






Multiple liver masses mimicking metastatic liver disease in an elderly patient

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QUESTION

A 68-year-old male was admitted with complaints of weakness, mild right upper quadrant pain, and right-side wrist arthralgia. The medical history of the patient included hypertension and benign prostate hyperplasia, and his long-term medications were indapamide, doxazosin, alfuzosin, perindopril, and amlodipine. He also had a 20 pack-year smoking history and no history of alcohol intake. Physical examination findings were unremarkable except for tenderness in the right wrist. The laboratory test results showed hemoglobin: 8.4 g/dL (normal range [NR]: 13.6-17.2), white blood cell: $11.9 \times 10^9/L$ (NR: 4.1-11.2), platelet: $269 \times 10^9/L$ (NR: 159-388), creatinine: 1.1 mg/dL (NR: 0.6-1.1), alanine-transaminase (ALT): 37 U/L (NR: 0-50), aspartate-transaminase (AST): 24 U/L (NR: 0-50), alkaline phosphatase (ALP): 272 U/L (NR: 30-120), gamma-glutamyl transferase (GGT): 211 U/L (NR: 0-55), total bilirubin: 0.58 mg/dL (NR: 0.3-1.2), albumin: 3 g/dL (NR: 3.5-5.2), and C-reactive protein (CRP): 15.5 mg/dL (NR: 0-0.8). Negative test results were obtained for hepatitis-B surface antigen, hepatitis C antibody, antimitochondrial antibody, antinuclear antibody, rheumatoid factor, antineutrophil cytoplasmic antibodies, and quantiferon for tuberculosis. Serum angiotensin-converting enzyme (ACE), B2 microglobulin, and immunoglobulin G and M levels were within the NR. On dynamic abdominal computed tomography (CT) scan, multiple irregularly shaped, hypodense masses that

were peripherally enhancing in the arterial phase were observed in all liver segments, the largest of which was 1.5 cm in size (Figure 1). Thoracic CT showed four nodules of millimetric size in the right lung parenchyma, and there was no mediastinal lymphadenopathy. Upper gastrointestinal endoscopy revealed antral gastritis, and colonoscopy revealed a polyp of millimetric size in the ascending colon. On further investigation, tests for leishmania, brucellosis, mycobacterium, aspergillus, toxoplasma, Epstein-Barr virus, and cytomegalovirus

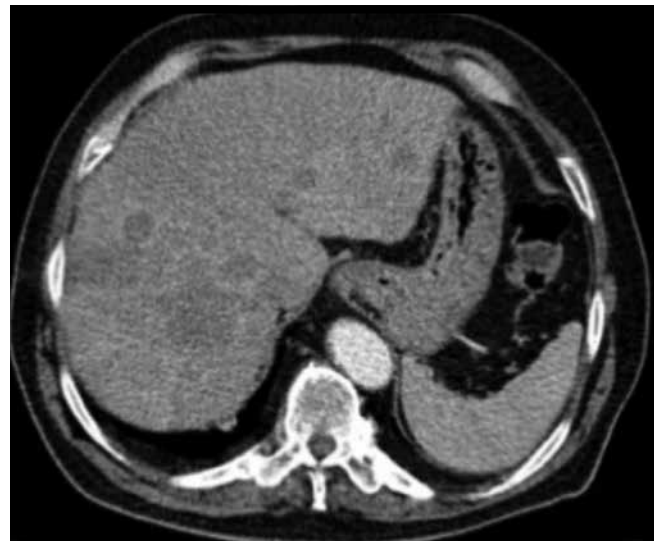


Figure 1. Arterial phase abdominal CT image showing multiple irregularly shaped hypodense lesions that were peripherally enhancing in all liver segments

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were negative as were blood, urine, and stool cultures. Hand-wrist ultrasonography showed extensor tenosynovitis without any erosive lesion. Positron emission tomography (PET) was applied to the patient, which showed increased fluorodeoxyglucose (FDG) uptake (maximum standardized uptake value [SUV]: 5,8) of the liver masses (Figure 2). A tru-cut biopsy was performed from the liver masses.

What is the patient's most likely diagnosis?



Figure 2. Whole body PET-CT images show multiple foci of F-18 FDG uptake in the liver region (SUV max of 5.8), whereas the rest of the body shows physiological distribution of the activity

ANSWER

Histopathological examination of the biopsy specimen showed non-caseating granulomas (Figure 3). Based on the clinical presentation of the patient, radiological demonstration of liver masses, detection of non-caseating granulomas on histopathological examination of the liver biopsy, and exclusion of other granulomatous hepatitis causes, the patient was diagnosed with isolated extrapulmonary sarcoidosis. After treatment with azathioprine (100 mg/day, Imuran; Glaxosmithkline) and gradually tapered prednisolone (initial dose: 40 mg, Deltacortil; Pfizer), the patient improved clinically, and the symptoms, including weakness, abdominal pain, and arthralgia were all resolved. The serum ALT, AST, ALP, GGT, and bilirubin levels of the patient were within NR at the 6-month follow-up examination, and the liver masses had disappeared on the control computed tomography at one year (Figure 4).

Sarcoidosis is a chronic inflammatory disease that is characterized by the development of noncaseified granulomatous lesions in the involved areas. The disease mainly affects the pulmonary system in more than 90% of cases. Extrapulmonary involvement occurs in approximately one-half of the patients, and almost any part of the body can be affected. The most common extrapulmonary sites are the liver, spleen, extrathoracic lymph nodes, eye, skin, kidney, heart, and central nervous system. In rare cases, sarcoidosis only affects extrapulmonary sites without any pulmonary system involvement and is known as "isolated extrapulmonary sarcoidosis" as in the case presented

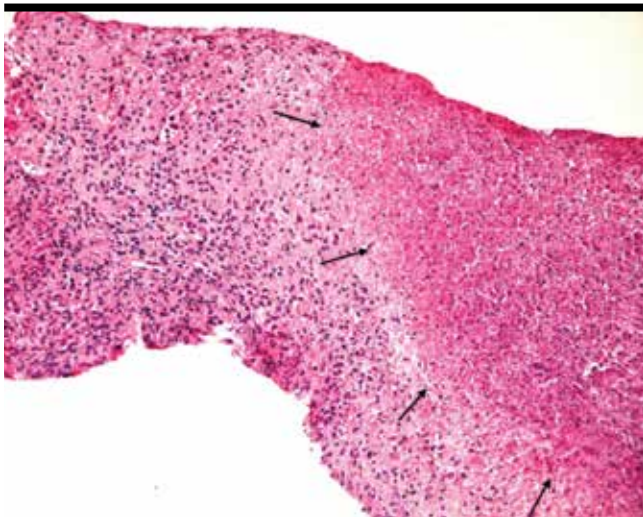


Figure 3. Histopathological examination of the liver biopsy specimen showing non-caseating granuloma (arrows)

here (1-3). The right wrist tenosynovium and liver were the only affected areas in this case.

In sarcoidosis patients with hepatic involvement, clinically significant liver disease has been reported in less than 20% of cases, and they present with a variety of clinical forms, including clinical hepatitis, chronic cholestasis, portal hypertension, and cirrhosis. Patients generally have minimal or no symptoms, although 5%-30% of patients have clinical signs and symptoms, including abdominal pain, pruritus, fatigue, jaundice, fever, arthralgia, and weight loss. Most cases with hepatic sarcoidosis have normal liver enzyme levels and increased levels are detected in 20%-40% of patients. A high serum ALP level is the most common laboratory abnormality. ALP/GGT levels can be detected 5-10 times higher than the normal levels and ALT/AST levels can increase moderately. The serum ACE level has low sensitivity and insufficient specificity for the diagnosis of sarcoidosis. Increased serum ACE levels can be detected in about 60% of the patients, and the levels are positively correlated with the extent and total load of granulomas. Although it has been shown that serum ACE levels are higher in patients with extrapulmonary involvement than in those without extrapulmonary involvement, there has been no study regarding the ACE levels and their diagnostic potential in patients with isolated extrapulmonary sarcoidosis (2-5).

On radiological evaluation of hepatic sarcoidosis, hepatomegaly is the most common finding. Parenchymal heterogeneity, biliary ductal dilatation, multiple liver nodules,

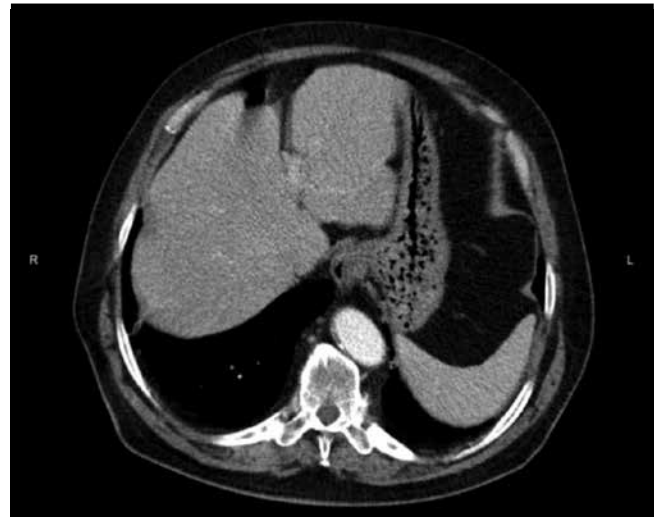


Figure 4. Liver masses of the patient had disappeared on control abdominal CT scan at one year

and cirrhosis-related findings can be detected less commonly with hepatic ultrasonography and magnetic resonance and CT imaging. Hepatic sarcoid nodules are detected radiologically in 5%-50% of patients. The nodules are always multiple in number, ranging in size from 0.5 to 2 cm in diameter (2). However, in rare cases, hepatic sarcoid nodules can have a mass-like appearance imitating primary liver malignancy or metastasis, and it is difficult to distinguish hepatic sarcoidosis from malignancy or metastasis in these cases (6,7). This was the case in the current patient as the CT findings were compatible with metastasis. Furthermore, the high uptake of FDG by the liver nodules on positron emission tomography (PET) also suggested the preliminary diagnosis of metastasis. However, the definitive diagnosis in the current case was made from liver biopsy and subsequent histopathological examination of the biopsy specimen (4,8).

The diagnosis of hepatic sarcoidosis is based on the combination of clinical, radiological, and histological findings and exclusion of other causes of granulomatous hepatitis, such as primary biliary cirrhosis, primary sclerosing cholangitis, Wegener's granulomatosis, drug reactions, mycobacterium, hepatitis C, leishmania, brucella, listeria, and fungal infections (4,8).

Treatment is not indicated for asymptomatic patients with hepatic sarcoidosis. Persistence of disease-related symptoms or long-standing cholestasis is the most common indication for medical treatment, for which corticosteroids and immunosuppressants are the most commonly used agents, although ursodeoxycholic acid can be of use in patients with cholestatic involvement. Medical treatment generally improves symptoms and reduces the liver enzyme levels, and the hepatic nodules generally decrease or disappear with treatment. However, the length of treatment and the effectiveness on disease prognosis is unclear. Liver transplantation can be performed for

patients with cirrhosis, although occasionally sarcoidosis may recur in the graft liver (2,8).

In conclusion, it should be considered that in rare cases, sarcoidosis can present as isolated extrapulmonary disease. The liver is one of the most common extrapulmonary affected sites in these patients, and liver involvement can present with multiple hepatic masses, which mimic primary liver malignancies or metastasis.

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