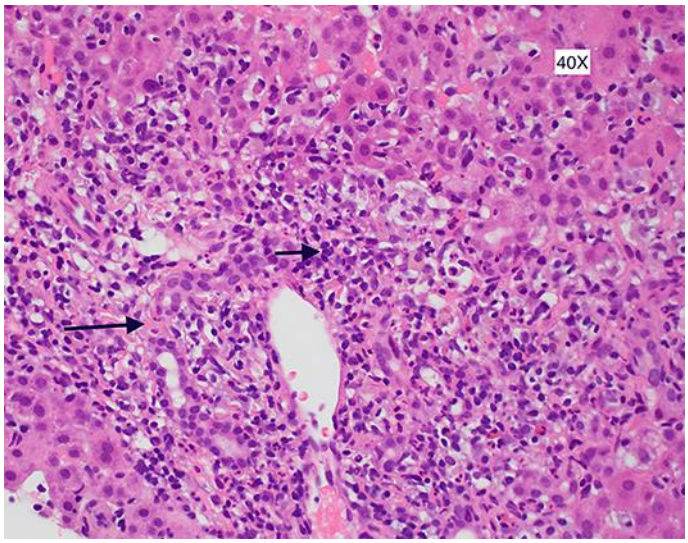

Fig. 2. Histology from the liver biopsy showing severe inflammation and interface hepatitis. The short arrow shows plasma cells and the long arrow eosinophil clusters.

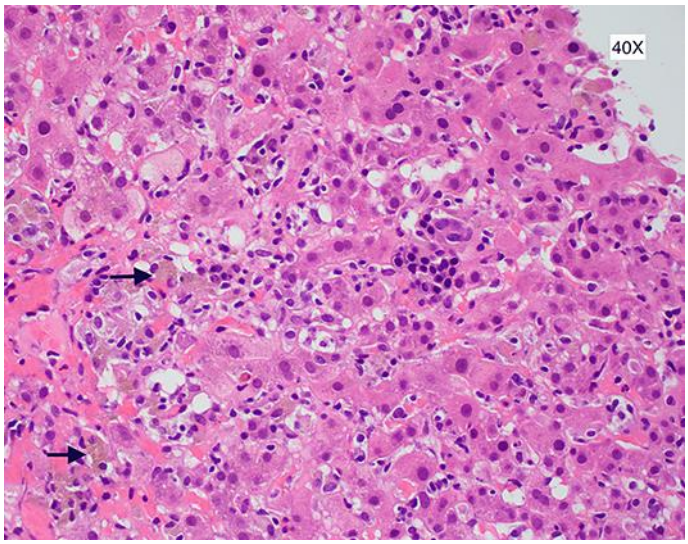

Fig. 3. Histology from the liver biopsy showing hepatocellular cholestasis. The arrows show bile lakes and bile plugs.

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Table 1. Resolution of transaminitis after removal of the levonorgestrel IUD

Time after IUD removal	Total bilirubin, mg/dL	AST, U/L	ALT, U/L	AP, U/L
10 days	6.9	1,179	1,697	138
20 days	3.9	240	704	108
60 days	1.2	20	21	81

ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; IUD, intrauterine device.