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BACTRIM-INDUCED ACUTE LIVER FAILURE: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Background: Drug-induced Liver Injury (DILI) is considered the most common cause of acute liver injury in the western world. Antibiotics are most frequently the offending agent in DILI. The treatment of DILI is the discontinuation of the offending agent. In the vast majority of cases, patients fully recover clinically and biochemically. **Case Presentation:** We present a 73-year-old male patient with a medical history significant for chronic obstructive pulmonary disease (COPD), hypertension, and recent community-acquired pneumonia (CAP) who presented to the emergency department (ED) for the evaluation of generalized pruritus and mild confusion. His presentation was concerning for acute liver injury. Bactrim was stopped on admission. Testing for Autoimmune, viral hepatitis, and acetaminophen toxicity was negative, with liver biopsy showing mild reactive changes and patchy hepatic steatosis consistent with DILI. The patient's LFTs started trending down, along with improved clinical symptoms over the next few days. **Discussion:** Trimethoprim-sulfamethoxazole is a commonly prescribed antibiotic in the USA. It induces liver injury through a hypersensitivity reaction and can vary from mild transaminitis to acute liver failure. The diagnosis is made by ruling out other causes of liver injury, and the treatment is generally supportive and rarely requires corticosteroids.

INTRODUCTION

Drug-induced Liver Injury (DILI) is considered the most common cause of acute liver failure (ALF) in the US and is accompanied by high morbidity and mortality.[1] The annual incidence of DILI is 1.3 to 19.1 per 100,000 persons exposed.[2] It is usually classified based on laboratory presentation (hepatocellular, cholestatic, or mixed), mechanism of hepatotoxicity, and histological findings from a liver biopsy. The isolated hepatocellular pattern is characterized by hepatocyte necrosis and is associated with poor prognosis.[3,4] The mechanism of DILI is either intrinsic, which is dose-dependent, or idiosyncratic, which is more unpredictable.[5,6] There have been no specific markers or diagnostic tests for DILI, and the diagnosis made after excluding other causes of liver injury. The essential step in managing DILI is discontinuing the offending agent, along with supportive care targeted to alleviate symptoms. Most patients fully recover clinically and biochemically after the removal of the offending agent. This article will review a case of acute liver injury induced by Trimethoprim-Sulfamethoxazole, the pattern of liver injury caused by the offending agent, and its outcome.

CASE PRESENTATION

We present a 73-year-old male patient with a medical history significant for chronic obstructive pulmonary disease (COPD) and hypertension (CAP) who presented to the ED for the evaluation of generalized pruritus and mild confusion for two days. The patient was recently diagnosed with community-acquired pneumonia (CAP) and was started on Bactrim. The last dose of Bactrim was one day prior to the admission. On admission, the patient's vitals were: blood pressure of 115/87, pulse rate of 88, respiratory rate of 21, and temperature of 100.3 F, saturating 95% on five liters of nasal cannula. On arrival, the patient had a mild headache accompanied by dizziness but was awake and oriented, with the physical examination positive for scleral icterus, bilateral conjunctival injection, sublingual jaundice, bilateral decreased breath sounds without crackles, and a diffuse erythematous rash on the chest, abdomen, and upper back. Laboratory studies were consistent with the

elevation of inflammatory markers, including ferritin and C-reactive protein (CRP). Complete metabolic profile revealed elevated liver function tests; ALT of 651 (reference range 10-43 U/L), AST 214 (reference range 13-41 U/L), alkaline phosphatase 247 (reference range 42-119 U/L), ferritin levels 7437 (reference range 13-41 ng/dl), ammonia levels 24 (reference range 11-32 mcmol/L), and total bilirubin level of 9.3 (reference range 0.2-1.2 mg/dl). INR level was 1.3 (Reference range 0.9-1.1) on admission. Abdominal imaging was unremarkable for any acute liver pathology. Computed tomography (CT) scan of the head was negative for any acute pathology. Work-up for common causes of acute hepatitis and liver failure, including autoimmune and viral etiologies, was negative. Bactrim was considered the offending agent and was discontinued from the day of admission. LFTs and bilirubin levels continued to rise for the next few days until they plateaued around day 4-5, followed by a decline in the levels. The trend of LFT and bilirubin rise is shown in table 1.

Table 1: Showing the trend of lab work over the first week.

Variables	Reference range	Day 0	Day 3	Day 6 (Discharge Day)
ALT (Units/L)	10-41	651	2084	743
AST (Units/L)	13-41	214	1564	321
ALP (Units/L)	42-119	247	309	282
GGT (Units/L)	5-30	1398	–	–
Total Bilirubin (mg/dl)	0.2-1.2	9.3	9.1	6.7
Direct Bilirubin (mg/dl)	0-0.3	7.2	7.8	5.4
PT (sec)	9.4-13.5	14.8	14.2	14.0
INR	0.9-1.1	1.3	1.2	1.2
WBC (k/cmm)	4-11	6.9	8.1	15.8
Hemoglobin (g/dl)	13-17.5	14.4	12.0	12.1
Platelets (k/cmm)	140-450	191	246	480
BUN (mg/dl)	5-21	32	34	32
Cr (mg/dl)	0.6-1.20	1.50	1.07	0.94
Ammonia level (mcmol/L)	11-32	—	24	—

Liver biopsy was done for a definitive diagnosis, which showed mild hepatitis and patchy hepatic steatosis consistent with a drug-induced reaction, as seen in **image 1**. The patient's generalized pruritus was treated successfully with antihistamines. The patient was discharged on the 6th day of hospitalization as his LFTs began to trend down. Follow-up labs two weeks after discharge revealed complete normalization of hepatic function tests.

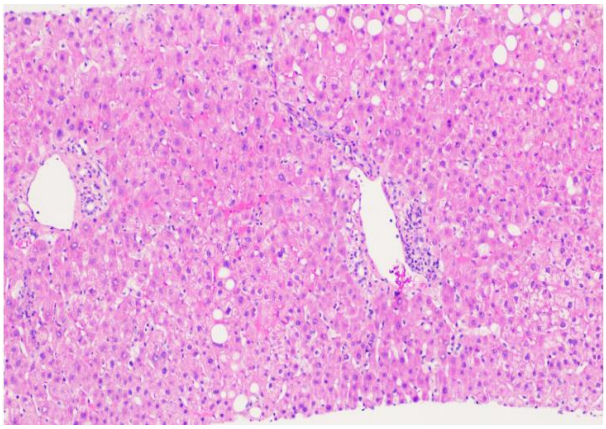

Figure 1: Liver biopsy showing patchy steatosis without significant fibrosis.

DISCUSSION

Our patient's clinical symptoms, physical exam findings, laboratory work-up, and biopsy findings were consistent with acute liver injury, with the potential trigger being Trimethoprim-Sulfamethoxazole (TMP-SMX). TMP-SMX consists of 2 antimicrobials, TMP and SMX, that act synergistically against many bacterial infections, including those of the urinary and respiratory tract. Both antimicrobials work together by inhibiting two sequential steps in the synthesis of bacterial tetrahydrofolic acid, a cofactor necessary for bacteria for protein and Nucleic acid synthesis. It is generally a well-tolerated drug. However, due to the presence of the sulfonamide component, it is associated with various adverse effects.[7] The commonly reported side effects (SE) are gastrointestinal (GI) toxicity, including nausea, vomiting, and anorexia. However, the drug also can affect other organ systems, including skin (resulting in Steven-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN)), and bone marrow, resulting in cytopenias.[8-11] Although rare, hepatic injury has also been reported with TMP-SMX, and mainly, it is idiosyncratic. All three patterns of liver injury have been noted, i.e., hepatocellular, cholestatic, and mixed patterns, with cholestatic being the most common one.[12,13,14] The clinical presentation ranges from mild elevation in liver enzymes to fulminant liver failure. TMP-SMX-induced liver injury results from a hypersensitivity reaction secondary to reactive metabolite production and is more common in Human Immunodeficiency Virus (HIV) infected individuals.[15,16] The usual symptoms of Bactrim-induced hepatotoxicity include nausea, vomiting, body rash, right upper quadrant pain, and hepatic encephalopathy in severe cases.[17] If hypersensitivity reaction is the primary mechanism involved in liver injury, rash, eosinophils, and thrombocytopenia can also be seen in those cases.[16] Diagnosis is usually made by excluding other causes of liver diseases, including autoimmune and infectious etiologies. If the symptoms do not improve after stopping the suspected offending agent, a liver biopsy can be considered for a definitive diagnosis.

Management is usually supportive, which involves stopping the drug immediately after the suspicion. In most cases, full recovery is seen within 2-3 weeks after the discontinuation of the offending agent. The cholestatic injury pattern is associated with a good prognosis, while the hepatocellular pattern is associated with a poor prognosis.[18]

R-Factor is an appreciated diagnostic approach to define the pattern of liver injury and helps differentiate cholestatic from the hepatocellular pattern of liver injury. R>5 indicates a hepatocellular pattern of liver injury, while R < 2 signifies a cholestatic pattern, with values between 2-5 reflecting a mixed pattern.[17] In our case, the patient likely developed a hypersensitivity reaction given the development of generalized body rash, low-grade fever, and thrombocytopenia. He had a hepatocellular pattern of liver injury, with the R factor >5. After stopping the Bactrim, the patient's symptoms and liver enzymes eventually improved, with the status back to baseline in 3 weeks.

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