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

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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/mm3. 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.
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. 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]-b-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/mm³                        |
| Human herpes virus 8 PCR              | Not detected                      |
| HBsAb, HBsAg, HBCAb, HCV Ab           | Nonreactive                       |
| Anti-nuclear 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.
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