Coexisting Sickle Cell Anemia and Sarcoidosis: A Management Conundrum!

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ABSTRACT: Sickle cell disease and Sarcoidosis are conditions that are more common in the African American population. In this report we share an unfortunate patient who had hepatic sarcoidosis but could not receive steroids since that precipitated acute liver failure. We have discussed potential therapy options but we need more options that improve mortality.

KEYWORDS: sickle cell disease, Liver failure

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Introduction

Sarcoidosis and hemoglobinopathies are 2 disorders commonly affecting the black population. Sarcoidosis occurs at a rate of about 30 to 40 per 100 000 in the general population, and approximately 0.15% of African Americans are homozygous and hence have sickle cell disease (SCD).[1] We are reporting a patient with SCD who survived childhood to later develop sarcoidosis which caused liver impairment. When oral steroids were used to manage hepatic sarcoidosis, it precipitated sickling. We could find no previous report in the published literature regarding guidance on management of such a patient. We realize this report raises more questions than answers but strongly believe these data need to be collected to formulate optimal care in patients with sickle cell hepatopathy or hepatic sarcoidosis or when they occur together.

Case Report

A 34-year-old African American man with known SCD on chronic exchange transfusions (secondary to stroke at the age of 6) was diagnosed with pulmonary and ocular sarcoid. He also had a history of atrial fibrillation, post defibrillator placement for cardiomyopathy, and history of sudden cardiac deaths in the family and was on rivaroxaban.

He was initially started on low-dose prednisone and methotrexate for sarcoidosis, which precipitated his first sickle cell crisis in more than a decade. He presented with pain and anemia, with his hemoglobin falling from a baseline of 8 to 6 g/dL requiring blood transfusions. His liver panel showed aspartate aminotransferase (AST) of 213 U/L, alanine aminotransferase (ALT) of 68 U/L, alkaline phosphatase of 373 U/L, total bilirubin of 26.3 mg/dL, conjugated bilirubin of 22.7 mg/dL, and international normalized ratio (INR) of 1.3. Liver biopsy showed exuberant granuloma with sinusoid sickling. Rivaroxaban was changed to warfarin after discussion with the family, mainly for the convenience of monitoring and reversing coagulopathy if needed.

He was admitted within a year of initial diagnosis of sarcoidosis for progressively worsening limb edema and ascites. Furosemide and spironolactone had minimal response. He had a large-volume paracentesis performed, which revealed no evidence of spontaneous bacterial peritonitis. The appearance of Ascitic fluid was orange in color with total nucleated cells of 26433/mm^3 among which total nucleated cells were 60/mm^3 L with 81% polymorphs. He was also found to be encephalopathic, and lactulose was initiated. Other causes of acute liver failure, including paracetamol ingestion, were ruled out because the levels were undetectable. Also, the patient was never found to have adverse effects of incompatible blood transfusion. Hepatitis C virus was negative and serum albumin was 2.9 mg/dL, with partial thromboplastin time elevated to more than 150 during his whole hospital course. D-dimer was moderately increased. Hepatology continued to advocate for azathioprine. Warfarin was held secondary to coagulopathy. He developed a nose bleed for which he was treated with fresh frozen plasma and vitamin K with some resolution of symptoms. His Model for End-Stage Liver Disease was calculated at 35, but because he did not have cirrhosis these scores were inaccurate. He was transferred to the intensive care unit after he started bleeding from the site of his paracentesis and had to have purse string sutures placed. The patient continued to be in acute liver failure, and despite optimal supportive therapy, he developed an intracranial bleed with adverse outcome. During this time period, his INR reached up to 7.5 which was corrected down to 3.1. International normalized ratio has been used here even after cessation of warfarin because it is a test for synthetic function too. Abdominal ultrasound during this period showed massive hemoperitoneum most prominent in the left lower quadrant. His AST peaked at 7922 U/L, ALT at 1389 U/L, alkaline phosphatase at 233 U/L, and total bilirubin at 47.7 mg/dL, with direct bilirubin greater than 30 mg/dL during this hospital course.

Laboratory values.

LABORATORY VALUES	AT THE TIME OF ADMISSION	PEAKED VALUES
AST	213 U/L	7922 U/L
ALT	68 U/L	1398 U/L
Alkaline phosphatase	373 U/L	233 U/L
Total bilirubin	26.3 mg/dL	47.7 mg/dL
Direct bilirubin	22.7 mg/dL	30 mg/dL

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Discussion

Sarcoidosis and hemoglobinopathies are 2 disorders commonly affecting the African American population. The prevalence of sarcoidosis is largely dependent on race and ethnicity. The association of sarcoidosis and SCD has been reported in few cases.[2]

Although sarcoid granulomas are present in the liver on histopathology in patients with pulmonary disease, these granulomas causing an abnormal liver panel are not very usual.[3,4] Liver panel abnormality reported in the form of elevated alkaline phosphatase (most common) in 20% to 40% of patients with sarcoid granulomas in the liver hardly ever causes symptoms in the form of hepatosplenomegaly (15%-40%) or lymphadenopathy (15%).[5]

Therefore, hepatic sarcoid can be classified into 4 groups. Group 1 patients have asymptomatic or incidental granulomas randomly found during liver biopsy or to substantiate the diagnosis of sarcoidosis. Group 2 patients have hepatomegaly or splenomegaly with evidence of mild hepatic derangement. Group 3 are patients with hepatocellular disease with or without portal hypertension. Group 4 are patients with portal hypertension as the major manifestation. Advanced signs of liver failure like in our patient include ascites, jaundice, hepatic encephalopathy, and bleeding diathesis.[6]

Life-threatening complications of sarcoidosis are rare. The mortality rates were estimated to be 4.32/1 000 000 between 1988 and 2007. Respiratory and cardiac complications are the most common causes of death. The leading cause of death in such patients is a result of pulmonary fibrosis followed by cardiac failure. Acute fulminant hepatic failure as a complication of sarcoidosis is rare, with an incidence of less than 5% in patients with hepatic sarcoidosis.

Although glucocorticoids are the most commonly used therapeutic agents for sarcoidosis, patients with SCD incur the risk of developing severe sickle cell–related clinical manifestation during treatment with steroids.[7] Delmonte et al[8] reported a patient with sarcoidosis and SCD successfully treated with low-dose prednisone and methotrexate.

There are no defined protocols or recommendations for indications of initiation of treatment, drug choice, and dosage or duration of therapy in patients with hepatic sarcoidosis. Although there are no randomized controlled trials, steroids have been shown to improve clinical symptoms, liver enzymes, and even reduce hepatomegaly. Azathioprine and infliximab have also been used for maintenance therapy. However, the effect of these agents on the natural history of hepatic sarcoidosis is unknown.[9]

Ahn et al. reported cases of sickle cell hepatopathy and classified the patients into 2 major groups. They defined sickle cell hepatopathy as serum bilirubin greater than 13 mg/dL not explained by acute hemolysis, viral hepatitis, extrahepatic obstruction, or hepatic sequestration. The patients in the first group had milder disease with no manifestation of severe hepatic damage and a mean bilirubin of 27.6 mg/dL. The patients in the second group had more severe hepatic dysfunction, with a mean bilirubin of 76.8 mg/dL, accompanied by altered mental status and/or prolonged coagulation times. Mortality in the first group was 4% and in the second group was 64%.[10] They found exchange transfusion to be the only effective treatment in early cases of sickle cell hepatopathy.

Liver transplantation used as a management strategy for sickle cell hepatopathy has not been widely studied. PubMed search identified 10 adults and 5 children with SCD who underwent orthotopic liver transplantation. Of the 10 adults, 4 died in the immediate postoperative period and 5 of the remaining 6 eventually died due to sickle cell–related allograft complications; in the pediatric group, 3 of the 5 patients survived postoperatively.[11–14] In successful adult patient with orthotopic liver transplant, it was noted that aggressive preoperative and postoperative red cell transfusions (to a goal hemoglobin of greater than *10 g/dL*—requiring 2 U every 4 weeks) prevented sickling in the graft liver. But this also placed the patient at risk of iron overload.

This patient is probably the first reported case of fatal SCD combined with hepatic sarcoidosis. A PubMed search did not reveal a prior reported case of the same. His sarcoidosis could not be treated with steroid, which is the first-line agent because it flared his sickle cell crisis. This led to stopping his steroids and other immunomodulators, but a combination of sickling in liver sinusoids and active sarcoid granulomas in his liver resulted in acute liver failure. We wonder whether liver transplantation would be the answer to this dilemma, but it would have probably resulted in recurrence of the disease processes in

the transplanted liver if the patient had survived the post-transplantation period.

Author Contributions

Nutan was the attending taking care of the patient and also contributed to the manuscript. Nagesh helped in literature search and the write up of discussion in the Manuscript.

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