IgG4-related Disease Involving Multiple Organs with Elevated Serum Interleukin-6 Levels

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Abstract

A 63-year-old woman presented to our hospital with elevated levels of serum IgG4, marked wall thickening of the gallbladder, hepatomegaly, and abdominal lymphadenopathy. She experienced a recurrent fever and leg edema. Her laboratory data demonstrated anemia, hypoalbuminemia, and elevated serum levels of interleukin-6 and C-reactive protein. The patient was eventually diagnosed with IgG4-related disease according to the comprehensive diagnostic criteria, although the patient exhibited common clinical manifestations of multicentric Castleman disease such as a fever, anemia, lymphadenopathy, and elevated levels of serum interleukin-6 and C-reactive protein. This case report highlights the difficulties in differentiating between these two diseases.

Key words: Castleman disease, diagnosis, IgG4-related disease, interleukin-6


Introduction

IgG4-related disease (IgG4-RD) is a systemic disease of unknown cause that is histologically characterized by an abundant infiltration of IgG4-positive cells and lymphocytes with massive fibrosis. This disease has been found to involve a wide range of organs, including the pancreas, bile duct, lacrimal glands, salivary glands, central nervous system, thyroid, lungs, liver, gastrointestinal tract, kidneys, prostate, retroperitoneum, arteries, lymph nodes, skin, and breast (1-3). IgG4-RD is radiologically characterized by diffuse or focal organ enlargement and mass-forming or nodular/thickened lesions in the affected organs. From the aspect of a serological examination, IgG4 levels are frequently elevated. Patients with multicentric Castleman disease (MCD) also occasionally have elevated serum IgG4 concentrations and abundant infiltration of IgG4-positive cells in affected organs (4-6). MCD is a polyclonal lymphoproliferative disorder accompanied by systemic symptoms that may result from increased production and circulation of interleukin-6 (IL-6) (7-9). According to previously published papers, laboratory findings including the IL-6 level, C-reactive protein (CRP) level, and platelet count appear to be important when distinguishing between IgG4-RD and MCD because an exacerbation of these inflammation parameters is less likely to be observed in patients with IgG4-RD (4, 5).

We herein describe a case of IgG4-RD involving multiple organs with high serum levels of IL-6 and CRP, highlighting the difficulties in differentiating between IgG4-RD and MCD.

Case Report

A 63-year-old woman presented to our hospital with a thickened gallbladder wall and hepatomegaly. She experienced a recurrent fever and leg edema, but no abdominal pain. No enlarged lymph nodes in the cervical, infra-axillary, or inguinal regions were observed on palpitation. Laboratory data on admission were as follows (Table 1):
fuse, pathologic uptake patterns with a maximum standard-
emission tomography (FDG-PET) of the liver revealed dif-
observed. Fluorine-18-fluorodeoxyglucose (FDG) positron
emission tomography (FDG-PET) of the liver revealed dif-
fuse, pathologic uptake patterns with a maximum standard-
ized uptake value of 6.4. In addition, the uptake of FDG
white blood cell, 10,000/μL (neutrophils: 48.0%, lympho-
cytes: 24.5%, eosinophil: 38.5%, basophil: 0.5% and mono-
cytes: 3.0%); hemoglobin, 8.3 g/dL; thrombocytes, 20.4×10 /
μL; total bilirubin, 1.4 mg/dL; total protein, 9.4 g/dL; albu-
mim, 1.4 g/dL; and CRP, 5.8 mg/dL. Serum levels of IgG4
were elevated (1,008 mg/dL; normal range 4.8-105 mg/dL).
LDH: Lactate dehydrogenase, T-Bil: Total bilirubin, BUN: Blood
urea nitrogen, FBS: Fasting blood sugar, TP: Total protein, Alb: Albumin, Ig: Immunoglobulin, CRP: C-reactive protein, IL-6: Interleukin-6, PT-INR : Prothrombin time-international normalized ratio,
A histological examination of percutaneous liver biopsy
specimens revealed dense lymphoplasmacytic infiltration
with fibrosis in the portal tract and interface hepatitis and
eosinophil infiltration (Fig. 3). Immunohistochemically,
marked IgG4-positive plasma cell infiltration (>10 cells/
HPF) and a high ratio of IgG4-positive/IgG-positive cells
 (>40%) were observed. Follicular lymphoid hyperplasia was
not evident.
A bone marrow biopsy demonstrated normocellular mar-
row and no evidence of increased eosinophils or eosino-
phile precursors.
Applying these findings to the comprehensive diagnostic
criteria (CDC) for IgG4-RD (3), the patient was diagnosed
with definitive IgG4-RD involving the liver, gallbladder,
pancreas and abdominal lymph nodes, although there was a
suspicion of MCD due to the enlarged lymph nodes and ele-
minated uptake value of 6.4. In addition, the uptake of FDG
was also observed in the gallbladder, pancreas, and enlarged
abdominal lymph nodes (Fig. 2).

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Table 1. Laboratory Findings on Admission.

<table>
<thead>
<tr>
<th>Blood Index</th>
<th>Result (Normal Range)</th>
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<th>Result (Normal Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>10,000/μL (8,500-3,500)</td>
<td>FBS</td>
<td>78 mg/dL (60-100)</td>
</tr>
<tr>
<td>RBC</td>
<td>300×10^9/μL (510-370)</td>
<td>TP</td>
<td>9.4 g/dL (6.5-8.2)</td>
</tr>
<tr>
<td>Hb</td>
<td>8.3 g/dL (11.3-15.4)</td>
<td>Alb</td>
<td>1.4 g/dL (3.8-5)</td>
</tr>
<tr>
<td>Hct</td>
<td>26.3% (34-46.3)</td>
<td>IgG</td>
<td>4,479 mg/dL (870-1,700)</td>
</tr>
<tr>
<td>Plt</td>
<td>20.4×10^11/μL (14-34)</td>
<td>IgG4</td>
<td>1,008 mg/dL (4.8-105)</td>
</tr>
<tr>
<td>AST</td>
<td>24 IU/L (13-35)</td>
<td>IgA</td>
<td>72 mg/dL (110-410)</td>
</tr>
<tr>
<td>ALT</td>
<td>10 IU/L (5-35)</td>
<td>IgM</td>
<td>75 mg/dL (46-260)</td>
</tr>
<tr>
<td>ALP</td>
<td>394 IU/L (107-340)</td>
<td>IgE</td>
<td>2,109 IU/mL (≤ 320)</td>
</tr>
<tr>
<td>γ-GTP</td>
<td>23 IU/L (8-45)</td>
<td>CRP</td>
<td>5.8 mg/dL (≤ 0.3)</td>
</tr>
<tr>
<td>LDH</td>
<td>160 IU/L (112-230)</td>
<td>IL-6</td>
<td>34 pg/mL (≤ 4)</td>
</tr>
<tr>
<td>T-Bil</td>
<td>1.9 mg/dL (0.2-1.2)</td>
<td>PT-INR</td>
<td>1.44 (0.85-1.15)</td>
</tr>
<tr>
<td>Amylase</td>
<td>28 IU/L (37-125)</td>
<td>APTT</td>
<td>35.3 sec. (23-35)</td>
</tr>
<tr>
<td>BUN</td>
<td>12 mg/dL (8-20)</td>
<td>CEA</td>
<td>1.0 ng/mL (≤ 5)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.0 mg/dL (0.4-0.8)</td>
<td>CA19-9</td>
<td>8.3 U/mL (≤ 37)</td>
</tr>
</tbody>
</table>


Figure 1. An abdominal ultrasonography image showing a thick-walled and edematous gallbladder (a). Contrast-enhanced computed tomography images showing hepatomegaly (b) and splenic hilar lymph nodes (c, arrows). Fluid collection around the pancreas is observed.
went steroid pulse therapy, which involved an intravenous administration of methylprednisolone at a dose of 500 mg per day for 3 consecutive days per week for 2 continuous weeks. After steroid pulse therapy, the elevated CRP levels, hypoalbuminemia, and prolonged plasma prothrombin time were ameliorated and the recurrent fever subsided. Subsequent maintenance therapy with oral prednisolone was performed, and the dose of prednisolone was gradually tapered. Eight weeks after the initiation of steroid therapy, the serum IgG4 and IL-6 concentrations normalized, and follow-up imaging showed resolution of the gallbladder wall thickening, swelling of the liver, and paraaortic and splenic hilar lymphadenopathy. Five months after the initiation of maintenance steroid therapy, however, the patient experienced recurrent leg edema despite the administration of prednisolone at 7.5 mg per day. A laboratory examination revealed ele-
Due to the recurrence of the disease, we administered azathioprine in addition to prednisolone. Two months after the initiation of immunosuppressant drug therapy, follow-up CT showed resolution of gallbladder wall thickening, swelling of the liver, and splenic hilar lymphadenopathy (Fig. 4). Additionally, on FDG-PET, an abnormal uptake of FDG in the liver, gallbladder, pancreas, and abdominal lymph nodes was not observed. Thereafter, no signs of relapse were observed.

Table 2. Comprehensive Diagnostic Criteria for IgG4-RD.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs.</td>
<td>Definite: 1) + 2) + 3)</td>
</tr>
<tr>
<td>Hematological examination shows elevated serum IgG4 concentrations (&lt;135 mg/dL).</td>
<td>Probable: 1) + 3)</td>
</tr>
<tr>
<td>Histopathologic examination shows:</td>
<td>Possible: 1) + 2)</td>
</tr>
<tr>
<td>(1) Marked lymphocyte and plasmacyte infiltration and fibrosis.</td>
<td></td>
</tr>
<tr>
<td>(2) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells &gt; 40% and &gt;10 IgG4+ plasma cells/HPF</td>
<td></td>
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</table>

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar disease (e.g. Sjögren’s syndrome, primary sclerosing cholangitis, Castleman’s disease, secondary retroperitoneal fibrosis, Wegener’s granulomatosis, sarcoidosis, Churg-Strauss syndrome) by additional histopathological examination.

Even when patients cannot be diagnosed using the comprehensive clinical diagnostic criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.

Discussion

IgG4-RD is a fibroinflammatory condition that is associated with abundant infiltration of IgG4-positive cells (1). To diagnose the disease, several organ-specific diagnostic criteria have been established, including the clinical diagnostic criteria for autoimmune pancreatitis (AIP) proposed by The Japan Pancreas Society (10), clinical diagnostic criteria of IgG4-related sclerosing cholangitis (11), diagnostic criteria for IgG4-related Mikulicz’s disease (12), and IgG4-related kidney disease (13). However, IgG4-RD is a systemic disease that occurs in a wide range of organs or sites either synchronously or metachronously (1-3). Therefore, to be applied to any affected organ, the CDC for IgG4-RD have been proposed (Table 2) (3). The criteria reflect the minimal consensus aimed at enabling general practitioners or other nonspecialists to comprehensively make the clinical diagnosis of systemic IgG4-RD.

In the present case, marked thickening of the gallbladder wall, hepatomegaly, and elevated serum levels of IgG4 were observed. The histological examination of the liver biopsy specimens revealed marked infiltration of lymphocytes and IgG4-positive plasma cells with fibrosis in the portal area. These findings fulfilled the CDC criteria for IgG4-RD, and thus, we were able to diagnose IgG4-RD involving multiple organs.

On the other hand, Castleman disease is an uncommon lymphoproliferative disorder. Clinically, the disease is classified into 2 forms: localized (unicentric) type and disseminated (multicentric) type (14). Most patients with unicentric Castleman disease are asymptomatic or exhibit only enlarged lymph nodes, whereas patients with MCD may present with systemic symptoms, such as a fever, anemia, night
sweats, and weight loss, which result from the hyperproduction of IL-6 in the affected lymphoid tissues (7-9). MCD occurs not only in the lymph nodes, but also in extranodal organs, such as the skin, bone marrow, liver, spleen, skin, lungs, and kidneys (7, 8, 15). Regarding its clinical prognosis, MCD typically takes an aggressive course. The diagnosis of MCD is challenging because no clinical, serological, or radiological findings appear to be specific for MCD (16, 17). Consequently, a biopsy of the affected lymph nodes appears to be mandatory in order to confirm the histologic characteristic findings, including numerous lymphoid follicles, active germinal centers, and interfollicular polyclonal plasmacytosis (4, 16, 17).

In the current patient, a histological evaluation of the abdominal swollen lymph nodes with a high FDG uptake should have been performed, however, we did not perform a surgical lymph node biopsy due to the increased risk of hemorrhaging, as indicated by the prolonged plasma prothrombin time. Therefore, we performed a liver biopsy because she had hepatomegaly with a pathologic uptake of FDG. The histological examination revealed enlarged portal tracts with severe inflammatory cell infiltration and interface hepatitis. An immunohistochemical evaluation of IgG4 revealed numerous infiltrations of IgG4-positive cells. Additional findings included eosinophilic infiltration, which is reported to be unobservable in MCD (4). These findings appear to resemble those observed in IgG4-associated autoimmune hepatitis previously reported by Umemura et al. (18).

The elevated serum levels of IgG4 and abundant infiltration of IgG4-positive cells are considered to be serological and immunohistochemical hallmarks of IgG4-RD, however, these findings are not sufficiently sensitive or specific to diagnose IgG4-RD (19-22). In fact, in MCD, elevated serum IgG4 levels and immunohistochemically assessed marked infiltration of IgG4-positive cells are occasionally observed, which appear to result from polyclonal increases in immunoglobulin titers due to hyper-IL-6 syndrome (7-9). Therefore, MCD patients who show swelling of the lymph nodes have the potential to fulfill the CDC criteria for IgG4-RD, leading to a misdiagnosis. Regarding the differentiation between IgG4-RD and MDC, Sato et al. reported that although some patients with IgG4-RD histologically exhibited Castleman disease-like features, anemia thrombocytosis, hypoalbuminemia, polyclonal hypergammaglobulinemia, and elevated serum IL-6 and CRP levels were significantly more often observed in patients with MCD with abundant IgG4-positive cells compared to systemic IgG4-related lymphadenopathy, suggesting that these findings were important for a differential diagnosis between the two diseases (4). Ogoshi et al. also reported that high levels of serum IL-6 and CRP were frequently observed in patients with MCD with diffuse parenchymal lung involvement compared with IgG4-RD with lung involvement (5). In the current patient, despite a diagnosis of IgG4-RD, anemia, hypoalbuminemia, and elevated levels of IL-6 and CRP, which were incompatible with the results of previous studies (4, 5), were observed. This discrepancy might have occurred because the degree of inflammation in the current patient was more severe than that in typical IgG4-RD, as suggested by the following facts: (1) multiple organs were affected, (2) relapse of the disease was observed during steroid tapering, and (3) immunosuppressant treatment was required for the induction of remission.

A limited number of studies on the serum IL-6 levels in IgG4-RD have been published (23-26). Yamamoto et al. reported that 5 of 27 patients (19%) with systemic IgG4-RD presented with elevated serum levels of IL-6, however, the clinical features of such patients were unclear (23). According to the clinical manifestations of our case, the serum levels of IL-6 in IgG4-RD may be associated with the clinical severity of the disease. Further studies on the serum levels of IL-6 in IgG4-RD are therefore needed.

Pancreatic parenchymal images on CT and pancreatic ductal images on MRCP showed almost normal findings except for peripancreatic fluid collection. Thus, the present patient did not fulfill the clinical diagnostic criteria for AIP (10). However, the abnormal accumulation of FDG in the pancreas on FDG-PET disappeared after steroid and immunosuppressant treatment, suggesting there might be pancreatic inflammation, including AIP, in the onset of the disease.

This report described a case of IgG4-RD involving multiple organs with high serum levels of IL-6. This case exhibited common clinical manifestations of MCD, emphasizing the difficulties in differentiating between the two diseases. A greater accumulation of cases is necessary to identify the clinical implications of high IL-6 levels in IgG4-RD.

The authors state that they have no Conflict of Interest (COI).

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References


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