CT and MR imaging findings of ocular adnexal mucosa-associated lymphoid tissue lymphoma associated with IgG4-related disease: multi-institutional case series

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Abstract

● AIM: To report CT and MR imaging findings of ocular adnexal mucosa-associated lymphoid tissue lymphoma associated with IgG4-related disease (IgG4-MALT lymphoma), a rare but clinically important complication of ocular adnexal IgG4-related disease.

● METHODS: We retrospectively reviewed all cases of histologically confirmed ocular adnexal IgG4-related disease at three tertiary and one secondary referral centers, between February 2003 and December 2016. Seven cases of histopathologically diagnosed IgG4-MALT lymphoma were identified. CT and MR images were analyzed by consensus of two experienced head and neck radiologists.

● RESULTS: Lacrimal glands were the main site of involvement in all seven patients. The lesions typically showed well-demarcated margins, iso- to hyperattenuation on precontrast CT, T2 hypo- to isointensity, T1 isointensity, and homogenous internal architecture with homogenous enhancement pattern. Lesions were mostly hyperdense and isointense to normal extraocular muscles on postcontrast CT and MR images, respectively.

● CONCLUSION: Unlike in typical ocular adnexal IgG4-related disease, T2 isointensity and hyperattenuation on precontrast CT images were noted in some IgG4-MALT lymphoma cases. Although the findings may be nonspecific, the possibility of accompanying MALT lymphoma may need to be considered, when ocular adnexal lesions in patients clinically suspected of having IgG4-related disease are refractory to glucocorticoids and show T2 isointensity and hyperattenuation on precontrast CT for the optimal management of the patients. However, this is a case series of a very rare complication of ocular adnexal IgG4-related disease, and thus caution is warranted to generalize the conclusion.

● KEYWORDS: CT; IgG4-related disease; MR; ocular adnexal mucosa-associated lymphoid tissue lymphoma

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INTRODUCTION

Over the past few years, many insights into clinical and histopathologic features of IgG4-related disease have been provided by numerous studies\[1-10\], and the definition of the disease entity has evolved concomitantly. IgG4-related disease, first recognized as a systemic condition in 2003, is a fibroinflammatory condition, which has been described in virtually every organ system, including the pancreas, liver, biliary tract, kidney, thyroid gland, retroperitoneum, lymph node, salivary gland, and ocular adnexa. The condition is now known to encompass medical conditions once referred to as Mikulicz’s syndrome, Küttner’s tumor, and Riedel’s thyroiditis. The current concept of IgG4-related disease considers the following features as the main diagnostic clues to the disease: 1) tumefactive lesions, 2) a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, 3) storiform fibrosis, and 4) often but not always, elevated serum IgG4 concentrations\[11\]. Chronic inflammation or autoimmune-related lymphoid hyperplasia, as in cases with Helicobacter pylori-associated chronic gastritis, has been proposed as a predisposing factor for the development of secondary lymphoma\[12-14\]. Recently, there have been a few case reports pertaining to histopathologic features of secondary mucosa-associated lymphoid tissue (MALT) lymphoma arising in ocular adnexal IgG4-related disease\[15-19\].

Despite its rarity, awareness of the potential complication of ocular adnexal IgG4-related disease would be clinically important, because treatment strategies differ between cases with ocular adnexal IgG4-related disease alone and those with combined lymphoma. In contrast to IgG4-related disease for which the first line of therapy is a glucocorticoid, various treatment options including surgery, chemotherapy, and radiotherapy need to be considered for the optimal management of the patients with combined lymphoma\[11,20\]. However, to our knowledge, characteristic radiologic findings of the newly emerged disease entity remains elusive. Therefore, the purpose of our study was to report CT and MR imaging findings of MALT lymphoma associated with IgG4-related disease (IgG4-MALT lymphoma), a rare but clinically important complication of ocular adnexal IgG4-related disease.

SUBJECTS AND METHODS

Ethical Approval  Local ethics approval was obtained at all sites and the requirement for informed consent was waived for this retrospective study. The principles outlined in the Declaration of Helsinki.

Patient Selection  Pathology database of Seoul National University Hospital, Seoul Metropolitan Government Seoul National University Boramae Medical Center, and Asan Medical Center between February 2003 and December 2016 were searched for cases which were histopathologically diagnosed as ocular adnexal IgG4-related disease via incisional or excisional biopsy. Inclusion criteria were as follows: the patients had 1) histopathologic diagnosis of the underlying ocular adnexal IgG4-related disease based on the combination of characteristic histological features and high numbers of IgG4-positive plasma cells (more than 100 per 0.14 mm² in the area with the highest number) or high IgG4/IgG-positive cell ratios (exceeding 30%\[10\], and 2) histopathologic diagnosis of IgG4-MALT lymphoma based on 2008 WHO classification of hematolymphoid neoplasm, with consideration of the quantity or ratio of IgG4-positive plasma cells\[21\]. One patient with a borderline ratio of IgG4/IgG-positive cells (30%) was excluded from the analysis.

The final study population consisted of seven patients (5 men (mean age, 62y; age range, 41-78y), 2 women (mean age, 38y; age range, 31-44y)). The serum levels of IgG4 and various other autoantibodies [including rheumatoid factor (RF), anti-Ro antibody, anti-La antibody, and anti-nuclear antibody (ANA)] at the time of CT or MR examinations were documented whenever possible.

Imaging Techniques  All patients underwent CT imaging at seven different scanners: HiSpeed CT/i (GE Healthcare, Milwaukee, WI, USA), LightSpeed Pro (GE Healthcare, Milwaukee, WI), LightSpeed Ultra (GE Healthcare, Milwaukee, WI, USA), LightSpeed VCT (GE Healthcare, Milwaukee, WI, USA), Optima CT660 (GE Healthcare, Milwaukee, WI, USA), Brilliance 16 (Philips Medical Systems, Best, the Netherlands), and Mx8000 IDT (Philips Medical Systems, Best, the Netherlands). Axial and coronal images were obtained using the following parameters: tube current, 128 to 300 mA; tube voltage, 120 kV; and field of view (FOV), 160×160 mm²; high-frequency reconstruction algorithm; and section thickness, 2.5-5.0 mm. Postcontrast CT images were acquired using 90 mL of a nonionic contrast medium, iopromide (Ultravist 370; Schering Korea, Seoul, Republic of Korea), iopamidol (Iopamiro 370; Bracco, Milano, Italy), or iohexol (Omnipaque 300; GE Healthcare, Piscataway, New Jersey, USA).

MR images were obtained for two patients at a 1T scanner (Magnetom Expert; Siemens, Erlangen, Germany) or a 1.5T scanner (Achieva; Philips, Best, the Netherlands), including fat-suppressed T2-weighted imaging (axial and coronal planes), precontrast axial T1-weighted imaging, and postcontrast fat-suppressed T1-weighted imaging (axial and coronal planes). Specific imaging parameters for the sequences were as follows: 1) for the axial fat-suppressed T2-weighted imaging, repetition time (TR), 2500-4500ms; echo time (TE), 70-96ms; flip angle, 70°-96°; matrix, 256×256; FOV, 440×440 mm²; section thickness, 3 mm; and number of excitations (NEX), 2; 2) for the coronal fat-suppressed T2-weighted imaging,
TR, 3305-5000ms; TE, 70-96ms; flip angle, 90°-180°; matrix, 256×252; FOV, 360×360 mm²; section thickness, 4 mm; and NEX, 2; 3) for the precontrast axial T1-weighted imaging, TR, 450-500ms; TE, 15-20ms; flip angle, 70°-90°; matrix, 252×191; FOV, 360×360 mm²; section thickness, 3 mm; and NEX, 2; 4) for the postcontrast axial fat-suppressed T1-weighted imaging, TR, 431-630ms; TE, 11-15ms; flip angle, 70°-90°; matrix, 252×207; FOV, 360×360 mm²; section thickness, 2 mm; and NEX, 2; and 4) for the postcontrast coronal fat-suppressed T1-weighted imaging, TR, 608-736ms; TE, 12-13ms; flip angle, 70°-90°; matrix, 252×191; FOV, 360×360 mm²; section thickness, 3-4 mm; and NEX, 1-2. Contrast-enhanced T1-weighted images were acquired after the intravenous administration of gadopentetate dimeglumine (Magnevist; Bayer HealthCare Pharmaceuticals, Wayne, New Jersey) or gadobutrol (Gadovist; Bayer Schering Pharma, Berlin, Germany) at a dose of 0.1 mmol/kg of body weight.

Image Analysis
All CT and MR images were analyzed by consensus of two experienced head and neck radiologists (Yoo RE and Park SW with 7y and 19y of experience, respectively) for the following: 1) laterality (unilateral vs bilateral), 2) anatomic location, 3) shape (lobulated/non-lobulated/infiltrative), and 4) margin (well-demarcated vs ill-defined). Furthermore, CT densities or MR signal intensities (T1 and T2) of the lesions relative to gray matter (hypo-/iso-/hyper-) on precontrast CT or MR images were analyzed. In addition, enhancement pattern (homogeneous vs heterogeneous), and enhancement degree relative to extraocular muscles (weaker/similar/stronger) were further investigated. Lastly, the presence and absence of other associated findings (including bone change such as bone remodeling or destruction, lymph node enlargement, and other extraorbital organ involvement as identified on positron emission tomography (PET)-CT scans or body imaging and laboratory results (whenever available) were analyzed.

Pathologic Analysis
Histopathological findings including immunohistochemical results were reviewed by two experienced pathologists (Kim JE and Choe JY with 20 and 6y of experience in hematopathology, respectively) and consensus was achieved for the final diagnosis. Diagnosis of IgG4-MALT lymphoma was made based on 2008 WHO classification of hematolymphoid neoplasm with consideration of the quantity or ratios of IgG4-positive plasma cells[21]. Specifically, cases of MALT lymphoma showing either a high number of IgG4-positive cells (more than 100 per 0.14 mm² in the area with the highest number or a high IgG4/IgG-positive cell ratio (exceeding 30%) were categorized as IgG4-MALT lymphoma[16]. Additional histopathological features such as diffuse sclerosis or obliterator phlebitis were also considered as supportive features of IgG4-MALT lymphoma.

RESULTS
Of 80 patients who had the diagnosis of ocular adnexal IgG4-related disease, histopathologic diagnosis of IgG4-MALT lymphoma was made in seven patients. Clinical presentation, imaging and pathologic findings of the patients were as follows.

Clinical Presentation
Five of the seven patients (Patient 3, 4, 5, 6, 7) presented to the Department of Ophthalmology with the upper eyelid swelling, which began several months to a year ago. One patient (Patient 1) presented with erythema and swelling of the upper eyelid. One patient (Patient 2) sought ophthalmology consultation because of diplopia, which developed one year ago. The serum IgG and IgG4 levels were available in three patients: Patient 4 (IgG: 28 mg/dL (<135 mg/dL); IgG4: 983 mg/dL (700-1600 mg/dL)), Patient 6 (IgG: 1230 mg/dL; IgG4: 330 mg/dL), and Patient 7 (IgG: 981 mg/dL; IgG4: 330 mg/dL). In addition, RF, Anti SS-A/B, and ANA were all negative in Patient 4.

CT and MR Findings
Table 1 provides the summary of CT and MR images of the seven patients. Three of the seven patients had bilateral involvement. With regard to locations, lacrimal glands were the main site of involvement in all seven patients. Multiple locations were involved in three patients: 1) preseptal soft tissue (n=2), 2) retrobulbar fat (n=1), and 3) upper and lower eyelids, extraocular muscles, optic nerve, maxillary nerves, and infraorbital nerve (n=1). A diffusely enlarged lacrimal gland with a well-demarcated margin and a non-lobulated shape was the most common pattern (86% (6 of 7)) in terms of the lesional shape and margin. Two patients had either a diffuse soft tissue lesion with a well-demarcated margin and a lobulated shape or a diffuse soft tissue infiltration. Precontrast CT images were available in two patients. The lesion had homogeneous isosattenuation relative to the gray matter in one patient and homogeneous hyperattenuation in the other patient. Additional MR imaging was obtained in two patients. On T1-weighted images, the lesions were isointense to the gray matter in both patients. On T2-weighted images, however, the lesion was isointense to the gray matter in one patient and hypo- to isointense to the gray matter in the other patient.

After administration of the contrast material, the lesion demonstrated homogeneous enhancement with a CT attenuation higher than that of normal extraocular muscles in six cases. In one of the six patients, the lesion was homogeneously enhanced to a stronger degree than normal extraocular muscles on CT but to a similar degree as the muscles on MR. In one case, the lesion showed heterogeneous contrast enhancement to a similar degree as the muscles on both CT and MR imaging. Bone change was absent in all seven patients. Lymph node or other extraorbital organ involvement were investigated in five
PATHOLOGIC FINDINGS Histopathologic specimens were obtained via incisional biopsy in three patients and excisional biopsy in four patients. Histologically, heavy infiltration of monotonous small lymphoid cells, which showed immunoreactivity for CD20 and kappa or lambda light chain restriction, and plasma cells was characteristic. Focal infiltration of eosinophils and fibrosis were also noted. Immunohistochemical staining for IgG4 demonstrated a predominance of IgG4-expressing plasma cells or plasmacytoid cells. The mean number of IgG4-positive cells and the ratio of IgG4/IgG-positive cells of the cases are provided in Table 2. Representative images of CT, MR imaging and histopathologic specimens in patients 1, 2, and 4 are shown in Figures 1-3.

DISCUSSION Ocular adnexal MALT lymphoma associated with IgG4-related disease was first recognized as a rare complication of ocular adnexal IgG4-related disease by Cheuk et al.[15] in 2008. In the report, two cases manifested as lacrimal gland swelling and one case presented as bilateral proptosis. Sato et al.[19] also suggested that MALT lymphoma may arise in a background of IgG4-related chronic inflammation, based on the finding that immunoglobulin heavy chain gene rearrangement was confirmed in two of their 17 patients diagnosed with ocular adnexal IgG4-related disease. A few other reports pertaining to the ocular adnexal IgG4-related disease displayed B-cell monoclonality followed thereafter, supporting the potential causal relationship between the ocular adnexal IgG4-related disease and MALT lymphoma.[16-18,22] Up to the present, B-cell monoclonality has been shown in approximately 10%-15% of ocular adnexal IgG4-related disease patients.[12,18-19] In this study, the incidence of IgG4-MALT lymphoma among the patients who had the diagnosis of ocular adnexal IgG4-related disease was 9%, in keeping with the previously reported incidence. On the other hand, despite the fact that IgG4-related disease has a predilection for involvement of various organs, including the pancreas and salivary gland, secondary lymphoma has not been documented in organs other than the ocular adnexa.[23-24]. In general, chronic inflammation or autoimmune-related lymphoid hyperplasia has been implicated in the emergence of secondary lymphoma.[15] Specifically, MALT lymphoma has been previously associated with Helicobacter pylori-associated chronic gastritis, Sjögren syndrome, and Hashimoto thyroiditis.[13-14,25-27] It has been speculated that chronic antigenic stimulation by the antigen self or nonself may trigger proliferation of lymphoid cells, which may in turn serve as the substrate for the emergence of autonomous B-cell clones and ultimately malignant lymphoma (often a low grade B-cell lymphoma of MALT type).[17]. In the same context, it has been speculated that chronic hyperplasia of the acquired lymphoid tissue in IgG4-related disease may also be a predisposing factor for secondary lymphoma.[15].

**Table 1 CT and MR imaging findings**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Laterality</th>
<th>Location</th>
<th>Shape</th>
<th>Margin</th>
<th>Precontrast CT density</th>
<th>Postcontrast CT enhancement Pattern</th>
<th>Degree</th>
<th>T1</th>
<th>T2</th>
<th>Enhancement pattern</th>
<th>Enhancement degree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Uni-</td>
<td>Lacrimal gl. (L)</td>
<td>NL</td>
<td>WD</td>
<td>Hyper-</td>
<td>Homo-</td>
<td>Stronger</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Bi-</td>
<td>Lacrimal gl. (R), retrobulbar space (B), preseptal fat (R)</td>
<td>L</td>
<td>WD</td>
<td>Iso-</td>
<td>Homo-</td>
<td>Stronger</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Uni-</td>
<td>Lacrimal gl. (L)</td>
<td>NL</td>
<td>WD</td>
<td>-</td>
<td>Homo-</td>
<td>Stronger</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Uni-</td>
<td>Lacrimal gl. (R)</td>
<td>NL</td>
<td>WD</td>
<td>-</td>
<td>Homo-</td>
<td>Stronger</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Bi-</td>
<td>Lacrimal gl. (R), preseptal fat (R)</td>
<td>NL</td>
<td>WD</td>
<td>-</td>
<td>Hetero-</td>
<td>Similar</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Bi-</td>
<td>Lacrimal gl. (R), upper/lower eyelids (R), optic nerve (R), extraocular muscles (R), CN V2 (B), infraorbital nerve (R)</td>
<td>I</td>
<td>ID</td>
<td>-</td>
<td>Homo-</td>
<td>Stronger</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Uni-</td>
<td>Lacrimal gl. (R)</td>
<td>NL</td>
<td>WD</td>
<td>-</td>
<td>Homo-</td>
<td>Stronger</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Pt.: Patient; R: Right; L: Left; Bi: Bilateral; NL: Non-lobulated; L: Lobulated; I: Infiltrative; WD: Well-demarcated; ID: Ill-defined.

**Table 2 Mean number of IgG4-positive cells and ratio of IgG4/ IgG-positive cells**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean number of IgG4-positive cells (/HPF)</th>
<th>Ratio of IgG4/IgG-positive cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>128</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>230</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>145</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>112</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>93</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>40-50</td>
</tr>
</tbody>
</table>

HPF: High-power field.
There are no universally accepted diagnostic criteria of IgG4-related sclerosing disease, and many researchers adopted different criteria in various occasions or tissue context. A high number of IgG4-positive plasma cells or a high IgG4/IgG-positive cell ratio per se does not suffice to make the diagnosis of IgG4-related disease, because variably high numbers of IgG4-positive plasma cells have been documented in diverse non-specific inflammatory conditions\(^\textsuperscript{[28]}\). Accordingly, histological features, such as dense lymphoplasmacytic infiltrate organized in a storiform pattern, obliterative phlebitis, and a mild-to-moderate eosinophil infiltrate, are known to serve as the fundamental diagnostic clues to IgG4-related disease\(^\textsuperscript{[11]}\). In our study, diagnosis of the underlying IgG4-related disease was based on the combination of characteristic histological features and high numbers of IgG4-positive plasma cells (more than 100 per 0.14 mm\(^2\) in the area with the highest number) or high IgG4/IgG-positive cell ratios (exceeding 30\%)\(^\textsuperscript{[16]}\). Final diagnosis of IgG4-MALT lymphoma made by consensus of two experienced pathologists was based on 2008 WHO classification of hematolymphoid neoplasm, with consideration of the quantity or ratio of IgG4-positive plasma cells\(^\textsuperscript{[21]}\). Ancillary histologic features such as dense fibrosis and obliterative phlebitis were not definite in some cases, possibly because of masking by neoplastic proliferation. On CT and MR imaging, all IgG4-MALT lymphoma cases in this study manifested as either unilateral or bilateral lacrimal gland enlargement, with extension to surrounding soft tissues including the preseptal, extra- or intraconal spaces, upper and lower eyelids, optic nerve, maxillary nerves, and infraorbital nerve in three cases. Typical radiologic findings included 1) well-demarcated margins, 2) iso- to hyperattenuation on precontrast CT images, 3) hypo- to isointensity on T2-weighted
MR images, 4) isointensity on T1-weighted MR images, and 5) homogenous internal architecture with homogenous enhancement pattern. Perilesional bone destruction was not evident in all seven cases. Some of the imaging findings overlapped with those previously reported in ocular adnexal IgG4-related disease-for example, predilection for lacrimal gland involvement, well-defined margins, T1 isointensity, homogenous internal architecture with homogenous enhancement pattern, and absence of perilesional bone destruction have been also described in ocular adnexal IgG4-related disease.[29-31]. However, unlike typical ocular adnexal IgG4-related disease with T2 hypointensity, our cases appeared either partially or completely isointense with respect to normal gray matter on T2-weighted MR images. It has been previously reported that ocular adnexal lymphoma is generally T2 isointense relative to normal gray matter.[32]. Therefore, it may not be surprising that IgG4-related disease, when complicated by MALT lymphoma, has MR signal characteristics similar to those of ocular adnexal lymphoma, and thus shows some T2 isointense portion. Furthermore, unlike typical ocular adnexal IgG4-related disease with isodensity on precontrast CT, case 1 was hyperdense to normal gray matter with a CT attenuation of 45 Hounsfield unit (HU), which is consistent with the previously reported value of 46 HU for orbital lymphoma.[29,31,33]

With regard to the postcontrast MR signal intensity, our cases demonstrated iso- or slightly hyperintensity relative to normal extraocular muscles. This finding is in agreement with that of the previous study in which all studied cases of ocular adnexal lymphoma (38 of 38) were shown to be isointense compared with normal extraocular muscles.[33]. On the other hand, the majority of our cases (85% (6 of 7)) had higher attenuation than extraocular muscles on postcontrast CT. The discrepancy may be explained by the early fill-in and early washout dynamic enhancement pattern of orbital lymphoma and scanning time difference between CT and MR imaging.[33]. Specifically, a CT scanner with a relatively short scanning time can acquire images at the early fill-in phase, when the lesion is hyperdense to normal extraocular muscle, whereas an MR scanner usually acquires those after the early washout.

Although the majority of our cases demonstrated homogenous internal architecture with homogeneous enhancement, heterogeneous enhancement was noted in one case (case 5), which showed heterogeneous, T2 hypo- to isointensity. The authors speculated that the heterogeneity in the internal architecture and enhancement pattern may be attributable to uneven histopathological distribution of associated MALT lymphoma in the underlying IgG4-related disease, with T2 isointense area being that mainly involved by lymphoma. In terms of the lesional shape, lobulated shape or a diffuse soft tissue infiltration were apparent in only two cases. Meanwhile, Politi et al.[32] have reported that ocular adnexal lymphoma (without underlying IgG4-related disease) frequently has a well-defined margin with lobulation. A further study with a larger number of cases is warranted to ascertain whether the discrepancy is due to the difference in histopathological background or time interval between symptom onset and the initial imaging work-up.

In conclusion, despite overlapping of imaging features between ocular adnexal IgG4-related disease and IgG4-MALT lymphoma, T2 isointensity and hyperattenuation on precontrast CT images were observed in some IgG4-MALT lymphoma cases, unlike in typical ocular adnexal IgG4-related disease. Although the findings may be nonspecific, our findings suggest that the possibility of accompanying MALT lymphoma may need to be considered, especially when ocular adnexal lesions in patients clinically suspected of having IgG4-related disease (i.e., patients with a past history of IgG4-related disease or elevated serum IgG4 level) are refractory to glucocorticoids and show T2 isointensity and hyperattenuation on precontrast CT. Awareness of the rare but clinically important complication of ocular adnexal IgG4-related disease would help achieve the optimal management of patients with ocular adnexal IgG4-related disease. However, this is a case series of a very rare complication of ocular adnexal IgG4-related disease, and thus caution is warranted to generalize the conclusion.

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