HIV-Associated Iron Overload: A Rare Cause of Elevated Transaminases in Patients With HIV

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INTRODUCTION

Common causes of mild to moderate elevation of liver enzymes include drug-induced liver injury (DILI), chronic viral hepatitis, alcohol-associated hepatitis, non-alcoholic fatty liver disease (NAFLD), cirrhosis, malignant infiltration of liver, or genetic disorders including Wilson's disease, hemochromatosis, and Alpha-1 antitrypsin deficiency. Here we present a case of a patient with advanced HIV, who in the absence of HFE gene mutation or history of blood transfusions, had drastically elevated ferritin levels and evidence of hemosiderosis in the liver with elevated transaminases, suspected to have HIV-associated iron overload, a rare cause of elevated transaminases in patients with HIV.

CLINICAL COURSE

A 44-year-old man with a medical history notable for HIV (diagnosed 15 years ago, not on antiretroviral therapy, CD4 count 0, viral load 799000) presented to ED initially with left upper extremity paresthesia and weakness, presumed to be transient ischemic attack which resolved after tPA infusion. He was incidentally found to have elevated transaminases and admitted to the infectious disease service for workup. Patient denied alcohol use for the past 4 years and any history of IV drug use. Physical exam was unremarkable with BMI of 17. Labs were notable for ALT 150 u/L, AST 320 u/L, ALP 431 u/L, GGT 1056 u/L, and total serum bilirubin 0.4 mg/dL. His liver enzymes were within normal limits until 3 months prior to presentation, when he was incidentally found to have ALT 165 u/L, AST 100 u/L, ALP 156 u/L, and total serum bilirubin 0.3 mg/dL. Of note, at that time, the patient had received a 21-day course of amoxicillin-clavulanate for cavitary methicillin-susceptible Staphylococcus aureus (MSSA) pneumonia. Patient remained asymptomatic. His liver function study remained elevated yet stable throughout this hospital course.

3 months prior to this hospitalization

- Patient received a course of amoxicillin-clavulanate for cavitary MSSA pneumonia
- ALT 165 u/L, AST 100 u/L, ALP 156 u/L, and total serum bilirubin 0.3 mg/dL.

This hospitalization

- At presentation: ALT 150 u/L, AST 320 u/L, ALP 431 u/L, GGT 1056 u/L, and total serum bilirubin 0.4 mg/dL
- Patient's liver function test remained elevated but stable throughout this hospitalization

WORK-UP

DILI was initially suspected due to the course of amoxicillin-clavulanate received in February, however, in DILI liver enzymes should have improved after drug withdrawal [1], while his liver enzymes continue to trend up after 3 months of drug withdrawal.

Initial workup as follows:

Right upper quadrant ultrasound

- Diffuse hepatic steatosis
- Multiple hyperechoic, rounded lesions and a hemangioma
- Gallbladder polyps

Infectious disease panel

- Toxoplasmosis IgG and IgM negative
- EBV panel indeterminant
- CMV IgG positive, PCR viral load <35
- HSV1 IgG positive; HSV2 IgG negative
- Hep A and Hep C IgM neg; Hep B serology study consistent with past infection.
- VDRL antibody titer 1:16

AIDS cholangiopathy, a chronic inflammation caused by opportunistic pathogens such as Cryptosporidium parvum and cytomegalovirus resulting in the development of biliary tract strictures, was also suspected. Magnetic resonance cholangiopancreatography (MRCP) was performed to work up AIDS cholangiopathy.

MRCP to work up AIDS cholangiopathy	• No imaging abnormality (e.g., strictures) of the biliary system • Excessive iron deposition in the liver and spleen consistent with hemosiderosis
Bronchoalveolar lavage to work up pneumonia	• Hemosiderin-laden macrophages present • No known history of cardiac conditions
Iron study and HFE allele genetic testing	• Ferritin 8260, serum iron 157, TIBC 272, and transferrin saturation of 58% • HFE gene testing negative

MRCP showed no imaging abnormality of the biliary system but revealed iron deposition in the liver and spleen consistent with hemosiderosis. On bronchoalveolar lavage to work up pneumonia, hemosiderin-laden macrophages were found in the setting of no known history of cardiac conditions. Iron study was then performed showing ferritin 8260, serum iron 157, TIBC 272, and transferrin saturation of 58%. Hemochromatosis gene (HFE) allele genetic testing was negative for mutation, and thus hereditary hemochromatosis was ruled out. As a result, this is likely a case of elevated transaminases caused by HIV-associated iron overload. Patient was discharged home with hepatology follow-up.

DISCUSSION

High serum ferritin level has been linked to advanced HIV stage in multiple studies [2][3][4]. Many of the activities of HIV-target cells are iron-dependent or modulate iron metabolism (e.g., through the production of cytokines); in particular, macrophages play a central role in iron metabolism as they are responsible for iron cycling and for phagocytosis of senescent erythrocytes [3]. In HIV patients, the iron burden is especially heavy in bone marrow, brain white matter, muscle, liver, and some other organs [4]. Excessive iron can exacerbate oxidative stress and impair already compromised immune defense mechanisms in many ways. [4] In addition, HIV viruses rely on irons for optimal DNA replication [3]. Due to the effect of excessive iron on host organ damage, host immune system suppression, and virus replication, some studies have suggested adding iron chelating agents to the treatment of HIV disease [5].

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