

Significantly Elevated Alkaline Phosphatase Caused by Congestive Hepatopathy in the Setting of Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Introduction: We report a rare case of significantly elevated alkaline phosphatase (ALP) caused by congestive hepatopathy in the setting of heart failure with preserved ejection fraction (HFpEF).

Case Presentation: A 44-year-old woman with multiple hospitalizations for acute decompensated HFpEF and abdominal pain had an ALP elevation to almost 8 times the upper limit of normal. A negative inflammatory, infectious, and autoimmune workup led to liver biopsy and diagnosis of congestive hepatopathy.

Discussion: The existing literature includes extensive research on the impact of liver function enzymes in heart failure with reduced ejection fraction (HFrEF); however, research on their impact on HFpEF is limited. ALP has been found to be normal or mildly elevated, with very few cases of significantly elevated ALP levels reported in HFrEF patients only.

Conclusion: Complex cardiohepatic interactions often result in the coexistence of heart failure and liver disease. Unexplained chronic cholestasis in the setting of congestive heart failure should raise the suspicion for congestive hepatopathy.

INTRODUCTION

Congestive hepatopathy is the manifestation of chronic passive congestion due to right heart failure. The signs and symptoms of right heart failure often predominate early presentation. Thus, patients with congestive changes often remain asymptomatic for a long time, with abnormalities in liver function tests frequently being the first indicator of hepatic pathology.^{1,2} Liver injury due to passive hepatic congestion presents with a characteristic mild change in serum cholestatic markers of alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and total bilirubin.³⁻⁶ The existing literature includes extensive research on the impact of liver function enzymes in heart failure with reduced ejection fraction (HFrEF); however, research on their impact on HFpEF is limited. In both HFrEF and the limited studies on HFpEF, ALP has been found to be normal or mildly elevated.⁷ There are even fewer case reports or studies that show significantly elevated ALP in congestive heart failure patients.^{6,8,9} Our patient is unique in that cases of significantly elevated ALP caused by congestive hepatopathy in the setting of HFpEF have not been described/reported in the literature.

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tase (ALP), gamma-glutamyltransferase (GGT), and total bilirubin.³⁻⁶ The existing literature includes extensive research on the impact of liver function enzymes in heart failure with reduced ejection fraction (HFrEF); however, research on their impact on heart failure with preserved ejection fraction (HFpEF) is limited. In both HFrEF and the limited studies on HFpEF, ALP has been found to be normal or mildly elevated.⁷ There are even fewer case reports or studies that show significantly elevated ALP in congestive heart failure patients.^{6,8,9} Our patient is unique in that cases of significantly elevated ALP caused by congestive hepatopathy in the setting of HFpEF have not been described/reported in the literature.

CASE PRESENTATION

A 44-year-old woman presented with severe right upper quadrant pain, two episodes of non-bloody emesis, and severe shortness of breath. Her medical history included chronic HFpEF, nephrotic syndrome, stage 3 chronic kidney disease, diabetes mellitus type 2, hypertension, hyperlipidemia, bilateral lower extremity chronic lymphedema, and severe morbid obesity—weighing 491 pounds and gaining approximately 50 pounds in the last 2 weeks. She was admitted and treated for acute decompensated HFpEF.

In the past half year, including this admission, the patient had been hospitalized for acute decompensated HFpEF and right upper quadrant pain 5 times with extensive workup. Of note, she had persistently elevated ALP levels of around 200 units/L (104 units/L upper limit of normal) dating as far back as 2013. Each admission, aspartate aminotransferase and alanine

Table. Admission Laboratory Trends

Admission Number	Date	Alkaline Phosphatase	NT-proBNP
1	Feb 21, 2020	231	2297
2	May 25, 2020	164	3181
3	June 8, 2020	N/A	4792
4	June 28, 2020	469	5084
5	July 30, 2020	826	4981

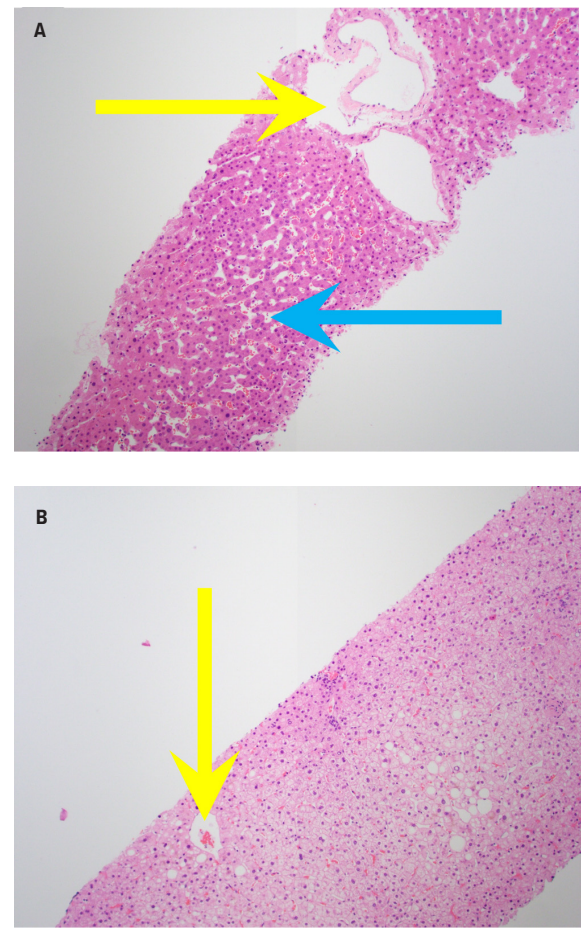
Abbreviation: N/A, not applicable.

aminotransferase levels ranged from normal to mildly elevated. Admission dates and trends of ALP and NT-proBNP levels are shown in the Table.

During the first admission, workup included a right upper quadrant ultrasound that showed cholelithiasis, mild hepatomegaly, and no pericholecystic fluid or gallbladder wall thickening to suggest acute cholecystitis. Tc99m-Mebrofenin hepatobiliary scintigraphy (HIDA scan) showed no cystic or common bile duct obstruction with normal gallbladder ejection fraction. Acute surgical intervention was not recommended at the time. During the second admission, transthoracic echocardiogram (TTE) showed new grade I diastolic dysfunction, new mild to moderate tricuspid regurgitation, and new moderate pulmonary hypertension (pHTN) in the setting of normal left ventricular ejection fraction (LVEF) of 64% without regional wall motion abnormalities. During the fourth admission, the LFTs showed a new significantly elevated ALP of 469 units/L and GGT of 496 units/L (6-42 units/L). The acute increase of ALP levels to more than twice her baseline prompted further evaluation. Right upper quadrant ultrasound was normal, which prompted evaluation of intrahepatic causes of cholestasis. Antimitochondrial antibody (AMA) IgG and F-Actin Smooth Muscle Antibody IgG were both negative. Hepatitis B surface antigen, surface antibody, and core IgM antibody and Hepatitis C antibody were all nonreactive. Cholestasis of uncertain etiology prompted magnetic resonance cholangiopancreatography (MRCP), which showed no biliary obstruction or dilation.

On this admission, LFTs showed a significantly elevated ALP of 826 units/L and GGT of 925 units/L. Like her previous admission, right upper quadrant ultrasound was normal. Hepatitis A antibody and Hepatitis A IgM antibody were both nonreactive. Alpha-1 antitrypsin, immunoglobulins IgA, IgG, and IgM were all normal. Repeat AMA IgG was again negative. After extensive workup, we ruled out all inflammatory, infectious, and autoimmune processes. Negative findings on extensive cholestasis workup led the team to suspect a cardiohepatic cause of cholestasis, prompting cardiac imaging. Limited TTE showed normal LVEF (64%), moderate tricuspid regurgitation, and moderate pHTN consistent with her last TTE from 2 months prior to this admission. To further work up a differential of congestive hepatopathy versus AMA negative primary biliary cholangitis

Figure. Photomicrographs (at 10X magnification) of Patient's Biopsy (A) With Comparison to a Normal Patient (B)



The yellow arrows point to the dilated central vein in the patient (A) and a normal sized central vein for comparison (B). The blue arrow points to an area of sinusoidal dilation in the patient's biopsy (A), while in the normal comparison, sinusoids are not dilated and therefore not readily seen.

Sinusoidal dilation and the appearance of dilation of central veins may be a histologic artifact and can be seen in a variety of clinical settings. In this patient's biopsy, there was dilation of many central veins and diffuse dilation of sinusoids strongly suggestive of venous outflow obstruction. This may occur in an acute or chronic setting. There was no fibrosis to suggest chronic passive congestion.

(PBC), ultrasound-guided core needle random liver biopsy was conducted. Liver biopsy found focal, mild bile duct epithelial damage without inflammation. Definitive histological features of PBC were not seen. Mild dilatation of central veins and adjacent sinusoids was consistent with congestive hepatopathy in light of the patient's cardiac history (Figure). No steatosis, fibrosis, cholestasis, or inflammation was identified. Based on clinical findings and our investigations, we diagnosed the patient with congestive hepatopathy. She was discharged once hemodynamically stable and referred to outpatient cardiology for follow-up and management of congestive hepatopathy in the setting of HFpEF.

DISCUSSION

This case represents a rare presentation of significantly elevated ALP levels in a patient with congestive hepatopathy due to HFpEF. Additionally, this case illustrates the diagnostic approach to evaluating a heart failure patient who presents with abnormal liver function. In such a case, biliary or primary hepatic pathology should be evaluated before attributing liver function abnormalities to cardiac disease.²

Our patient had a history of chronic ALP elevation with levels of around 200 units/L dating as far back as 2013. Cholestasis is considered chronic if it persists for greater than 6 months.^{10,11} Acute elevations in the setting of chronic cholestasis prompted further evaluation in our patient. The first step in diagnostic workup of cholestasis after taking a detailed history and conducting a physical exam is to differentiate between intra- and extrahepatic cholestasis. Abdominal ultrasound is most often the first diagnostic step due to its high sensitivity, noninvasive nature, lack of radiation, portability, and relatively inexpensive cost.^{10,11} Extrahepatic obstruction can result from stones, malignant masses, strictures, cyst, or parasitic infections, with choledocholithiasis being the most common cause of extrahepatic cholestasis.^{10,12} Biliary ductal dilation on ultrasound strongly suggests an extrahepatic cause of cholestasis while a negative ultrasound prompts workup for intrahepatic cholestasis.

The most common cause of chronic intrahepatic cholestatic liver disease in adults is PBC. Per the 2018 Practice Guidance from the American Association for the Study of Liver Diseases concerning PBC, PBC should be suspected in the setting of chronic cholestasis after exclusion of common causes of biliary obstruction, particularly in middle-aged females with unexplained elevations in serum ALP, like our patient.¹³ Thus, a workup of intrahepatic cholestasis should begin with an AMA. In the case of a negative AMA, PBC-specific antinuclear antibodies such as anti-sp100 and anti-gp210 should be ordered to potentially reduce the necessity of liver biopsy.^{11,13} Concurrently, other causes of cholestasis should be explored with testing for hepatitis A, B, C, and E, immunoglobulins, smooth muscle antibodies, and alpha-1-antitrypsin. Negative workup with ultrasound and labs should prompt visualization of intra- and extrahepatic bile ducts via MRCP, which is essential in the detection of strictures and primary sclerosing cholangitis. If the diagnosis is still unclear, a liver biopsy should be performed.⁹⁻¹¹

In our patient, extensive negative workup and concern for a cardiohepatic etiology of cholestasis prompted a liver biopsy, which showed venous outflow obstruction. Interference of venous outflow results from a multitude of causes—from congestive heart failure to occlusion of smaller branches of the hepatic veins within the liver. Space-occupying lesions (granulomas, tumor, amyloid) may not be present within the biopsy material but may cause localized obstruction affecting only parts of the liver.

The history of chronic cholestasis and heart failure in our

patient is highly suggestive of congestive hepatopathy. Elevated central venous pressures are transmitted back to the hepatic sinusoids, resulting in sinusoid dilation and edema and hepatocyte necrosis.¹ Signs and symptoms of right heart failure often predominate early presentation, as evidenced by our patient's frequent presentation with shortness of breath and hospitalizations for acute exacerbation of HFpEF. Congestive hepatopathy patients frequently remain asymptomatic from their liver disease for a long time and often are identified with a delay due to abnormalities in liver function tests on routine laboratory evaluations.^{1,2}

The association of liver function abnormalities with heart failure has been well documented in literature. In the setting of cardiogenic shock characterized by marked hypotension and hypoperfusion, transaminase levels can be significantly elevated.² By contrast, liver injury due to passive hepatic congestion presents with a characteristic cholestatic profile. However, serum cholestatic markers of ALP, GGT, and total bilirubin typically are only mildly elevated, in contrast to our patient who had significantly elevated ALP levels of almost 8 times the upper limit of normal.³⁻⁶ Some common causes of significantly elevated levels of liver ALP are observed in patients with benign and malignant biliary obstruction, infiltrative liver disorders, and sepsis.¹⁴ There are very few reports in the literature of significantly elevated ALP levels in congestive hepatopathy, and these reports are in HFrEF not HFpEF patients.^{6,8,9} Additionally, the majority of studies analyzing the association of liver function enzymes and heart failure were conducted in HFrEF, with only a few studies including HFpEF patients.^{3,7,15} In the limited studies including both HFrEF and HFpEF patients, liver function tests were not markedly different between the 2 groups, with both groups consistent with a cholestatic picture, demonstrating only a mild increase in cholestatic enzymes.^{3,7}

Our case is rare in that cases of significantly elevated ALP caused by congestive hepatopathy in the setting of HFpEF have not been described/reported in the literature. Liver disease related to congestive hepatopathy is rarely responsible for significant morbidity or mortality with the underlying cardiac disease generally determining clinical outcomes. Thus, management of congestive hepatopathy requires treatment of the underlying cardiac disorder, which can lead to improvements in liver function tests.¹

CONCLUSIONS

A structured approach that consists of clinical, biochemical, and technical diagnostic measures is important in the evaluation of elevated alkaline phosphatase. An unexplained chronic cholestasis in the setting of congestive heart failure should raise the suspicion for congestive hepatopathy. Complex cardiohepatic interactions often result in the coexistence of heart failure and liver disease. Studies analyzing the relationship between heart failure and liver enzymes predominantly conducted in HFrEF patients demon-

strated that congestive hepatopathy classically presents with a mild cholestatic picture. The general scarcity of research studying the relationship between liver function parameters and HFpEF demonstrates the need for further research in this area.

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