Hepatic Sarcoidosis with an Increased Serum Level of Immunoglobulin G4

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Abstract

A 70-year-old woman with an increased uptake of 18-Fluorodeoxyglucose (FDG) in whole liver on positron emission tomography (PET) was referred to our hospital. Laboratory examinations showed increased serum levels of total immunoglobulin G (IgG) and IgG4. Gallium scintigraphy showed a remarkable uptake in the liver but not in any other organs. On computed tomography (CT) and magnetic resonance imaging (MRI), multiple foci of abnormal density were observed in the liver, but the pancreas and bile duct lacked any indications of IgG4-related sclerosing disease. A liver biopsy specimen revealed multiple non-necrotizing granulomas. This is the first report of hepatic sarcoidosis in a patient with an elevated serum level of IgG4.

Key words: hepatic sarcoidosis, immunoglobulin G4, liver biopsy, granuloma


Introduction

Sarcoidosis is a systemic inflammatory disorder of unknown etiology characterized by the formation of noncaseating granulomas in the tissues and lymph nodes involved (1). Sarcoidosis typically affects multiple organs, including the skin, bones, muscles, eyes, lungs, heart, liver, spleen, and lymph nodes (2). Although hepatic involvement is not common, the liver is an important target of sarcoidosis (3). Immunoglobulin G4 (IgG4)-related disease is another systemic inflammatory condition characterized by elevated serum IgG4 concentrations and lymphoplasmacytic infiltrates rich in IgG4-positive plasma cells in affected tissues (4). Because of their similarities, including multi-organ involvement and tumefactive lesions, sarcoidosis and IgG4-related diseases need to be carefully differentiated. Both laboratory testing for serum IgG4 and pathological examinations of biopsy samples are thus considered to be important to address this issue (5).

We herein describe an unusual case of hepatic sarcoidosis with a high serum level of IgG4.

Case Report

A 70-year-old woman was referred to our hospital because of an increased 18-Fluorodeoxyglucose (FDG) uptake in the whole liver on positron emission tomography (PET) and an elevated serum level of CA19-9. On admission, she did not have any symptoms. The patient had been receiving antihypertensive agents for 10 years, but had no surgical history and no family history of an inherited disorder. A physical examination showed slight hepatomegaly but no superficial lymphadenopathy. Although the serum levels of transaminases were normal, those of alkaline phosphatase (ALP, 499 U/L) and gamma-glutamyltransferase (γ-GTP, 63 U/L) were mildly elevated (Table). Serological tests for hepatitis-B and C were negative. The CA19-9 level increased to 84.7 U/mL, but the alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) levels were normal. Importantly, the levels of total IgG and IgG4 increased to 2,561 mg/dL and 263 mg/dL, respectively. Although the patient

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Table. Laboratory Data on Admission

<table>
<thead>
<tr>
<th>Blood cell count</th>
<th>Blood chemistry</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 9,300/μL</td>
<td>TP 8.4 g/dL</td>
<td>IgG 2.561 mg/dL</td>
</tr>
<tr>
<td>RBC 4.92×10¹²/μL</td>
<td>Alb 3.8 g/dL</td>
<td>IgG 4 263 mg/dL</td>
</tr>
<tr>
<td>Hb 14.4 g/dL</td>
<td>MCV 100 fL</td>
<td></td>
</tr>
<tr>
<td>Ht 41.4%</td>
<td>MCH 35 fL</td>
<td></td>
</tr>
<tr>
<td>Ph 28.7×10¹¹/μL</td>
<td>ALT 28 IU/L</td>
<td>CRP 0.5 mg/dL</td>
</tr>
<tr>
<td>PT 93%</td>
<td>ALP 201 IU/L</td>
<td></td>
</tr>
<tr>
<td>ESR 40 mm/H</td>
<td>HCV-Ab (-)</td>
<td></td>
</tr>
</tbody>
</table>

**Elevated serum levels of angiotensin-converting enzyme (ACE, 45.2 IU/L) and lysozyme (56.1 μg/mL) were also observed. In addition, the patient exhibited a negative reaction to the tuberculin skin test. Electrocardiography showed no evidence of a conduction abnormality, and ocular involvement, such as granulomatous uveitis, was not observed. The patient was finally diagnosed to have hepatic sarcoidosis. Because of her advanced age and the absence of any symptoms, she was followed closely without the administration of corticosteroids.**

**Discussion**

Sarcoidosis is a multi-systemic granulomatous disease that frequently involves many organs. The clinical features of sarcoidosis are wide-ranging, but pulmonary manifestations, such as BHL and lung parenchymal lesions, are observed in approximately 90% of these patients (6). In addition, hepatic involvement can be identified in 11.5-24.0% of cases by liver biopsy (7, 8). Although the course of the hepatic involvement is usually asymptomatic, patients can sometimes exhibit various clinical features including portal hypertension and intrahepatic cholestasis (9, 10). In our case, the FDG-PET and gallium scintigraphy examinations indicated isolated hepatic involvement. In line with previous reports concerning radiological findings, MRI showed a large number of small foci of hypointensity on both T2WI and DWI (11, 12).

Interestingly, the patient showed an elevated serum level of IgG4. Human IgG is divided into four subclasses; IgGs 1-4. IgG4 is the least abundant subclass and generally accounts for approximately 5% of all IgGs (13). Although it has been reported that the total serum IgG levels and the levels of the four subclasses tend to increase in patients with sarcoidosis (14), not only the serum IgG4 level, but also the IgG4/total IgG ratio (10.3%) was elevated in our case. Therefore, we considered the possibility of an association with IgG4-related disease. However, no features of sclerosing cholangitis, a typical hepatic manifestation of IgG4-related disease, were identified (15). A recent study proposed a comparatively new disease entity named IgG4-associated autoimmune hepatitis (AIH), which accounts for more than 3% of classical AIH cases (16). Of importance, IgG4-associated AIH shows intrahepatic infiltration of IgG4-positive plasma cells despite the absence of radiological abnormalities in the pancreatobiliary system. In our case, neither the normal level of transaminases nor the liver histology met the criteria for IgG4-associated AIH. Taking into consideration the hypercalcemia and increased levels of lysozyme and ACE in the patient, the patient was diagnosed with hepatic sarcoidosis. The presence of a concomitant IgG4-related disease, including IgG4-associated AIH, appeared to be unlikely in this case.

Because the number of sarcoidosis patients with concomitant IgG4 hyper-gammaglobulinemia is limited, the mechanism responsible for the increase in the serum IgG4 level is still poorly understood. A previous report demonstrated no significant difference in the serum IgG4 levels among sarcoidosis patients with or without cardiac involvement (17). In contrast, some patients with pulmonary sarcoidosis have
been reported to show increased levels of IgG4 in both their serum and bronchoalvolar lavage fluid (18). It has also been pointed that exposure to a wide range of antigens is closely associated with the onset of lung sarcoidosis. Of importance, lung T lymphocytes, but not circulating T lymphocytes, cause multiple clones of B lymphocytes to differentiate into plasma cells, thus resulting in the overproduction of polyclonal immunoglobulins (19).

It has been reported that IgG4 is easily transformed to an asymmetric antibody with two different fragment antigen-binding (Fab) arms, which results in the loss of its ability to form immune complexes (4, 20). Moreover, the half-life of IgG tends to shorten in IgG4-related diseases with high IgG levels (21). Taken together, the enhanced production of IgG4, rather than a decrease in the catabolic rate of IgG4, might therefore have contributed to the elevated serum level of IgG4 in this patient. Because the liver biopsy specimen in our case scarcely showed any hepatic infiltration of lymphocytes and plasma cells, other organs, such as lymph nodes, might have been responsible for the IgG4 production.

In conclusion, we herein reported a case of hepatic sarcoidosis with hyper-IgG4 gammaglobulinemia. Although corticosteroids were not administered to the patient, it is considered important to closely monitor such cases not only for the progression of sarcoidosis, but also the onset of IgG4-related disease. To our knowledge, hepatic sarcoidosis with an elevated serum level of IgG4 has not been documented previously. Further examinations in large numbers of sarcoi-

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**Figure 1.** Findings of CT (a), MRI (b, c) and MRCP (d) examinations. (a) A contrast-enhanced CT scan in the portal-dominant phase showed a large number of small hypointense foci. (b) T2WI showed multiple small foci of hypointensity. (c) DWI showed multiple hypointense foci. An enlarged lymph node was also observed in the porta hepatitis (arrow). (d) The MRCP image showed normal findings.

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**Figure 2.** Gallium scintigraphy. Increased uptake was clearly observed in the liver.
The authors state that they have no Conflict of Interest (COI).

References


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