**CLINICAL VIGNETTE**

# A Challenging Case of Hepatic Granulomatous Disease

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***Case Presentation***

A 77-year-old Indian man with diastolic CHF, CAD s/p PCI, and rheumatoid arthritis treated previously with adalimumab and methotrexate was sent to the hospital for further evaluation of elevated liver tests and jaundice found in the outpatient setting. The patient complained of right upper quadrant pain and abdominal distention for one week. He denied shortness of breath, chest pain, cough, night sweats, fevers, or chills. He reported occasional hot flashes and 10 pounds of intentional weight loss over the past few months.

Vitals signs showed a temperature 97.5°F, blood pressure 134/64, heart rate 60 beats/min, respiratory rate 19 breaths/min, and oxygen saturation 95% on room air. Physical examination revealed an obese, oriented elderly man with scleral icterus and jaundice. Lungs were clear to auscultation bilaterally. His abdomen was protuberant with mild right upper tenderness. He had 2+ lower extremity edema bilaterally.

Laboratory studies showed AST 274 U/L, ALT 325 U/L, total bilirubin 10.1 mg/dL, and alkaline phosphatase 728 U/L with normal liver tests 3 months prior. White blood cells and platelets were within normal limits with a mild normocytic anemia. INR was 1.3. Initial acute hepatitis panel was negative. CMV, EBV, and leptospirosis antibodies were negative. ANA, anti-mitochondrial antibody, anti-smooth muscle antibody, and tissue tranglutaminase antibodies were negative. Alpha-1 antitrypsin and ceruloplasmin were negative. Malaria smear was negative. MTB quantiferon gold ELISA (QFT-G) was negative. Angiotensin converting enzyme (ACE) was elevated 120 U/L (normal 13-69 U/L). Salmonella antibodies for a/b/d were positive.

Abdominal ultrasound showed a liver of normal size with fatty infiltration without surrounding ascites. The gallbladder was contracted without calculi or wall thickening. Doppler imaging of the liver was normal.

Liver biopsy revealed granulomatous hepatitis suggestive of drug-induced injury, infection, or sarcoidosis. Special staining for acid-fast bacilli (AFB) and fungus was negative.

The patient was diagnosed with drug-induced versus salmonella hepatitis. The patient was initially treated with levofloxacin, but it was subsequently changed to ceftriaxone due to recurrent fevers. After improving liver tests and temperatures, he was discharged with an AST 84 U/L, ALT 83 U/L, and total bilirubin 3.5 mg/dL after a one-month hospitalization.

Six weeks later, the patient was re-hospitalized with worsening dyspnea at rest and a nonproductive cough. He denied fever. Cardiac enzymes were elevated and transthoracic echocardiogram revealed a left ventricular ejection fraction of 45% compared to 60-65% previously and new inferolateral and apical wall motion abnormalities. Cardiac catheterization showed occlusion of the left circumflex artery and a drug-eluting stent was placed. In the days following the procedure, the patient had a temperature of 102.9°F. The patient had progressively worsening hypoxia without cough or sputum production despite diuretic treatment.

High-resolution CT of the thorax showed cardiomegaly with patchy areas of pulmonary edema and small calcified granulomas in the right upper lobe. Bacterial blood cultures were negative.

The patient was started on levofloxacin, rifabutin, and amikacin for possible tuberculosis. The patient was also given intravenous furosemide for an exacerbation of heart failure and intravenous prednisolone for possible sarcoidosis.

The patient was intubated and placed on mechanical ventilator due to respiratory failure. Bronchial lavage grew S. aureus and E. coli. AFB smear was negative.

Due to development of pancytopenia, bone marrow biopsy was performed and showed normocellular bone marrow with small clusters of histiocytic collections suggestive of ill-defined granulomas. Special staining was negative for acid-fast bacilli and fungus.

Four months after initial hospitalization, the patient expired. Two days later and 3 weeks after the bronchoscopy, mycobacterial cultures returned positive for mycobacterium tuberculosis.

***Discussion***

In this challenging case, our patient presented with elevated liver tests and jaundice. A liver biopsy was pursued in the setting of abnormal liver biochemical testing with a negative

serological work-up, and granulomas were seen. Granulomas are found in 2% to 10% of liver biopsy specimens and 13% to 36% have no discoverable etiology.[1] Hepatic granulomas may be due to autoimmune disorders (primary biliary cirrhosis, sarcoidosis), systemic infections (tuberculosis, HIV, fungal etiology, Q fever, brucellosis), malignancy, medication-induced, or idiopathic.

In our patient, serologic work-up for granulomatous disease resulted in a positive ACE level and a negative QFT-G despite an eventual definitive diagnosis of miliary tuberculosis (TB) by sputum culture. An elevated ACE level is most commonly associated with the diagnosis of sarcoidosis. One study showed that 75% of untreated patients with sarcoidosis had an elevated ACE level. However, the use of an ACE level as a diagnostic tool is limited due to its poor sensitivity and specificity (~10%).[2] In addition, a prospective study showed that 4 of 21 patients (19%) with smear—or culture—proven tuberculosis had ACE levels higher than the expected range ($p < 0.05$).[3]

Our patient with culture-proven tuberculosis also tested negative for QFT-G. QFT-G is an interferon-gamma release assay primarily used as a screening test for latent TB. The use of QFT-G for the diagnosis of active tuberculosis is limited. A systematic review and meta-analysis showed a pooled sensitivity and specificity of 80% (95% CI 75-84%) and 48% (95% CI 39-58%) respectively for the diagnosis of active TB.[4] Another study including 44 patients with miliary TB noted a positive QFT-G in 68% of cases.[5] A QFT-G supports the diagnosis of active TB, but a negative result does not rule out active TB disease.

It is estimated that one third of the world population is infected with latent tuberculosis.[6] In 2015, about 10.4 million people became ill with tuberculosis and 1.8 million patients died.[6] In 2014, 9421 cases of TB were reported in the United States with 10% of cases presenting with both pulmonary and extrapulmonary manifestation and 21% with extrapulmonary findings only.[7] Risk factors for miliary TB include age and immunosuppressed states. In one study of 40 patients with miliary TB, 62% of cases were associated with tumor necrosis factor-alpha inhibitors such as adalimumab.[8]

Before the use of antibiotics, the mortality of miliary TB was nearly 100%. Since then, the mortality rate of miliary TB in adults remains elevated at 25-30%.[9] A definitive diagnosis for TB requires a positive culture. As seen in our case, a mycobacterium culture can take weeks result in a positive finding. Until more rapid diagnostic tools are readily available, it is important to have a high level of suspicion for TB in order to initiate treatment as early as possible. This is especially important, as seen in our case, given that the serologic workup for granulomatous disease can be misleading.

## REFERENCES


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