• Letter to the Editor •

A case of IgG4-related ophthalmic disease with bone destruction presenting as unilateral painful blepharitis

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Dear Editor,

I am Yuki Tanaka from Hakodate Central General Hospital, Japan. Mikulicz's disease is characterized by symmetrical swelling of lacrimal and salivary glands. In 2012, a Japanese study group proposed comprehensive diagnostic criteria for immunoglobulin G4-related disease (IgG4-RD)[1]. They have revealed that Mikulicz's disease is a systemic IgG4-RD and attracted attentions of ophthalmologists. In 2014, the criteria for IgG4-related ophthalmic disease (IgG4-ROD) were established. In 2023, the criteria for IgG4-ROD have been revised, composed of the following 3 major factors: 1) imaging examination shows enlargement of affected ocular adnexal tissues such as the lacrimal glands, trigeminal nerves, and extraocular muscles; 2) histopathological features of orbital mass lesions include infiltration of $IgG4^+$ plasma cells, fibrosis, and rarely obliterative phlebitis; 3) blood test shows elevated serum IgG4 (>135 mg/dL). Diagnosis is classified as "definitive" if all 3 factors are satisfied[2].

Ophthalmic symptoms of IgG4-ROD are commonly eyelid swelling, dry eye-like symptoms, proptosis, and diplopia[3-4]. Eyelid swellings of IgG4-ROD are typically bilateral and painless[5], but rarely associated with bone destruction.

Here we report a rare case of a man presenting with refractory unilateral blepharitis of IgG4-ROD associated with bone destruction of the paranasal sinuses.

CASE REPORT

Ethical Approval This study was carried out in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patient.

A 49-year-old male was suffering from the right upper eyelid swelling with a continuous pain, which repeated exacerbations and remissions for 11mo. The patient had a history of hypertension. He was given topical corticosteroid treatment, which turned out to be ineffective. He was then referred to our department. At the initial visit, the best-corrected visual acuity was 20/20, and the intraocular pressure was 17 and 18 mm Hg in his right and left eyes, respectively. A subcutaneous elastic hard mass with erythema and tenderness was palpated on the upper eyelid skin of the right eye (Figure 1). Tenderness was also noted on the right lacrimal gland. The right upper eyelid conjunctiva was hyperemic with follicle formation. The slit-lamp examination detected mild cataracts in both eyes, mildly enlarged optic nerve head excavation (vertical cup-to-disc ratio: 0.6), and papillary hemorrhage in the right eye, which implied normal tension glaucoma without any correlation with IgG4-ROD, otherwise unremarkable. The blood examination revealed an elevated serum IgG4 level of 3.43 g/L (reference value: 0.11-1.21 g/L). Serum C-reactive protein, erythrocyte sedimentation rate, and fibrinogen levels were 1.37 mg/dL (reference value: 0-0.30 mg/dL), 53 mm/h (reference value: 2-10 mm/h), and 484 mg/dL (reference value: 150-400 mg/dL), respectively. Soluble interleukin-2 receptor was 343 U/mL (reference value: 157-474 U/mL). Contrast-enhanced CT showed enlargement of the right lacrimal gland and a contiguous subcutaneous mass lesion with contrast enhancement at the right upper eyelid (Figure 2A). There were bone defects in the inferior wall of the right frontal sinus and the inner walls of bilateral maxillary sinuses (Figure 2B, 2C). An incisional biopsy of the subcutaneous mass was performed. Histopathologic findings showed extensive inflammatory cell infiltration and mild fibrosis. There was a marked

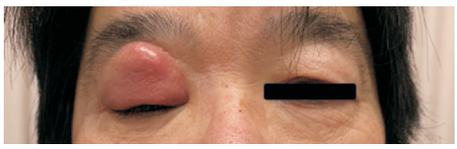

Figure 1 External eye finding (at the initial visit) The patient presented with redness and swelling of the right upper eyelid. He had ptosis and difficulty opening the eyelid.

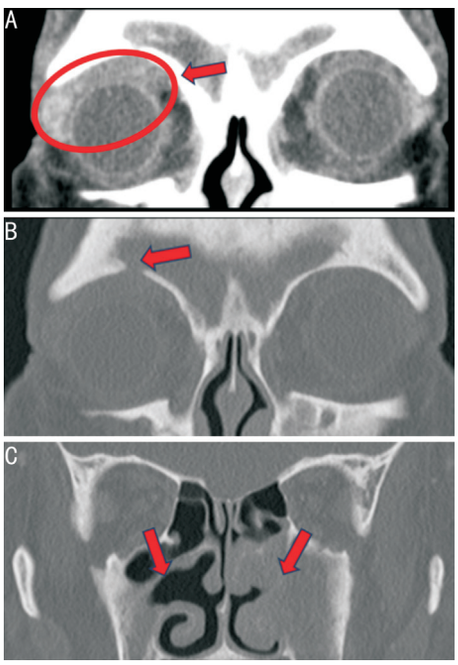

Figure 2 Coronal contrast-enhanced CT (at the initial visit) CT scans show enlargement of the right lacrimal gland and a mass lesion with enhancement at the right upper eyelid (A), with bone defects in the inferior wall of the right frontal sinus (B) and the inner walls of both maxillary sinuses (C). CT: Computed tomography.

infiltration of lymphocytes and plasma cells with spindle cell proliferation (Figure 3A). Elastica-Masson staining revealed obliterative phlebitis (Figure 3B). Immunohistochemical study demonstrated that the ratio of $IgG4^+$ to IgG^+ plasma cells was approximately 15% and there were more than 50 $IgG4^+$ plasma cells per high-power field (at ×400 magnification) (Figure 3C) where alpha-smooth muscle actin $(\alpha SMA)^+$ spindle cells were intermingled (Figure 3D). In contrast, anaplastic lymphoma kinase (ALK) was negative in spindle cells (data not shown). In this case, enlargement of the right lacrimal gland, existence of over 50 $IgG4^+$ plasma cells per high-power field, and elevated serum IgG4 level met all the 3 factors necessary for a definitive diagnosis of IgG4-ROD. As soon as a definitive diagnosis was made, oral corticosteroid therapy from prednisolone 30 mg/d was administered. After 3mo, the right eyelid swelling has improved (Figure 4). A contrast-enhanced CT scan showed that the mass lesion significantly reduced in size (Figure 5). At present, he is on a maintenance dose of prednisolone 5 mg/d, and he has had no sign of recurrence for 10mo.

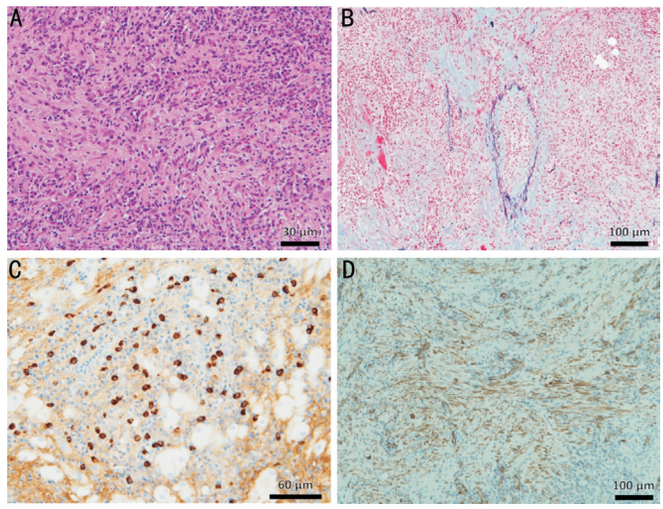

Figure 3 Histopathological findings A: Hematoxylin and eosin staining: infiltration of lymphocytes/plasma cells intermingled with spindle cells; B: Elastica-Masson staining: obliterative phlebitis; C: Immunohistochemical staining for IgG4: over 50 $IgG4^+$ plasma cells per high-power field (at ×400 magnification); D: Immunohistochemical staining for αSMA: αSMA^+ spindle cell proliferation. IgG4: Immunoglobulin G4; αSMA: Alpha-smooth muscle actin.

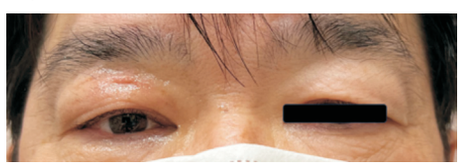

Figure 4 External ocular finding (3mo after commencing therapy) Eyelid redness and swelling have improved.

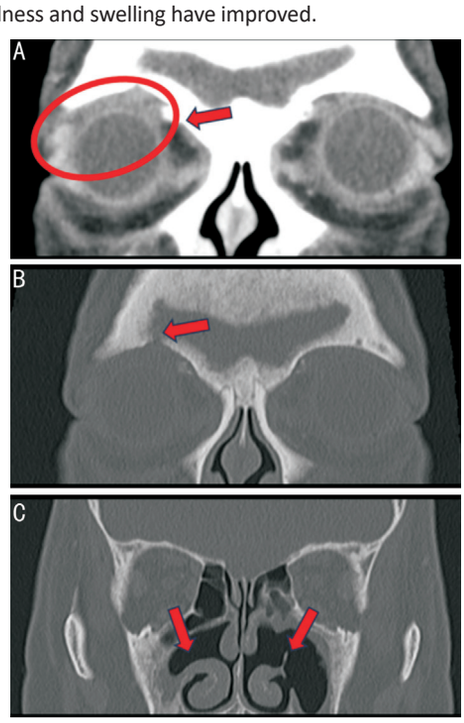

Figure 5 Coronal contrast-enhanced CT (3mo after commencing therapy) A, B: The orbital mass lesion has significantly reduced in size; C: Bone destruction has remained. CT: Computed tomography.

DISCUSSION

Goto *et al*[3] conducted a multicenter study to elucidate the

clinical features and symptoms of IgG4-ROD. The lacrimal glands were the most commonly affected site (86%), while eyelids were less commonly affected site (12%). In addition, dry eye was the most frequent ophthalmic symptom of the patients (22%), followed by diplopia (20%), decreased visual acuity (8%), and visual field defect (5%)[3]. In another report, eyelid swelling was the most frequent ophthalmic symptom (74%), followed by dry eye (49%), proptosis (12%), and decreased vision (2.7%)[5]. Although eyelid swelling is frequently observed in IgG4-ROD, it is usually painless. A report indicates that only 17% of patients suffered from pain associated with eyelid swelling or mass lesions[5].

This is a rare case because of unilateral painful eyelid swelling, requiring it to be distinguished from other inflammatory disorders such as chalazion and orbital cellulitis, and idiopathic orbital inflammation. Moreover, IgG4-ROD needs to be distinguished from other diseases such as mucosa associated lymphoid tissne (MALT) lymphoma and granulomatosis with polyangiitis. Therefore, histological examinations would be necessary to make a correct diagnosis. A few representative cases of IgG4-ROD with bone destruction and cranial nerve involvements have been reported in the past[6-7]. The first case is about a woman in her 20s who presented with unilateral otalgia, hearing loss, and vertigo. She also had a mild sixth nerve palsy. A contrast-enhanced CT scan revealed the destruction of the left mastoid air cells and petrous bones. Histology confirmed prominent infiltration of $IgG4^+$ plasma cells, storiform fibrosis, and scattered spindle cells[6]. The second case is about a 46-year-old man who had swelling excised from the right upper gingival area. A nasofacial lesion slowly developed superior to the surgical site and extended to the upper and lower eyelids, associated with conjunctival chemosis and proptosis. A CT scan revealed an orbital mass with osteolysis of the right sphenoid bone. Histopathologically, abundant fibrocollagenous tissue and obliterative phlebitis were observed with marked $IgG4^+$ plasma cells[7].

Our case shares similar findings of unilateral eyelid lesions complicated by bone destruction with the two above cases. The fact that systemic corticosteroid therapy was effective implies that inflammation of IgG4-ROD would be correlated with bone destruction, although its mechanism is uncertain. In our case, corticosteroid therapy was quite effective. If this case had been steroid-resistant, rituximab would be another treatment option as a steroid-soaring agent[8].

Inflammatory myofibroblastic tumor (IMT) is a neoplasm composed of myofibroblastic and fibroblastic spindle cells accompanied by inflammatory cells[9]. Histopathological findings of IMT are characterized by the presence of neoplastic proliferation of myofibroblasts with low malignant potential. IMT is known to be positive for αSMA in spindle cells in almost all cases[10-11]. Moreover, IMT is reported to cause bone destruction[12]. Although ALK is immunohistochemically negative, our case has IMT-like features such as αSMA^+ myofibroblast infiltration with bone destruction. Indeed, the role of myofibroblast infiltration in IgG4-ROD has not been well analyzed; however, this study suggests that the existence of αSMA^+ myofibroblasts might play a potential role in the more invasive nature of IgG4-ROD.

In conclusion, this is a rare case of IgG4-ROD because the subcutaneous mass lesion was painful and associated with bone destruction. Refractory eyelid skin lesions should be considered a possible diagnosis with IgG4-ROD.

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Conflicts of Interest: Tanaka Y, None; **Kase S,** None; **Matsuno Y,** None; **Nakazato S,** None; **Ishida S,** None.

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