Ocular Adnexal IgG4-Related Lymphoplasmacytic Infiltrative Disorder

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Objective: To determine the clinicopathological characteristics of patients with infiltration of IgG4-positive plasma cells into the ocular adnexa.

Methods: We designed a prospective study to evaluate 24 patients with ocular adnexal lymphoplasmacytic infiltrative lesions, including sclerosing inflammation and reactive lymphoid hyperplasia. We analyzed peripheral blood and biopsy specimens from all patients. The classification criteria for placement in the IgG4-related group included having both an elevated serum level of IgG4 of 135 mg/dL or greater and an IgG4:IgG ratio of infiltrating plasma cells of 30% or greater.

Results: Ten patients met the classification criteria (IgG4-related group), 9 patients did not meet the criteria (IgG4-unrelated group), and 5 patients met 1 but not both criteria (indeterminate group). Patients in the IgG4-related group had significantly higher bilateral involvement ($P=.02$), a higher number of allergic diseases ($P=.01$), and elevated IgE serum levels ($P=.01$). Of the 10 patients in the IgG4-related group, 3 also had polyclonal hypergammaglobulinemia, 6 had systemic lymphadenopathy or salivary gland enlargement, and 1 developed autoimmune pancreatitis. Patients in the IgG4-unrelated group did not have these serum and/or systemic abnormalities.

Conclusion: The IgG4-related and IgG4-unrelated groups have different patterns of tissue involvement and systemic disease associations and possibly different prognoses.


Ocular adnexal inflammation includes a wide spectrum of diseases, including idiopathic sclerosing inflammation and sclerosing dacryoadenitis. The pathogenesis of ocular adnexal sclerosing inflammation remains undetermined. Thus, these diseases have been considered a distinct clinical entity with histological characteristics similar to retroperitoneal fibrosis or an idiopathic orbital inflammation that has progressed from the acute or subacute stage to a chronic inflammatory stage with fibrosis. Some cases of ocular adnexal sclerosing inflammation may progress to ocular adnexal lesions with multifocal fibrosclerosis.

An ocular adnexal reactive lymphoid hyperplasia is made up of lymphoplasmacytic infiltrations and reactive lymphoid follicles. The pathogenesis of ocular adnexal reactive lymphoid hyperplasia has not been determined, although some cases are associated with autoimmune diseases.

Sclerosing dacryoadenitis and cases with idiopathic, bilateral, and symmetrical swelling of the lacrimal and/or salivary glands are lymphoplasmacytic lesions with reactive lymphoid hyperplasia and sclerosing inflammation of the lacrimal gland. They may be associated with elevated serum levels of IgG4 and an infiltration of IgG4-positive plasma cells. Furthermore, ocular adnexal lymphomas arising from sclerosing dacryoadenitis with IgG4-positive plasma cells have been identified.

The purpose of this study was to determine the characteristics of patients with infiltration of IgG4-positive plasma cells into the ocular adnexa and elevated levels of serum IgG4. To accomplish this, we studied patients with ocular adnexal lymphoplasmacytic lesions, including those with sclerosing inflammation and reactive lymphoid hyperplasia.

METHODS

PATIENTS

The procedures used in this study conformed to the tenets of the Declaration of Helsinki and...
were approved by the Ethics Committee at Nagoya Medical Center. All patients provided signed informed consent after the procedures and possible outcomes were explained to them.

We designed a prospective study to evaluate ocular adnexal lymphoplasmacytic infiltrative lesions, including those with sclerosing inflammation and reactive lymphoid hyperplasia. Patients were examined between February 1, 2005, and February 28, 2009. Patients with Sjögren syndrome, distinct autoimmune diseases, lymphoma, thyroid orbitopathy, vasculitis (eg, Wegener granulomatosis), and granulomatous lesions (eg, xanthogranuloma and sarcoidosis) were excluded. Twenty-four patients met the inclusion criteria.

**CLINICAL DATA**

We recorded the patients’ age, sex, symptoms at the initial examination and their duration, previous treatments, laterality, anatomical location of the lesion, laboratory data, systemic conditions, treatments and treatment outcomes, and duration of follow-up. All patients underwent evaluation for systemic involvement by palpation and chest radiography. In addition, patients with suspicious extraocular involvement underwent evaluation by computed tomography at the initial examination and each of the follow-up examinations. Patients 1, 2, 3, 5, 7, and 8 also underwent imaging with gallium citrate Ga 67 scintigraphy or fluorodeoxyglucose F 18–positron emission tomography (FDG-PET) at the initial examination and each of the follow-up examinations.

**HISTOPATHOLOGY, IMMUNOHISTOCHEMISTRY, AND MOLECULAR GENETIC ANALYSIS**

Biopsy specimens from ocular adnexal lesions were collected from all patients. Part of the biopsy specimen was embedded in paraffin for conventional histological and immunohistochemical analyses, and the remainder was immediately frozen and used for Southern blot analysis. All biopsy specimens were diagnosed by means of the morphologic features and immunophenotype, mainly CD3, CD5, CD20, CD68, and CD138 (DAKO, Glostrup, Denmark) and κ and λ (by means of in situ hybridization [Ventana Medical Systems, Oro Valley, Arizona]). The IgG- and IgG4-positive plasma cells were detected by immunostaining for IgG (polyclonal [DAKO]) and IgG4 (MC011 [The Binding Site Group, Ltd, Birmingham, England]). To determine the number of IgG4- or IgG-positive cells, the areas with the highest density of IgG4-positive cells were evaluated. In each specimen, the mean number of IgG4-positive plasma cells was determined from 6 high-power fields. One high-power field covered an area of 0.196 mm² (original magnification ×400 [Nikon microscope, Tokyo, Japan]). Patients with an IgG4:IgG plasma cell ratio of 30% or greater in a high-power field were placed in the IgG4-related group, and those with a ratio of less than 30% were placed in the IgG4-unrelated group. Southern blot analysis was performed on all but 3 biopsy specimens to detect B-cell clonality (immunoglobulin heavy-chain gene rearrangements).

**LABORATORY DATA**

Laboratory data were determined from peripheral blood samples collected from all patients at the time of diagnosis and at follow-up visits, with emphasis on the serum levels of IgG, IgG4, and IgE. Patients whose serum had an IgG4 level of 135 mg/dL or greater (to convert to grams per liter, multiply by 0.01) were placed in the IgG4-related group, and those with a level of less than 135 mg/dL were placed in the IgG4-unrelated group. Patients with elevated serum levels of soluble interleukin 2 (IL-2) receptor were examined to determine whether an in vivo activation of the immune system had occurred. Patients with systemic lymphadenopathy were examined for serum levels of IL-6 to determine whether they had multicentric Castleman disease.

**TREATMENTS**

The treatments, including the patients’ prior treatments, are shown in Table 1. We evaluated the response to treatment of the ocular adnexal lesions by computed tomography or magnetic resonance imaging before and after each treatment.

**STATISTICAL ANALYSES**

Patients whose serum IgG4 level was 135 mg/dL or greater and who had an IgG4:IgG ratio of 30% or greater plasma cells infiltrating the ocular adnexal lesion were placed in the IgG4-related group; patients who did not meet either of these criteria were placed in the IgG4-unrelated group; and patients who met only 1 of the criteria were placed in the indeterminate group. We compared the systemic associations and laterality between the IgG4-related and IgG4-unrelated groups using the χ² test or the Fisher exact test. We compared the laboratory results between groups using the Mann-Whitney test. All statistical analyses were performed on a personal computer with a commercially available statistical software package (SPSS for Windows, version 12.0; SPSS, Inc, Chicago, Illinois). P < .05 was considered to be statistically significant.

**RESULTS**

Ten patients met both classification criteria (IgG4-related group); 9 patients did not meet either criterion (IgG4-unrelated group); and 5 patients met 1 but not both criteria (indeterminate group). The age, sex, symptoms at the initial examination, duration of symptoms, previous treatments, laterality, anatomical location, complications, systemic involvements, treatments and outcome, and follow-up periods are summarized in Table 1. The mean (SD) age of the patients was 58 (10) years in the IgG4-related group, 56 (14) years in the IgG4-unrelated group, and 53 (18) years in the indeterminate group. The male to female ratios were 1.0, 1.3, and 0.7, respectively. Bilateral ocular adnexal lesions were significantly more frequent in the IgG4-related group than in the IgG4-unrelated group (8 patients [80%] vs 2 [22%]; P = .02, Fisher exact test). Allergic diseases including atopic dermatitis, asthma, and allergic rhinitis were also significantly more frequent in the IgG4-related group than in the IgG4-unrelated group (6 patients [60%] vs none; P = .01, Fisher exact test).

Palpation and computed tomography revealed an enlargement of the salivary gland in patients 2 through 5, 11, and 15. Gallium citrate Ga 67 scintigraphy or FDG-PET, although performed only in patients 1, 2, 3, 5, 7, and 8, revealed accumulations not only in ocular adnexal lesions but also in the salivary gland (patients 2, 3, 5, and 8), left subclavian lymph nodes (patient 1), cervical lymph nodes (patients 1 and 3), bronchomedastinal lymph nodes (patients 1, 2, 3, and 5). Figure 1,
and the external and internal iliac lymph nodes (patient 1) at the time of diagnosis. The uptake of $^{67}$Ga and FDG decreased after corticosteroid therapy during follow-up. Patient 6 developed autoimmune pancreatitis during the study.

**HISTOPATHOLOGY, IMMUNOHISTOCHEMISTRY, AND MOLECULAR GENETIC ANALYSIS**

The results of the histological examinations, IgG4:IgG ratios, and Southern blot evaluations of B-cell clonality are

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**Table 1. Clinical Data of Patients With Ocular Adnexal Lymphoplasmacytic Infiltration**

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, ya</th>
<th>Initial Symptoms (Duration); Treatment</th>
<th>Laterality</th>
<th>Anatomical Location</th>
<th>Systemic Associations</th>
<th>Systemic Involvement</th>
<th>Treatments (Response)</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG4-related group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/M/73</td>
<td>Swollen eyelids and proptosis (5 y)</td>
<td>B</td>
<td>Infiltration into orbit</td>
<td>Atopic dermatitis</td>
<td>S LN</td>
<td>First: Rd (poor); second: corticosteroid, 30 mg (good)</td>
<td>15</td>
</tr>
<tr>
<td>2/M/64</td>
<td>Swollen eyelids and proptosis (7 y)</td>
<td>B</td>
<td>Infiltration into orbit</td>
<td>Asthma, DM</td>
<td>B SG, S LN</td>
<td>Rd (partial)</td>
<td>50</td>
</tr>
<tr>
<td>3/F/63 4/F/59</td>
<td>Swollen eyelids (2 y); pulse plus corticosteroids, 60 mg, good outcome with recurrence</td>
<td>B</td>
<td>LG</td>
<td>None</td>
<td>L SG, S LN</td>
<td>Observation Corticosteroid, 30 mg, and maintenance (good)</td>
<td>4</td>
</tr>
<tr>
<td>5/M/63</td>
<td>Swollen eyelids (2 mo)</td>
<td>L</td>
<td>Periocular</td>
<td>Asthma</td>
<td>S LN, B SG</td>
<td>Corticosteroid, 30 mg (good)</td>
<td>10</td>
</tr>
<tr>
<td>6/F/38</td>
<td>Swollen eyelids (2 y)</td>
<td>B</td>
<td>L periocular, R LG</td>
<td>None</td>
<td>Autoimmune pancreatitis</td>
<td>First: corticosteroid, 30 mg (good but recurrence); second: corticosteroids, 30 mg, and maintenance (good)</td>
<td>44</td>
</tr>
<tr>
<td>7/F/49</td>
<td>Swollen eyelids (1.5 y)</td>
<td>B</td>
<td>LG</td>
<td>AR</td>
<td>None</td>
<td>Corticosteroid, 30 mg (good)</td>
<td>14</td>
</tr>
<tr>
<td>8/M/42</td>
<td>Swollen eyelids (2 y)</td>
<td>B</td>
<td>EOMs, periocular</td>
<td>AR</td>
<td>B SG</td>
<td>First: Rd (poor); second: corticosteroid (good)</td>
<td>13&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>9/F/63 10/M/62</td>
<td>Swollen eyelids (1 y)</td>
<td>B</td>
<td>LG</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>4</td>
</tr>
<tr>
<td>11/F/21</td>
<td>Swollen eyelids (1.5 y)</td>
<td>R</td>
<td>Periocular</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>23</td>
</tr>
<tr>
<td>12/M/62</td>
<td>Swollen eyelids (2 y)</td>
<td>L</td>
<td>Periocular</td>
<td>Asthma, AR</td>
<td>None</td>
<td>Rd (good)</td>
<td>17</td>
</tr>
<tr>
<td>13/F/57</td>
<td>Swollen eyelids (2 mo)</td>
<td>B</td>
<td>LG</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>19</td>
</tr>
<tr>
<td>14/F/75</td>
<td>Swollen eyelids and proptosis (3 y)</td>
<td>R</td>
<td>EOMs</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>16</td>
</tr>
<tr>
<td>15/M/48</td>
<td>Swollen eyelids (4 mo)</td>
<td>R</td>
<td>LG</td>
<td>AR</td>
<td>L SG</td>
<td>First: corticosteroid, 30 mg (good but recurrence); second: corticosteroid, 30 mg, and maintenance (good)</td>
<td>32&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>IgG4-unrelated group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16/F/79 17/M/60</td>
<td>Swollen eyelids (4 mo)</td>
<td>L</td>
<td>LG</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>17</td>
</tr>
<tr>
<td>18/F/70</td>
<td>Swollen eyelids (2 mo)</td>
<td>L</td>
<td>LG</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>22</td>
</tr>
<tr>
<td>19/F/65 20/M/38</td>
<td>Swollen eyelids (1 wk)</td>
<td>L</td>
<td>EOMs</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>30</td>
</tr>
<tr>
<td>21/M/67</td>
<td>Conjunctival mass (4 y)</td>
<td>R</td>
<td>Conjunctiva</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>36</td>
</tr>
<tr>
<td>22/F/56 23/M/42</td>
<td>Conjunctival mass (1 y)</td>
<td>L</td>
<td>Conjunctiva</td>
<td>None</td>
<td>None</td>
<td>Observation</td>
<td>26</td>
</tr>
<tr>
<td>24/M/38</td>
<td>Conjunctival mass (2 y)</td>
<td>B</td>
<td>Conjunctiva</td>
<td>None</td>
<td>None</td>
<td>Pulse (good)</td>
<td>34</td>
</tr>
</tbody>
</table>

Abbreviations: AR, allergic rhinitis; B, bilateral; DM, diabetes mellitus; EOMs, extraocular muscles; L, left; LG, lacrimal gland; LN, lymph node; R, right; Rd, radiation therapy (30 Gy); S, systemic; SG, salivary gland.

<sup>a</sup> Groups are described in the “Laboratory Data” subsection of the “Methods” section.

<sup>b</sup> Corticosteroid therapy consisted of prednisolone dose with slow taper; corticosteroid and maintenance therapy consisted of prednisolone dose with slow taper and maintenance dose (2-5 mg); and pulse consisted of corticosteroid pulse therapy (1000 mg intravenous methylprednisolone sodium succinate daily for 3 days).

<sup>c</sup> No recurrence and dissemination as a lymphoma.

<sup>d</sup> Died of pancreatic carcinoma.
shown in Table 2. The ocular adnexal lesions in the IgG4-related group consisted of different degrees of lymphoplasmacytic infiltration, reactive lymphoid follicles, and sclerosing lesions. We classified the histological findings in Table 2 as follows: the ocular adnexal lesions that dominate sclerosing lesions with lymphoplasmacytic infiltration rather than reactive lymphoid follicles were defined as sclerosing inflammation in contrast to reactive lymphoid follicle with few sclerosing lesions, which were defined as reactive lymphoid hyperplasia. The ocular adnexal lesions with lymphoplasmacytic infiltration and nonspecific polymorphous cells were defined as lymphoplasmacytic lesions. Thus, an ocular adnexal lesion with a high degree of sclerosis was considered to be a sclerosing inflammation (Figure 2) in contrast to ocular adnexal lesions with abundant reactive lymphoid follicles, which were considered to be reactive lymphoid hyperplasia (Figure 3). Another ocular adnexal lesion in the IgG4-related group had an infiltration by lymphoplasmacytic cells and macrophages containing eosinophilic material (Figure 4), which were defined as lymphoplasmacytic and eosinophilic lesions. The biopsy specimen of lymphadenopathy of the cervical node in patient 3 appeared 6 years before ocular adnexal symptoms revealed reactive follicular hyperplasia with IgG4-positive plasma cells. The histological and immunohistochemical findings of the salivary gland biopsy specimens (patients 3 and 11) were the same as those of the ocular adnexal lesions.

The biopsy specimen from patient 8 showed B-cell clonality, but specimens from the other patients did not.
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The serum levels of IgG, IgG4, and IgE and the serum IgG4:IgG ratio in our patients are summarized in Table 2. The serum levels of soluble IL-2 receptor and IL-6 in patients in the IgG4-related group are shown in Table 3. Of all 24 patients, 3 (patients 1, 2, and 3) had hypergammaglobulinemia and polyclonal hypergamma-globulinemia at the time of diagnosis based on results of immunoelectrophoretic analyses. The mean (SD) serum levels of IgG4 (reference range, 4.8-105 mg/dL) were 907 (841) mg/dL in the IgG4-related group and 34 (24) mg/dL in the IgG4-unrelated group. The serum levels of IgG4 in the IgG4-related group were decreased after corticosteroid treatment (data not shown). The mean (SD) IgG4:IgG ratio (reference level, <4%) was 27% (11%) in the IgG4-related group and 2% (1%) in the IgG4-unrelated group.

The mean (SD) serum level of IgE (reference level, <170 µg/L [to convert to milligrams per liter, multiply by 0.001]) was significantly higher in the IgG4-related group than in the IgG4-unrelated group (1020 [1100] vs 118 [91] µg/L; P=.01, Mann-Whitney test). In the IgG4-related group, patients had a mild or markedly elevated serum level of soluble IL-2 receptor (Table 3). Patients with high serum levels of IgG4 had high serum levels of soluble IL-2 receptor. The serum level of IL-6 in patients with systemic lymphadenopathy (patients 1, 2, 3, 5, and 8) was below the reference cutoff (<4.0 pg/mL).

TREATMENTS AND OUTCOME

The treatments and outcomes, including previous treatments, are shown in Table 1. The response to radiation treatment in the IgG4-related group (patients 1, 2, and 8) was variable. Thus, patient 2's ocular adnexal lesion achieved a partial response despite sclerosing inflammations; however, those of patients 1 and 8 responded poorly. Patient 12 in the indeterminate group responded well to radiotherapy. The outcome of corticosteroid treatment improved the clinical signs and symptoms in the IgG4-related group. However, a recurrence was seen in patients 4, 6, 11, and 15 in the IgG4-related and indeterminate groups. In the IgG4-unrelated group, all patients achieved clinical improvement after corticosteroid treatment or had an indolent clinical course.

COMMENT

Patients in the IgG4-related group had not only elevated serum levels of IgG4 and an infiltration of
IgG4-positive plasma cells but also polyclonal hypergammaglobulinemia, allergic diseases, and systemic involvement. Patients with ocular adnexal reactive lymphoid hyperplasia have an indolent clinical course; however, some patients have a history of asthma, hypergammaglobulinemia, and systemic involvement. Although there is no information on the serum levels of IgG4 and IgG4 immunostaining, these clinical characteristics correspond with those of the IgG4-related group in our study. We suggest that ocular adnexal lymphoplasmacytic lesions can be classified on the basis of serum levels of IgG4 and the infiltration of IgG4-positive plasma cells. Thus, the 2 subgroups have different pattern of tissue involvement and systemic association, even though the conventional histological findings are much the same in the IgG4-related and IgG4-unrelated groups.

One patient in the IgG4-related group developed autoimmune pancreatitis. Some cases of autoimmune pancreatitis are characterized histologically by lymphoplasmacytic infiltration of IgG4-positive plasma cells and elevated serum levels of IgG4. The IgG4-related diseases, including multifocal fibrosclerosis (eg, retroperitoneal fibrosis), sclerosing cholangitis, and autoimmune pancreatitis, are commonly characterized by higher serum levels of IgG4, an infiltration of IgG4-positive plasma cells, associations with allergic rhinitis, a high serum level of IgE, and lymphadenopathy. The clinical and histological characteristics of the IgG4-related group in our patients closely fit these systemic IgG4-related diseases.

Patients with polyclonal hypergammaglobulinemia and lymphadenopathy must be differentiated from those with multicentric Castleman disease. The elevated IL-6 serum level that leads to an overproduction of IL-6 from germinal-center B cells is implicated in the pathogenesis of multicentric Castleman disease. These changes were not found in our cases.

Patients in the IgG4-related group were typically associated with atopy, elevated soluble IL-2 receptor

Figure 2. Histological and immunohistochemical findings in ocular adnexal lesions with IgG4-positive plasma cells from patient 2. A, Low magnification shows sclerosing inflammation (hematoxylin-eosin, original magnification ×200). High magnification (inset) of sclerosing inflammation shows infiltration of inflammatory cells made up mainly of lymphocytes and plasma cells and occasional eosinophils (arrow) (hematoxylin-eosin, original magnification ×400). B, Immunostaining for IgG4 reveals IgG4-positive plasma cells in the sclerosing lesions (immunoperoxidase, original magnification ×400).

Figure 3. Histological and immunohistochemical findings in ocular adnexal lesions with IgG4-positive plasma cells from patient 7. A, Histological examination shows reactive lymphoid hyperplasia (hematoxylin-eosin, original magnification ×40). B, Immunostaining for IgG4 reveals IgG4-positive plasma cells (immunoperoxidase, original magnification ×400).
and IgE levels, and polyclonal hypergammaglobulinemia. Although a cause in the IgG4-related group has been not determined, a plausible hypothesis for these serological and immunological abnormalities may be an in vivo activation of the immune system by activated helper T cells type 2 (TH2). In patients with persistent atopic asthma, the condition is stimulated by activated TH2 cells and associated with elevated IgE and soluble IL-2 receptors.18 Activated TH2 cells also produce IgE and induce polyclonal B-cell activation,19 and IgG4 is induced by a modified TH2 response.20 Elevated soluble IL-2 receptors reflect the in vivo activation of the immune system.21 Thus, a cause of ocular adnexal lesions in the IgG4-related group may be correlated with systemic immunological imbalances or activation.

There are a number of limitations to our study. First, further studies in a larger number of patients are needed to confirm the correlation between the infiltration of ocular adnexal IgG4-positive plasma cells and lymphoma. Cheuk et al22 report that transformation of ocular adnexal lymphoma occurs in approximately 10%. Southern blot analyses of specimens collected from our patients also showed that 1 case (10%) in the IgG4-related group exhibited B-cell clonality.

Second, further studies that include a larger number of cases and longer follow-up are needed to confirm the

Table 3. Serum Levels of Interleukins in Patients in the IgG4-Related Group

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Soluble IL-2 Receptor, pg/mL</th>
<th>IL-6, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1676</td>
<td>2.7</td>
</tr>
<tr>
<td>2</td>
<td>2131</td>
<td>2.1</td>
</tr>
<tr>
<td>3</td>
<td>935</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>815</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>634</td>
<td>1.7</td>
</tr>
<tr>
<td>6</td>
<td>ND</td>
<td>1.3</td>
</tr>
<tr>
<td>7</td>
<td>696</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>592</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>356</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>634</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: IL, interleukin; ND, not determined.

*The reference level for soluble IL-2 receptor was 135 to 483 pg/mL and for IL-6, less than 4.0 pg/mL.
treatment outcomes. We treated our patients mostly with prednisolone and radiotherapy, which is similar to published treatments for idiopathic sclerosing inflammation of the ocular adnexa and reactive lymphoid hyperplasia. Although ocular adnexal lesions in the IgG4-positive group responded favorably to corticosteroid therapy, it is difficult to evaluate the treatment outcomes because ocular adnexal lesions in the IgG4-positive group have a possibility of recurrence when corticosteroid therapy is discontinued. Published data suggest that lesions of IgG4-related disease recur when corticosteroid therapy is discontinued.

A third limitation was that the ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder needs to be confirmed with further refined criteria. We used working criteria to analyze our patients.

Fourth, we could not determine whether there was a discrepancy in the indeterminate group, especially in patient 11, who had negative findings of the IgG4 immunostaining despite presumably typical IgG4-related disease.

A fifth limitation was that patients in the IgG4-related group were more carefully evaluated using 99mTc scintigraphy and/or FDG-PET than patients in the IgG4-unrelated group. If patients in the IgG4-unrelated group had undergone the same level of evaluation, they might have shown a higher prevalence of systemic disease.

A sixth limitation was that the biopsy specimen of patient 8 (Figure 4) differed from all other specimens in the IgG4-related group and consisted of many macrophages. We could not determine the reasons for this histological appearance.

In summary, we suggest that the ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder has different patterns from IgG4-unrelated lesions. It is characterized by an elevated serum level of IgG4 and an infiltration of IgG4-positive plasma cells and is often associated with allergic diseases, bilateral involvement, systemic lymphadenopathy, and salivary gland enlargements. Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder is occasionally associated with other IgG4-related diseases and B-cell clonality. Further studies are needed to confirm our observations.

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REFERENCES