ISSN: 2754-4931

Journal of Gastroenterology & Hepatology Reports

SCIENTIFIC Research and Community

Case Report

Open Access

An Uncommon Cause of Elevated Liver Transaminases: Immune Reconstitution Inflammatory Syndrome from Unmasking of Occult Mycobacterium Avium Complex Infection in an HIV Infected Patient

John Ingram[1], Abdallah Abdallah[2], Zachary Field[2], Tulip A Jhaveri[3], Nathan Usry[1], Neha Varshney[4], William Daley[4] and Joydeep Chakraborty[2*]

[1]Department of Internal Medicine, University of Mississippi Medical Center, Jackson, USA

[2]Division of Gastroenterology and Hepatology, University of Mississippi Medical Center, Jackson, USA

[3]Division of Infectious Diseases, University of Mississippi Medical Center, Jackson, USA

[4]Department of Pathology, University of Mississippi Medical Center, Jackson, USA

ABSTRACT

Abnormal liver chemistry from the development of immune reconstitution inflammatory syndrome (IRIS) may reflect an unmasking of subclinical disease. We present the case of a 37-year-old female with a mixed pattern of liver injury from disseminated mycobacterium avium complex infection after starting antiretroviral therapy (ART). Presenting symptoms were fever, confusion, dysphagia, and abdominal discomfort for one week. Exam revealed a fever of 103.2°F, hypotension, encephalopathy, and abdominal tenderness. Lab work was significant for acute normocytic anemia, leukopenia, absolute CD4 count 28 cells/cmm, HIV viral load 276 viral copies/ml (vc/ml), ALT 267 U/L, AST 484 U/L, alkaline phosphatase 342 U/L, and normal total bilirubin. Imaging revealed hepatomegaly with steatosis and mesenteric and retroperitoneal lymphadenopathy. Percutaneous liver biopsy demonstrated noncaseating granulomas with AFB-positive organisms, with AFB blood cultures growing *Mycobacterium avium* complex (MAC), consistent with disseminated MAC infection. Clinicians must have a high index of suspicion for IRIS when determining the etiology of elevated liver transaminases in patients with HIV.

***Corresponding author**

Joydeep Chakraborty, Division of Gastroenterology and Hepatology, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216, USA.

Received: April 20, 2024; **Accepted:** April 25, 2024; **Published:** April 30, 2024

Keywords: Elevated Liver Enzymes, Elevated Transaminases, Immune Reconstitution Inflammatory Syndrome, Mycobacterium Avium Complex, Human Immunodeficiency Virus, Acid Fast Bacilli, Opportunistic Infection

Abbreviation

IRIS: Immune Reconstitution Inflammatory Syndrome
ART: Antiretroviral Therapy
Cells/cmm: Cells Per Cubic Millimeter
vc/ml: Viral Copies Per Milliliter
CD: Cluster of differentiation
ALT: Alanine Transaminase
AST: Aspartate Transaminase
U/L: Units Per Liter
AFB: Acid Fast Bacilli
MAC: Mycobacterium Avium Complex
HIV: Human Immunodeficiency Virus
mg/dl: Milligram Per Deciliter
CT: Computed tomography
TB: Tuberculosis
MRI: Magnetic Resonance Imaging
CSF: Cerebrospinal Fluid
CNS: Central Nervous System

Introduction

Abnormal liver chemistry is common in patients with HIV. Causes of abnormal liver enzymes in this population include viral hepatitis such as hepatitis B or C, opportunistic infections, and drug toxicity [1]. HIV has contributed to the rise in TB, and the risk of extrapulmonary TB increases with decreasing CD4 counts. This is further complicated by HIV associated IRIS that occurs in 10–32% of people initiating ART [2]. We present an HIV-infected patient with abnormal liver chemistries.

Case Report

A 37-year-old female living with HIV was re-initiated on ART with bictegravir/emtricitabine/tenofovir alafenamide six weeks prior to presentation, after having been non-compliant with ART for many years. She presented to the emergency department with fevers, confusion, dysphagia, and abdominal discomfort. Exam was notable for temperature of 103.2°F, hypotension necessitating the use of vasopressors, and right upper quadrant abdominal tenderness. Labs were significant for leukopenia, normocytic anemia, ALT 267 U/L [Normal: 0-33 U/L], AST 484 U/L [Normal: 0-32 U/L], alkaline phosphatase 342 U/L [Normal: 35-104 U/L], normal total bilirubin, and R factor of 2.5, showing mixed pattern of hepatobiliary injury. Of note, the patient's liver chemistries

were completely normal at the time of ART initiation six weeks ago. Extensive workup for alternate etiologies of elevated transaminases were positive for anti-nuclear antibody 1:320, anti-smooth muscle antibody 1:80, elevated Immunoglobulin Gamma 2632 mg/dL [normal: 767-1590 mg/dL]. Other etiology workup including hepatitis A IgM, hepatitis B serologies, hepatitis C antibody, and polymerase chain reaction testing for herpes simplex virus, cytomegalovirus, and Epstein-Barr virus were negative. HIV viral load was 257 vc/mL and CD4 count was 28 cells/cmm. Abdominal ultrasound revealed hepatomegaly with steatosis. Contrasted abdominal MRI displayed mesenteric and retroperitoneal lymphadenopathy, hepatosplenomegaly and T2 hypointense, non-enhancing splenic lesions. Based on our workup and considering the temporal association of elevated liver transaminases with the recent initiation of ART, IRIS was our primary differential. ART was held at the time of admission. The positive autoimmune serologies and elevated Immunoglobulin G, though non-specific, made autoimmune hepatitis a secondary differential.

Further workup included a brain MRI which was unremarkable. Esophagogastroduodenoscopy showed no significant abnormalities. Due to persistently elevated liver transaminases and our suspicion of IRIS, the patient underwent a percutaneous liver biopsy, which demonstrated noncaseating granulomas (Figure 1) with numerous AFB positive bacilli (Figure 2) and no signs of autoimmune hepatitis. In addition, lumbar puncture was performed. CSF analysis showed 5 WBCs with 97% lymphocytes, normal protein, and glucose; CSF cultures grew AFB. Multiple sets of AFB isolator blood cultures turned positive as well. This confirmed our suspicion of IRIS due to occult mycobacterial infection causing the elevated liver transaminases.

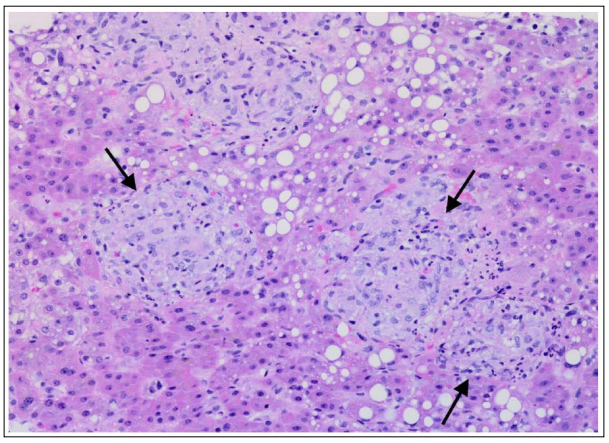

Figure 1: Percutaneous Liver Biopsy Specimen with Hematoxylin and Eosin (H&E) Stain at 200x Magnification: Hepatic Parenchyma with the Diffuse Multiple Non-Caseating Granulomas (Arrows)

She was started on an empiric anti-mycobacterial regimen, which included rifampin, isoniazid, ethambutol, and azithromycin, while ART was held, pending species identification. Dexamethasone 28 milligrams per day was started and tapered off over 4-week period to mitigate IRIS. The patient's liver chemistries and infectious markers improved, and she was eventually discharged on the above antimicrobial regimen with close follow-up with infectious disease clinic.

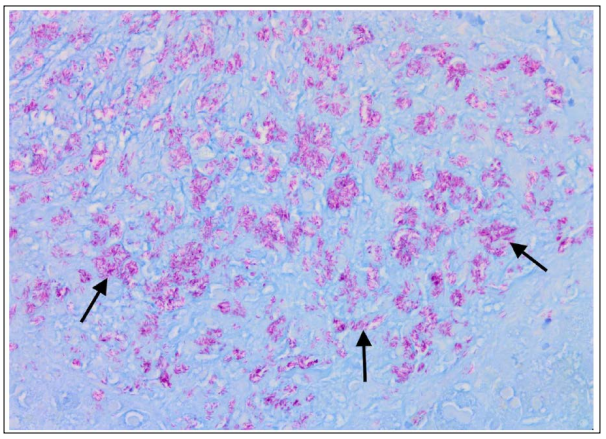

Figure 2: Percutaneous Liver Biopsy specimen with Ziehl-Neelsen AFB Stain at 400X Magnification: Innumerable Acid-Fast Bacilli. Arrows Indicating Some Areas Representative of Positive Staining for Acid Fast Bacilli.

After discharge, the patient remained compliant with her therapy. After six weeks, the AFB from AFB isolator blood cultures was eventually identified as Mycobacterium avium complex, thus confirming the diagnosis of disseminated MAC infection. The patient's ART was resumed without complication. Treatment for disseminated MAC was adjusted to rifampin, ethambutol, and azithromycin, which was continued for 12 months. She subsequently began to gain an appropriate amount of weight (25 pounds in 2 months). She continued to have serial comprehensive metabolic profiles which showed normalization of liver enzymes.

Discussion

Since the introduction of ART, there has been a focus on drug-associated hepatotoxicity in HIV. Chronic liver diseases like hepatitis B, C, alcohol associated, and metabolic dysfunctionassociated steatohepatitis remain leading causes of liver dysfunction in patients with HIV [3]. IRIS due to occult infection was our topmost differential for the etiology of elevated liver enzymes as this is more likely in patients with low CD4 counts and within the first few weeks to months after initiating ART [4].

IRIS is a hyper-inflammatory response to pathogens, most commonly Mycobacterium tuberculosis and other opportunistic infections. The agreed upon criteria for diagnosing IRIS are the following: the presence of advanced HIV with low pretreatment CD4 count; a positive virologic and immunological response to antiretroviral therapy; the absence of superimposed infection, drug allergy or adverse drug reaction, medication noncompliance, or reduced drug levels; the presence of clinical manifestations consistent with an inflammatory condition; and a temporal association between ART initiation and the onset of clinical features of illness [5,6]. IRIS typically falls under two recognized categories: paradoxical IRIS and unmasking IRIS. Paradoxical IRIS is defined as exacerbation of a recognized, new, recurrent, or worsening of coinfection after starting ART. Unmasking IRIS is defined as worsening of unrecognized preexisting infection after starting ART. IRIS associated with mycobacterial infections is an underrecognized cause of hepatic dysfunction [7]. Hepatic manifestations of mycobacterial infections likely result from rapid restoration of granulomatous inflammation in response to mycobacteria trapped within the hepatic portal tracts during hematogenous dissemination. Liver biopsy histopathology typically shows large granulomas, which could explain the development of hepatomegaly. Abdominal discomfort can be attributed to the stretching of the liver capsule during liver expansion.

Management of IRIS largely focuses on symptom control as well as antimicrobials against the underlying infection. Typically, ART is continued unless there is severe ART related toxicity or CNS involvement. Supportive management for treatment of IRIS includes adequate hydration, correction of electrolyte abnormalities, and nutrition optimization. Addition of steroids can also be implemented for CNS involvement or to mitigate severe IRIS. For severe CNS involvement resistant to steroids, biologics including TNF-alpha antagonist can be used [4]. Treatment of disseminated MAC typically involves a multidrug regimen. Current recommendations for patients with advanced HIV include a macrolide (either clarithromycin or azithromycin) along with ethambutol and in appropriates cases, agents such as rifampin, rifabutin, clofazimine, ciprofloxacin or parenteral amikacin can be added. The goal of therapy is to have culture negativity for 12 months [8]. This case underscores the importance of individualizing our differential diagnosis of elevated liver transaminases based on a patient's unique clinical presentation.

References

1. Shiferaw MB, Tulu KT, Zegeye AM, Wubante AA (2016) Liver Enzymes Abnormalities among Highly Active Antiretroviral Therapy Experienced and HAART Naïve HIV-1 Infected Patients at Debre Tabor Hospital, North West Ethiopia: A Comparative CrossSectional Study. AIDS Res Treat 1985452.
2. Lewis J Haddow, Philippa J Easterbrook, Anisa Mosam, Nonhlanhla G Khanyile, Raveen Parboosing, et al. (2009) Defining Immune Reconstitution Inflammatory Syndrome: Evaluation of Expert Opinion versus 2 Case Definitions in a South African Cohort. Clinical Infectious Diseases 49: 1424-1432.
3. Kaspar MB, Sterling RK (2017) Mechanisms of liver disease in patients infected with HIV. BMJ Open Gastroenterol 4: e000166.
4. Thapa S, Shrestha U (2023) Immune Reconstitution Inflammatory Syndrome. Treasure Island (FL): StatPearls https://www.ncbi.nlm.nih.gov/books/NBK567803/.
5. Breton G, Duval X, Estellat C, Poaletti X, Bonnet D, et al. (2004) Determinants of immune reconstitution inflammatory syndrome in HIV type 1infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 39: 1709-1712.
6. Ratnam I, Chiu C, Kandala NB, Easterbrook PJ (2006) Incidence and risk factors for immune reconstitution inflammatory syndrome in an ethnically diverse HIV type 1infected cohort. Clin Infect Dis 42: 418-427.
7. Bruchfeld J, Correia-Neves M, Källenius G (2015) Tuberculosis and HIV Coinfection. Cold Spring Harb Perspect Med 5: a017871.
8. Akram SM, Attia FN (2024) Mycobacterium avium Complex. Treasure Island (FL): StatPearls Publishing https://www.ncbi.nlm.nih.gov/books/NBK431110/.