Churg-Strauss Syndrome Concomitant with Chronic Symmetrical Dacryoadenitis Suggesting Mikulicz’s Disease

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Abstract

A case of Churg-Strauss syndrome complicated by chronic symmetrical dacryoadenitis suggestive of Mikulicz’s disease is herein presented. A 72-year-old Japanese man, who had been previously diagnosed with asthma, presented with weakness of the left leg and purpura on the lower extremities. A neurological examination showed multiple mononeuropathies and a laboratory examination revealed elevated eosinophil counts, IgE levels and the presence of Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCAs). Churg-Strauss syndrome was diagnosed, although the patient also exhibited bilateral swelling of the lachrymal glands. Furthermore, elevated serum IgG4 levels, an infiltration of a relatively large number of IgG4-positive plasmacytes in the nasal mucosa and hypocomplementemia were also observed. These findings were consistent with a diagnosis of Mikulicz’s disease (MD). Oral prednisolone (30 mg) was administered and the swelling of the lachrymal glands resolved. Churg-Strauss syndrome may be accompanied by Mikulicz’s disease (an IgG4-related disease), and common pathogeneses between Churg-Strauss syndrome and IgG4-related disease may exist.

Key words: Churg-Strauss syndrome, Mikulicz’s disease, IgG4-related disease


Introduction

IgG4-related disease (IgG4-RD) was first reported to be autoimmune pancreatitis and then was established to be a systemic disorder characterized by high levels of serum IgG4 and massive fibrosis consisting of highly IgG4-positive plasmacytes infiltrating into various organs (1). A diagnosis of IgG4-RD is not straightforward, as some known pathological conditions meet the same criteria and may be diagnosed as IgG4-RD “in a wide sense.” Yamamoto et al. claimed that in order to diagnosis IgG4-RD “in a narrow sense,” both swelling of the involved organs and a lack of systemic inflammation must be present (2). Because the definition of IgG4-RD has not yet been established, determining the correct criteria for diagnosing IgG4-RD is difficult. In this study, we defined IgG4-RD in the “narrow sense.”

IgG4-RD includes various diseases such as autoimmune pancreatitis, retroperitoneal fibrosis, chronic periaortitis and Kuttner’s tumor. Mikulicz’s disease (MD), also a component of IgG4-RD, is characterized by symmetrical and persistent enlargement of the lachrymal and salivary glands and hyposecretion of tears and saliva.

Churg-Strauss syndrome (CSS) is a systemic vasculitis of the small and medium vessels and is associated with extravascular eosinophilic granulomas, peripheral eosinophilia and asthma. Recently, Yamamoto et al. reported that high levels of serum IgG4 and tissue involvement of IgG4-positive plasmacytes are seen in patients with CSS (2).
Table. Laboratory Examination

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 6,680/μL</td>
<td>BUN 21.8 mg/dL</td>
</tr>
<tr>
<td>Neut. 52.8%</td>
<td>Cre 0.81 mg/dL</td>
</tr>
<tr>
<td>Lyp. 13.5%</td>
<td>Amy 68 IU/L</td>
</tr>
<tr>
<td>Eos. 32.3%</td>
<td>Na 141 mEq/L</td>
</tr>
<tr>
<td>Hb 12.6 g/dL</td>
<td>K 4.3 mEq/L</td>
</tr>
<tr>
<td>Ht 36.8%</td>
<td>Cl 107 mEq/L</td>
</tr>
<tr>
<td>Ph 19.9 × 10^6/μL</td>
<td>Ca 8.7 mg/dL</td>
</tr>
<tr>
<td>CRP 2.32 mg/dL</td>
<td>IP 3.3 mg/dL</td>
</tr>
<tr>
<td>AST 33 IU/L</td>
<td>IgG 2,092 mg/dL</td>
</tr>
<tr>
<td>ALT 32 IU/L</td>
<td>IgA 284 mg/dL</td>
</tr>
<tr>
<td>γ-GTP 18 IU/L</td>
<td>IgM 131 mg/dL</td>
</tr>
<tr>
<td>LDH 328 IU/L</td>
<td>IgE 454 IU/mL</td>
</tr>
<tr>
<td>TP 6.8 mg/dL</td>
<td>PR3-ANCA &lt; 1.5 IU/mL</td>
</tr>
<tr>
<td>Alb 3.1 mg/dL</td>
<td>MPO-ANCA 758 U/mL</td>
</tr>
<tr>
<td>IgG4 343 mg/dL</td>
<td>Anti-SS-A-Ab &lt; 5.0</td>
</tr>
<tr>
<td>IgG4/IgG 16.4%</td>
<td>Anti-SS-B-Ab &lt; 5.0</td>
</tr>
<tr>
<td>C3 49.1 mg/dL</td>
<td>Anti-nuclear-Ab &lt; 40</td>
</tr>
<tr>
<td>C4 4.5 mg/dL</td>
<td>Anti-dsDNA-Ab &lt; 7.0 IU/mL</td>
</tr>
<tr>
<td>CH50 16.9 U/mL</td>
<td>Anti-Sm-Ab Negative</td>
</tr>
</tbody>
</table>

Vaglio et al. also reported high serum IgG4 levels in active CSS patients (3). This may be one reason why CSS and IgG4-RD share common clinical features such as allergic symptoms. However, CSS does not typically present with swelling of the affected organs. When seen in association with the presence of systemic inflammation, CSS is not included in a strict diagnosis of IgG4-RD.

A case of CSS accompanied by bilateral swelling of the lachrymal glands that was diagnosed concomitantly with MD, a component of narrowly-defined IgG4-RD, is herein reported.

Case Report

A 72-year-old Japanese man was admitted to our hospital with edema, purpura and sensory abnormalities in both lower extremities that had persisted for several weeks. The patient had been diagnosed with asthma three years previously and was not taking any medications. It had become impossible for him to flex his left ankle or to walk. On admission, he was afebrile with normal blood pressure and heart rate. A physical examination revealed both mild edema in the legs and purpura in the ankle joints bilaterally. The neurological findings included a decrease in pallesthesia in both lower limbs and the right upper arm segmentally. The patient also complained of an abnormal feeling in the areas of the left median and left sural nerves. He was unable to dorsally flex his left ankle joint because of loss of strength.

The head and neck findings are described below, and no other abnormal findings were observed. Laboratory examinations revealed the following data: hemoglobin: 12.6 g/dL; white blood cell count: 6,800/μL with 32.3% eosinophils (2,150/μL); C-reactive protein: 2.32 mg/dL; immunoglobulin (Ig) E: 454 IU/mL; rheumatoid factor: 284 IU/mL; and MPO-ANCA: positive with an extremely elevated titer of 758.0 U/mL (normal range: <6.5 U/mL). Other laboratory data are shown in Table a. A nerve conduction study revealed the presence of multiple mononeuropathies in the left ulnar, bilateral median, bilateral peritoneal, left sural and left tibial regions. A skin biopsy of the purpura revealed leukocytoclastic vasculitis with numerous eosinophil infiltrates. The patient fulfilled both the 1990 American College of Rheumatology classification for Churg-Strauss syndrome (4) and the criteria for Churg-Strauss syndrome created by the Committee on the Study of Arteritis sponsored by the Ministry of Health, Labour and Welfare in Japan (5), and therefore CSS was diagnosed.

The physical findings of the head and neck are described below. The lachrymal glands were found to be swollen bilaterally without tenderness or erythema (Fig. 1A). The glands were as hard as stone, and this condition had been present for approximately three months. Schirmer’s test revealed decreased lachrymal secretion bilaterally (right/left = 4/5 mm). These findings confused the diagnosis of MD with that of Sjögren syndrome (SjS); therefore, computed tomography (CT) and additional laboratory examinations were performed.
cally; therefore, intravenous methylprednisolone (1,000 mg)
patient’s neurological symptoms did not improve dramati-
rum complement levels returned to the normal range. The
The lachrymal gland swelling improved quickly and the se-
not reach the cut-off level reported in the literature (Fig. 2).
be infiltrating the nasal mucosa; however, the number did
of IgG4-positive plasmacytes and eosinophils were found to
performed in the present case. An abnormally high number
of serum IgG4 and tissue involvement of IgG4-positive plas-
formed due to technical problems. Takano et al. has reported
was considered for further study; however, it was not per-
strongly suspected to have MD. A lachrymal gland biopsy
was discharged after 67 days of hospitalization.

Discussion

The present case was diagnosed as CSS because the pa-
ient had multiple mononeuropathies, a history of asthma,
paranasal sinus abnormalities, eosinophilia and high levels
of serum IgE. In addition, extravascular eosinophils were
noted on a skin biopsy and the patient was positive for
MPO-ANCA. In the present case, the serum IgG4 level
was significantly elevated and the nasal mucosa biopsy
specimen showed infiltration of numerous IgG4-positive plasmacytes. Recently, Yamamoto et al. reported a high level
of serum IgG4 and tissue involvement of IgG4-positive plas-
macyes to be seen in patients with CSS (2). Therefore, it is
possible that CSS can be included as a component of IgG4-
RD. However, CSS is essentially systemic vasculitis with
elements that are different from those of IgG4-RD. In fact,
the presence of mononeuropathies is not characteristic of
IgG4-RD. Therefore, it is unreasonable to conclude that all
of the clinical symptoms observed in the present case result
from IgG4-RD or that CSS should not be included in IgG4-
RD. The patient in the present case exhibited bilateral lach-
rymal gland swelling. Although CSS is a systemic vasculitis,
it does not present with swelling of the affected organs.
Therefore, it is also unreasonable to conclude that all of the
clinical symptoms observed in the present case are the result
of CSS.

Furthermore, the present case included uncommon find-
ings for CSS, such as hypocomplementemia. No previous
reports have described the serum complement levels of CSS
in detail; however, no review has shown hypocomplemen-
temia in CSS until now. The five cases of CSS described
by Yamamoto et al. also showed normal or high levels of
CH50 (2). In patients with IgG4-RD, including those with

Figure 1. A: Enlarged lachrymal glands. Swelling of the lachrymal glands was without tenderness
or erythema. B and C: Contrast-enhanced CT of the head. Slice B displays bilateral swollen lachry-
mal glands. Slice C: displays thickening of the nasal mucosa and mucous membranes of the maxil-
lar sinus. Slices D1 and D2: show the mild swelling in both the submandibular glands. The swelling
was diminished by administration of oral glucocorticoids.
MD, the serum levels of complement are frequently at low levels and reflect the disease activity (7). The present case showed significantly low levels of C3, C4 and CH50. Hypocomplementemia can occur in patients with systemic lupus erythematosus and several other diseases, except for IgG4-RD. However, the clinicopathological findings in the present case did not match those of systemic lupus erythematosus or other diseases characterized by hypocomplementemia. Therefore, a concomitant diagnosis of IgG4-RD was more likely. A diagnosis of MD (IgG4-RD) was confirmed in the present study.

MD is characterized by symmetric chronic inflammation of the lachrymal and salivary glands. The histology is characterized by lymphoplasmacytic inflammation with numerous IgG4-positive plasmacytes and exuberant fibrosis. Additionally, MD is included in IgG4-RD. Although performing a lachrymal gland biopsy was impossible in the present case because of technical problems, a biopsy of the nasal mucosa showed infiltration of many IgG4-positive plasmacytes. In addition to showing lachrymal enlargement, the patient also exhibited bilateral mildly enlarged submandibular glands (as noted by a radiologist). The size of the submandibular glands reduced after steroid therapy was administered. Although histological confirmation was not obtained, it was determined that the patient fulfilled the Clinical Diagnostic Criteria of IgG4-Related Mikulicz’s Disease advocated by the Japanese Medical Society for Sjogren’s Syndrome (8). A limitation to the present study includes the fact that the size of the submandibular glands may be not clinically significant; however, a final diagnosis of chronic sclerosing dacryoadenitis (a subset of IgG4-RD) was made (9).

Both IgG4 and IgE are produced as a result of Th2 cytokines (for example, IL-4, IL-5 and IL-10), and IgG4 is considered to be derived from an IgE-blocking antibody. The mechanisms underlying the elevation of IgE and the association between high levels of serum IgE and elevated serum IgG4 levels seen in patients with IgG4-RD are well-understood. Although CSS differs completely from MD, they share common characteristics: both diseases develop in patients with allergic symptoms such as asthma or atopic dermatitis. This is evidence for the existence of a similar pathological foundation involving the actions of Th2 cells in both CSS and IgG4-RD. A few cases of CSS associated with lachrymal gland swelling have been previously reported (10, 11). Takanashi et al. reported that a patient with CSS presented with chronic bilateral dacryoadenitis (11). Additionally, there are two reports of CSS associated with chronic peritonitis (12, 13). Unfortunately, these reports did not examine the IgG4 and serum complement levels. The complications associated with CSS are possibly also associated with IgG4-related lesions, as in the present case.

In conclusion, we herein reported a case of CSS concomitant with IgG4-RD. Clinical observations and the serum complement levels are thus considered to be useful for diagnosing IgG4-RD. In addition, there may be a common pathogenesis between CSS and IgG4-RD.

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


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