

Diagnostic Challenge: Hepatic Granulomas Associated with FUO

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A 35-year-old man living in Sistan was referred to our center because of fever, night sweats, myalgia, fatigue and elevated Alk-P, ALT and AST from which he was suffering for 8 weeks.

He had no history of blood transfusion, IV drug abuse, systemic disease, or family history of hepatitis. He had not received any drugs for 3 months. He had a history of extramarital sexual contact 6 months before. Physical examination revealed hepatomegaly. There was no lymphadenopathy, rash, cough, icterus, and arthritis. He had lost 5 kilograms in weight.

Laboratory tests showed Hgb 12, WBC 10000, PMN 65%, lym 40%, Plt 200,000, ESR - 95, ALT 70, AST 65, Alk-P 700, GGT 650, total bilirubin 1.7, direct bilirubin 0.5, Wright (-), 2ME (-), VDRL negative, PPD test 8mm, anti-HIV negative, HBsAg negative, anti-HCV negative, anti-HAV IgM negative, CPK 40, LDH 370, anti-CMV IgM negative, EBV antiviral capsid IgM negative and angiotensin converting enzyme (ACE) normal. Three blood cultures after 3 weeks were sterile. Abdominal and chest CT scan were normal. The results of echocardiography and bone marrow biopsy were normal. A liver biopsy was performed. Examination of the smear revealed noncaseating granulomas with epithelioid cells. These were distributed randomly through parenchyma. A liver sample was referred for mycobacterium tuberculosis PCR test, the result of which was negative. Acid fast staining for tubercle bacilli was negative. A portion of the fresh biopsy specimen was sent for culture, and after 6 weeks, the result of the culture was negative.

Discussion

Hepatic granulomas can be caused by a variety of conditions. Some of these causes associate with fever of unknown origin. For this reason, liver biopsy is one of the invasive procedures to evaluate a patient with FUO, especially when there are abnormalities in LFTs (1). The results of liver biopsy may provide histologic evidence of the specific etiology (such as caseation of TB). However, the morphologic patterns are often nonspecific and diagnosis must be pursued with appropriate studies (culture, skin test, laboratory tests, x-rays).

Our patient was admitted due to prolonged fever and abnormalities in Alk-P and aminotransferases, also liver biopsy showed hepatic granulomas scattered in the lobule. We discuss causes of hepatic granulomas that are associated with fever of unknown origin.

Differential Diagnosis

Brucellosis: Brucellosis is a systemic infection in which liver can be involved. The species abortus, melitensis, suis and to a lesser extent, canis are the

predominant causes of the disease in humans and animals. Different pathologic findings can be seen in brucella hepatitis. *Brucella abortus* is the most common species that can cause hepatic granulomas. The granulomas in brucellosis tend to be in lobule rather than confined to the periportal area.(2)

Iran is an endemic area for brucellosis and the presence of prolonged fever, night sweats and fatigue in a patient raises the possibility of brucellosis. However, serologic tests for brucellosis were negative and blood cultures after 3 weeks were sterile. Thus, it seems that is an unlikely diagnosis for this case.

Syphilis

One of the unusual manifestations of secondary syphilis is hepatitis. It is characterized by high Alk-P and mild elevated bilirubin. Hepatic granulomas

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can be seen in syphilitic hepatitis (3). In this case, however syphilis could not be considered because syphilitic hepatitis does not present as FUO and occurs most often with syphilitic proctitis. Also VDRL test was negative.

AIDS related causes

Several infections may be associated with granulomas in patients with AIDS. They include TB, MAC, cryptococcus neoformans, CMV and toxoplasmosis. However, serologic test for HIV was negative (4).

Q Fever, cat-scratch disease, some of the fungal diseases and visceral leishmaniasis can present as prolonged fever and hepatic granulomas (5), but they cannot be considered in this case.

Malignancy

The most common malignancy that is associated with hepatic granulomas is Hodgkin's lymphoma and less frequently non-Hodgkin lymphoma and renal cell carcinoma (6,7). Hodgkin's disease is associated with fibrin-ring granulomas in which epithelioid cells surround a vacuole that has an encircling fibrin ring (8). Lymphoma can present as FUO, but in this case there was no peripheral lymphadenopathy, also thoracic and abdominal CT scan and bone marrow biopsy were normal. Thus, lymphoma is an unlikely diagnosis for this case.

Drug-induced hepatitis

Many drugs have been associated with hepatic granulomas such as methyl dopa, allopurinol, phenytoin and quinidine (9, 10). Some of these drugs can cause low grade fever, but in this case, there was no drug history.

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of unknown etiology. The most commonly affected organs are lungs and mediastinal lymph nodes. Hepatic involvement is usually silent (11,12). Patients may present with FUO (11, 13). In a third of patients, there is a disproportionate elevation in Alk-P in comparison to the transaminases (11). The granulomas of liver are noncaseating and often located in the portal tracts (11, 14). Confirmation of the diagnosis requires the presence of a compatible clinical picture, histologic evidence of noncaseating granulomas and excluding of other causes.

In this case, the absence of pulmonary findings,

mediastinal lymphadenopathy, arthropathy or other clinical signs suggesting sarcoidosis and normal level of ACE, make such diagnosis unlikely.

Tuberculosis

In many studies, tuberculosis and sarcoidosis have been two most common causes of hepatic granulomas. Hepatic granulomas are present in more than 90 percent of patients with miliary tuberculosis and about 70 percent of patients with extrapulmonary tuberculosis and 25 percent of patients with pulmonary infections (11). Furthermore, tuberculosis may present primarily as a liver disease; that is, involvement of the hepatobiliary tract with tuberculosis without apparent involvement elsewhere, or only with local lymph node and splenic involvement (4, 14). Clinical symptoms include fever, night sweat, fatigue and weight loss. Jaundice is an unusual finding. Granulomas are found randomly scattered in the paranchyma and also in the portal tracts. However, in some reports granulomas tend to be in portal area, and caseation may be seen.

It is unusual to find acid-fast organisms in liver smears. PCR for mycobacterium tuberculosis has been performed on samples (4, 11). This test has a specificity of 96 percent but the sensitivity is 53 percent. In our patient, although liver granulomas were noncaseating and the result of acid-fast staining and PCR on liver samples were negative, tuberculous hepatitis should be considered because of prolonged fever and hepatic granulomas, and that he was from a high incidence area for TB.

Idiopathic granulomatous hepatitis

After excluding the known causes of FUO resulting in granulomatous hepatitis, there remains a group of patients with unclear etiology or idiopathic granulomatous hepatitis. This syndrome is characterized by a prolonged fever myalgias, arthralgias, hepatosplenomegaly and nonspecific laboratory findings (16,17,18). There are many granulomas that are predominantly lobular (18). Furthermore, granulomas may be seen in the spleen, bone marrow and lymph nodes.

The diagnosis of idiopathic granulomatous hepatitis is made when other causes of hepatic granulomas especially sarcoidosis and tuberculosis have been excluded (18). An empiric course of anti-tuberculosis therapy should be considered if fever and other nonspecific symptoms are present and a specific diagnosis cannot be made (18). If there is no clinical response after 4 to 8 weeks, empiric

corticosteroids should be instituted, which usually lead to rapid improvement in fever and regression of the granulomas^(18, 19).

Our patient did not meet the criteria for sarcoidosis because of the absence of pulmonary or extrapulmonary findings suggesting sarcoidosis such as arthritis or uveitis, thus, sarcoidosis can be ruled out.

In this case, however, tuberculosis can explain all features of the case and we cannot exclude hepatitis in spite of negative results for acid-fast staining and PCR. Therefore, we began a course of anti-tuberculous treatment, but his condition did not improve after 7 weeks. Then, anti-tuberculous treatment was stopped and prednisolone (1.5 mg/kg/day) was begun. The patient became afebrile within 10 days of starting steroid and hepatomegaly regressed gradually. Prednisolone was successfully tapered and discontinued within 4 months. After one year liver biopsy was performed, which showed regression in granulomas. In our patient, prolonged fever, hepatomegaly and hepatic noncaseating granulomas that were scattered randomly in liver parenchyma would suggest idiopathic granulomatous hepatitis (IGH). Excluding other causes of hepatic granulomas and no response to empiric anti-TB therapy raised the possibility of IGH. Dramatic clinical and pathological response to steroids can confirm diagnosis of IGH.

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