ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Increasing Alkaline Phosphatase as the Primary Manifestation of Disseminated Histoplasmosis in an AIDS Patient Without Pulmonary Disease

Triston Berger, MD[1], Sebastian Borja, MD[1], Jonathan Kandiah, MD[2], Jaspreet Suri, MD[2], and Harvey Riback, MD[2]

[1]*Department of Internal Medicine, Norwalk Hospital, Affiliated with Yale School of Medicine, Norwalk, CT*
[2]*Division of Gastroenterology and Hepatology, Norwalk Hospital, Affiliated with Yale School of Medicine, Norwalk, CT*

ABSTRACT

Histoplasmosis is an infection caused by the dimorphic fungi Histoplasma. Hepatic involvement in the setting of disseminated histoplasmosis from a pulmonary source is well documented. Hepatic involvement as the primary manifestation in the absence of pulmonary disease is rare. We present a patient with acquired immune deficiency syndrome found to have disseminated histoplasmosis with worsening alkaline phosphatase as the primary manifestation of disease, which has not been reported in a review of the literature. After diagnosis, the patient was started on appropriate therapy with alkaline phosphatase return to baseline.

INTRODUCTION

Histoplasmosis is an infection caused by the dimorphic fungi Histoplasma found in the soil of central and eastern United States. It is the most common endemic mycosis in the United States, particularly in patients with acquired immune deficiency syndrome (AIDS).[1,2] Immunocompetent hosts typically present with a self-limited illness. In those who are immunocompromised, histoplasmosis may result in more serious infections including cavitary pulmonary disease, fibrosing mediastinitis, or disseminated disease.[3] The symptoms of disseminated histoplasmosis (DH) are nonspecific and may include fever, anorexia, weight loss, and cough.[3] The constellation of nonspecific symptoms makes it difficult to diagnose and treat DH in a timely manner. Hepatic involvement in the setting of DH from a pulmonary source is well documented. Hepatic involvement as the primary manifestation of disseminated disease is rare.[4,5] Specifically, the isolated worsening of alkaline phosphatase (ALP) as the primary manifestation of DH without pulmonary involvement has not been reported in our review of the literature. We present a 51-year-old woman with AIDS diagnosed with DH after hepatic biopsy due to persistently increasing ALP.

CASE REPORT

A 51-year-old woman with a medical history of AIDS, type 2 diabetes with insulin dependence, intravenous drug use, esophageal candidiasis, and Crohn's disease on adalimumab presented with weakness, night sweats, poor oral intake, and diarrhea over 4 days. She reported taking her adalimumab as prescribed but was not adherent to antiretrovirals. Initial laboratory test results showed pancytopenia and disseminated intravascular coagulation. Her renal function was preserved. Liver function tests included ALP 241 U/L, aspartate aminotransferase (AST) 75 U/L, alanine aminotransferase (ALT) 8 U/L, and a total bilirubin level of 0.7 mg/dL (baseline 181, 31, 14 U/L, 0.7 mg/dL with laboratory reference ranges 30–103 U/L, 10–50 U/L, 10–55 U/L, 0.0–1.2 mg/dL, respectively). HIV testing revealed an HIV-1 load of >76,112 copy/mL and an absolute $CD4^+$ count of 4 cells/mm^3. Imaging included a computerized tomography (CT) of the head without acute intracranial pathology; chest x-ray without evidence of cardiopulmonary disease; and a CT of the chest/abdomen/pelvis showing severe hepatic steatosis, diffuse moderate esophageal mucosal thickening, persistent splenomegaly, diffuse colonic mucosal thickening, and retroperitoneal and mesenteric lymphadenopathy (with prior biopsy supporting HIV lymphadenopathy). There was no evidence of focal lung disease or pulmonary embolism.

ACG Case Rep J 2022;9:e00865. doi:10.14309/crj.0000000000000865. Published online: October 6, 2022

Correspondence: Triston Berger, MD (triston.berger@nuvancehealth.org).

Initial treatment began with broad-spectrum antibiotics for severe sepsis. Her diarrhea had resolved within 24 hours of admission and suspicion for infectious colitis was low. By day 3, symptoms largely resolved and multiple blood cultures returned negative. Antibiotics were discontinued. By day 6, the patient felt at baseline. Despite clinical improvement and discontinuation of potentially hepatotoxic medications, ALP levels continued to rise with stabilization of AST/ALT. Magnetic resonance cholangiopancreatography was performed showing periportal edema; fatty liver; splenomegaly; and mesenteric and retroperitoneal adenopathy without intrahepatic or extrahepatic ductal beading, structures, dilation, or obstruction (Figure 1). Infectious workup remained negative including antibody tests for serum histoplasma yeast and mycelial forms (Table 1). Twelve days into hospital stay, the ALP level increased to 1,681 U/L, with isoenzymes supporting hepatic etiology. Given the rapid increase in ALP, a hepatic biopsy was performed. The following day, the Histoplasma urine antigen returned positive. The tissue sample showed marked steatosis, stage 2/4 fibrosis, Epstein-Barr virus (EBV) positivity, and intracellular yeast forms consistent with histoplasma (Figure 2). She had no history of Histoplasma infections.

The patient was started on liposomal amphotericin B for 16 days before transition to itraconazole 200 mg daily. Two days after initiating therapy, her ALP began to decline. She remained adherent to all medications and follow-up appointments and saw improvement in the CD4 cell count with ALP return to baseline.

DISCUSSION

We present a case of DH in an acquired immunodeficiency syndrome patient with an isolated worsening of ALP as the primary manifestation of disease. Although there was an initial increase in AST (75 U/L day 0, 128 day 1), it remained stable through the hospital course with a range between 114 and 145 U/L. ALT also fluctuated, but was never above the high-normal reference range. Given the persistent increase in ALP despite discontinuation of potentially hepatotoxic medications, lack of hepatotoxic home medications, extensive laboratory workup, ALP isoenzymes confirming hepatic origin, and the improvement of ALP after initiation of amphotericin B, it is felt that there is sufficient evidence to attribute the elevations in ALP to DH. EBV viremia and positivity on biopsy could contribute to the abnormal liver function tests; however, a positive immunoglobulin G with negative immunoglobulin M and positive Epstein-Barr nuclear antigen antibody suggests chronic infection. This makes it unlikely that EBV is the primary factor in acute ALP elevation, especially considering the resolution of ALP to baseline after the treatment of histoplasmosis without treatment directed to EBV. Another differential in this case is AIDS cholangiopathy, in which opportunistic infections promote stricture formation in the bile tract causing obstruction and cholestatic liver damage. Magnetic resonance cholangiopancreatography is the favored diagnostic imaging modality and typically demonstrates papillary stenosis or intrahepatic or extrahepatic biliary strictures. In addition, hepatic biopsy of AIDS cholangiopathy is typically consistent with sclerosing cholangitis.[6] None of these features were seen on studies obtained in hospital,

Table 1. Pertinent laboratory results before biopsy

Laboratory test	Result
Serum complement fixation histoplasma yeast antibody	Negative
Serum complement fixation histoplasma mycelial antibody	Negative
[1,3]-β-D-glucan	Positive
Cryptococcal antigen	Negative
QuantiFERON-TB gold	Negative
ALP isoenzymes	Total ALP 1,107 U/L; 10.5% bone; 37.4% liver 1; 52.1% liver 2
CD4 count	4 cell/mm^3
Human herpes virus 8 PCR	Not detected
HBsAb, HBsAg, HBcAb, HCV Ab	Nonreactive
Antinuclear antibody	Negative
Anti-smooth muscle antibody	Weak positive [1:80]
Mitochondrial IgG antibody	Negative
Herpes simplex virus 1 and 2, parvovirus B19, human herpes virus 6	IgG-positive and IgM-negative
Cytomegalovirus	IgG-positive, IgM-negative, and PCR not detected
EBV	IgG-positive, IgM-negative, EBNA-positive, and PCR 4,98,000 copies

ALP, alkaline phosphatase; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein-Barr virus; HBcAB, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HbsAg, hepatitis B surface antigen; HCV Ab, hepatitis C virus antibody; PCR, polymerase chain reaction; IgG, Immunoglobulin G; IgM, Immunoglobulin M.

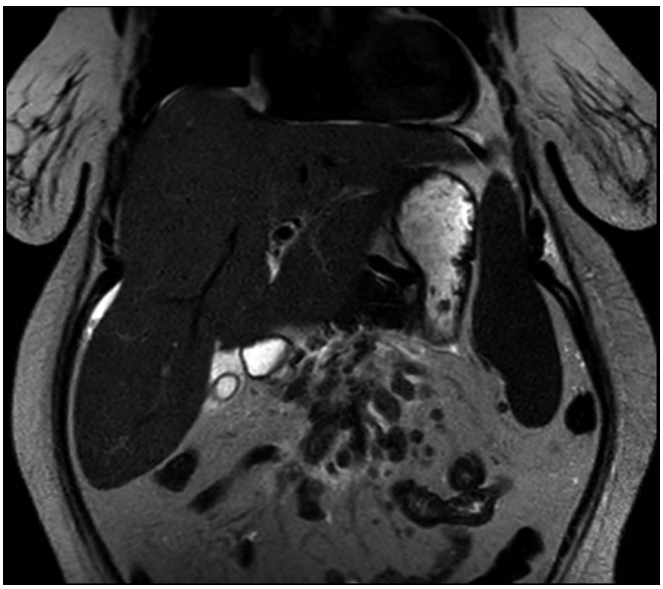

Figure 1. Magnetic resonance cholangiopancreatography demonstrating hepatosplenomegaly. No intra or extrahepatic ductal obstruction, strictures, or dilations were identified.

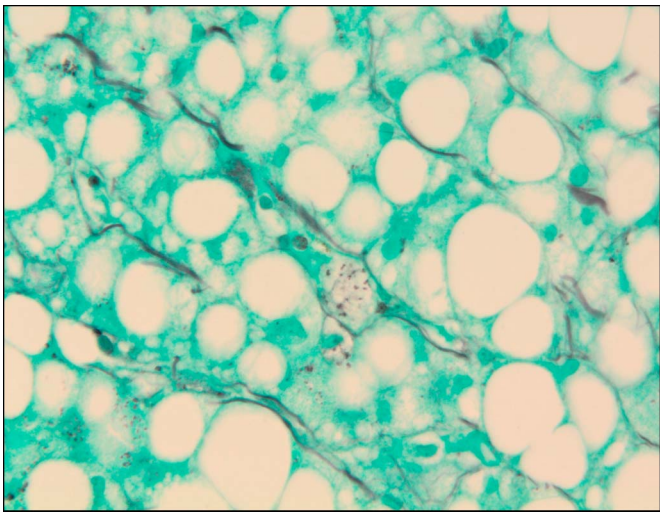

Figure 2. Core hepatic biopsy with Grocott-Gomori's methenamine silver stain at 400× magnification demonstrating intracellular yeast and marked steatosis.

making this diagnosis unlikely. The pathophysiology behind the ALP elevation is unclear. The general cause of elevations in hepatobiliary disorders is because of increased enzyme synthesis as opposed to reduced excretion, but the underlining reason for increased translation of ALP in the setting of histoplasma infection is difficult to elucidate.[7]

Although Histoplasma serum antibody and urine antigen studies were sent early, the initial serum antibodies for Histoplasma returned negative. According to ARUP Laboratories, the complement fixation test is positive for titers to one or both antibodies in approximately 90%–95% of cases.[8] Given our patient's uncontrolled AIDS, she was likely unable to mount an appropriate immune response to stimulate the formation of antibodies to a detectable level. Given the increased rates of false-negatives in patients with severely immunocompromised states and the length of return time for the urine antigen, it may be beneficial to consider tissue sampling earlier in the hospital course when a source is not quickly identified. This is especially important in disseminated infections because of the high mortality. In the case of DH, there is a 100% fatality rate in patients without adequate treatment, and 50% of patients will not respond to therapy.[4,9–11]

DISCLOSURES

Author contributions: T. Berger wrote the manuscript and is the article guarantor. S. Borja, J. Kandiah, and J. Suri critically reviewed and edited the manuscript. H. Riback provided supervision.

Financial disclosures: None to report.

Previous presentation: This case was presented at the American College of Gastroenterology 2021 Annual Scientific Meeting as a poster presentation at the Mandalay Bay Convention Center in Las Vegas, NV on October 25, 2021.

Informed consent was obtained for this case report.

Received December 4, 2021; Accepted August 8, 2022

REFERENCES

1. Panackal A, Hajjeh R, Cetron M, Warnock D. Fungal infections among returning travelers. *Clin Infect Dis.* 2002;35(9):1088–95.
2. Baddley J. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis.* 2011;17(9):1664–9.
3. Kauffman CA. Histoplasmosis: A clinical and laboratory update. *Clin Microbiol Rev.* 2007;20(1):115–32.
4. Rihana N, Kandula M, Velez A, Dahal K, O'Neill E. Histoplasmosis presenting as granulomatous hepatitis: Case report and review of the literature. *Case Rep Med.* 2014;2014:879535.
5. Park S, Cheong J, Kyi K, et al. Cholestasis and disseminated histoplasmosis in a psoriatic patient on infliximab: Case report and review of literature. *BMC Gastroenterol.* 2020;20(1):141.
6. Naseer M, Dailey FE, Juboori AA, Samiullah S, Tahan V. Epidemiology, determinants, and management of AIDS cholangiopathy: A review. *World J Gastroenterol.* 2018;24(7):767–74.
7. Lowe D, Sanvictores T, John S. *National Center for Biotechnology Information.* National Library of Medicine (https://www.ncbi.nlm.nih.gov/books/NBK459201/) (2021). Accessed June 9, 2022.
8. *Histoplasma Antibodies by CF|ARUP Laboratories Test Directory*. ARUP Laboratories. (https://ltd.aruplab.com/Tests/Pub/0050625) (2021). Accessed November 30, 2021.
9. Subramanian S, Abraham OC, Rupali P, Zachariah A, Mathews MS, Mathai D. Disseminated histoplasmosis. *J Assoc Physicians India* 2005;53:185–9.
10. Baddley JW. Epidemiology and clinical manifestations of histoplasmosis in patients with HIV. In: Post TW (ed). UpToDate. *UpToDate* (https://www-uptodate-com.ezproxy.uvm.edu/contents/epidemiology-and-clinical-manifestations-of-histoplasmosis-in-patients-with-hiv?search=Epidemiology%20and%20clinical%20manifestations%20of%20histoplasmosis%20in%20patients%20with%20HIV&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1) (2021). Accessed November 30, 2021.
11. Baddley JW. Diagnosis and treatment of histoplasmosis in patients with HIV. In: Post TW (ed). UpToDate. *UpToDate* (https://www-uptodate-com.ezproxy.uvm.edu/contents/diagnosis-and-treatment-of-histoplasmosis-in-patients-with-hiv?search=Diagnosis%20and%20treatment%20of%20histoplasmosis%20in%20patients%20with%20HIV&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1) (2021). Accessed November 30, 2021.