IgG4-related Inflammation of the Orbit Simulating Malignant Lymphoma

SATORU KASE[1], MIKA NODA[1], KAN ISHIJIMA[1], TEPPEI YAMAMOTO[1], KANAKO HATANAKA[2] and SUSUMU ISHIDA[1]

[1]*Department of Ophthalmology, Graduate School of Medicine, Hokkaido University, Sapporo, Japan;*
[2]*Department of Surgical Pathology, Hokkaido University Hospital, Sapporo, Japan*

Abstract. *Immunoglobulin (IgG) 4-related disease is characterized by elevated serum IgG4 and tissue infiltration by IgG4-positive plasma cells. We report a case of IgG4-related inflammation of the orbit simulating extranodal marginal zone B-cell lymphoma (EMZL). A 72-year-old female complained of bilateral eyelid swelling for three years. A MRI scan demonstrated two kinds of lesions, tumor 1, presenting with a predominantly low density, and tumor 2, of relatively high density. Laboratory tests showed high serum IgG4 concentrations, measuring 991 mg/dl. Partial resection of each tumor was conducted in September 2011. Based on the clinicopathological findings, tumors 1 and 2 were diagnosed as IgG4-related inflammation and EMZL, respectively. The patient initially received oral prednisolone at 30 mg/per day, followed by irradiation with a total dosage of 30 Gy to both eyes. The bilateral tumors consequently diminished, and she is currently well with no recurrence or systemic involvement. In conclusion, EMZL can arise from massive IgG4-related orbital inflammation. Since IgG4-related inflammation can represent multiple nodular lesions, biopsies from multiple sites within the lesion are required to make a correct diagnosis in selected cases. Oral prednisolone combined with radiotherapy is an effective treatment for patients with IgG4-related ophthalmic disease simulating EMZL.*

Immunoglobulin (IgG) 4-related disease is characterized by elevated serum IgG4 and tissue infiltration by IgG4-positive plasma cells (1, 2); however, the natural course of the disease remains largely unknown. We recently reported a case of bilateral IgG4-related dacryoadenitis, which spontaneously regressed without any treatment (3). In contrast, a few reports disclosed that extranodal marginal zone B-cell lymphoma (EMZL) can arise from IgG4-related dacryoadenitis (4, 5). We herein report a case of IgG4-related inflammation of the orbit simulating EMZL.

Correspondence to: Satoru Kase, Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Nishi 7, Kita 15, Kita-ku, Sapporo 060-8638, Japan. Tel: + 81 117065944, Fax: + 81 117065948, e-mail: kaseron@med.hokudai.ac.jp

Key Words: IgG4, inflammation, lymphoma, orbit.

Case Report

A 72-year-old female complained of bilateral eyelid swelling for three years. Since orbital tumors were detected at the initial clinic, she was referred to Hokkaido University Hospital on September 12th, 2011. She had a medical history of bronchial asthma, hypertension, and hyperlipidemia. The patient exhibited bilateral superior and inferior eyelid swelling (Figure 1 A). Multiple subcutaneous masses were palpable without pain. Laboratory tests showed high serum IgG4 and IgE concentrations, measuring 991 mg/dl and 389 U/ml, respectively, while serum IgG was almost normal (1.755 mg/dl). T2-Weighted magnetic resonance imaging (MRI) demonstrated massive bilateral lesions adjacent to the orbicularis oculi muscle of the eyelid extending to the deep orbit (Figure 1 B-D). There were two kinds of lesions, tumor type 1, presenting with a predominantly low density, and tumor type 2 with a relatively high density (Figure1 E).

Each orbital tumor tissue was partially removed to confirm the histopathological diagnosis following a subciliary cutaneous incision. During the operation, tumor type 1 was a hard whitish nodule, while tumor 2 was a soft pink nodule. Tumor type 1 histologically demonstrated cellular infiltration together with fibrosis and lymphoid follicle formation (Figure 2 A). At a high magnification, the tissue consisted of an aggregation of plasma cells and small lymphocytes admixed with blood vessels and fibroblasts (Figure 2B). Marked cluster of differentiation (CD) 138-positive plasma cells infiltrated outside the lymphoid follicle (Figure 2C). Marked IgG4 immunoreactivity was also detected in the tissue (Figure 2 D). Infiltrating small lymphocytes were CD20-positive B-cells, especially in the lymphoid follicle (Figure 2E). Orbital tissue from tumor 1 showed no IgH gene

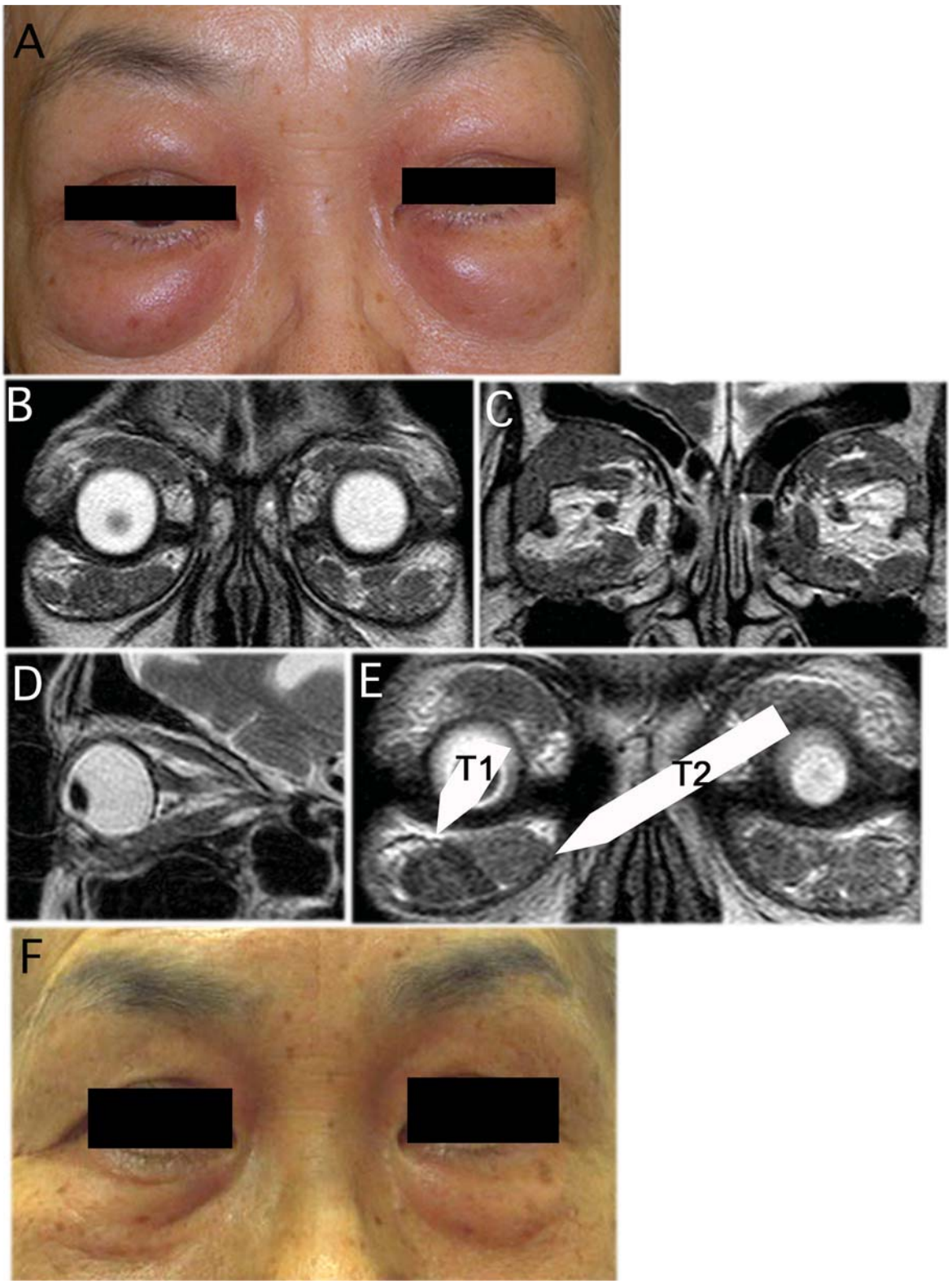

Figure 1. *Facial photograph before and after treatment (A and F, respectively), and magnetic resonance imaging (MRI) at the initial presentation (B-E). A: The patient exhibits bilateral superior and inferior eyelid swelling without pain. B-D: T2-Weighted MRI demonstrates massive bilateral orbital lesions from the subcutaneous layer to deep orbit with a low density. E: There are two kinds of lesion, one presenting with a low density (tumor type 1, T1) and are with relatively high density (tumor type 2, T2). F: Eyelid swelling completely resolved after treatment.*

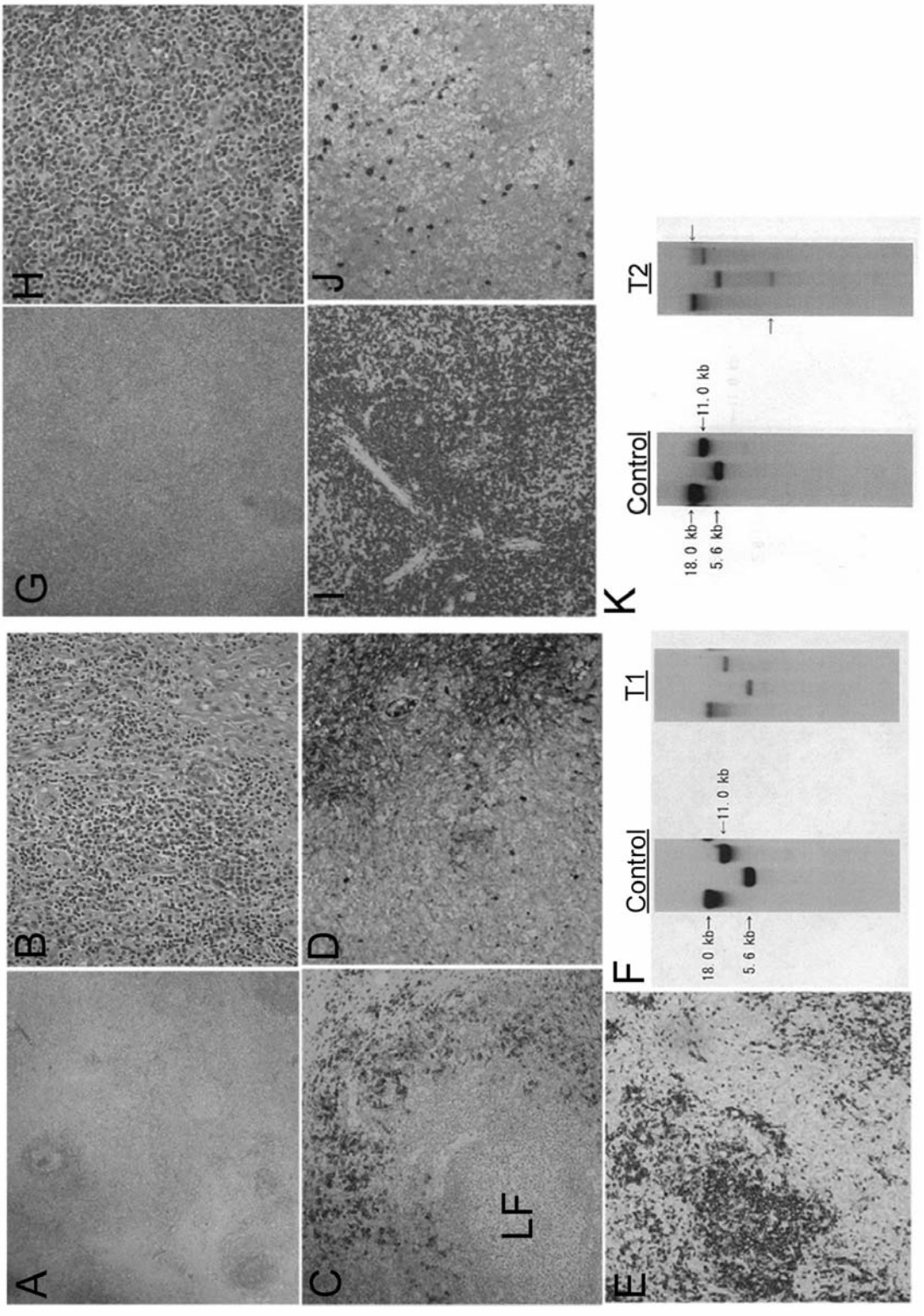

Figure 2. *Pathological analyses of tumor type 1 (A-F) and tumor type 2 (G-K). Hematoxylin and eosin staining (A, B, G, H) and immunoreactivity for cluster of differentiation (CD) 138 (C), immunoglobulin (IgG) 4 (D, J), and CD20 (E, I), and immunoglobulin heavy chain (IgH) gene rearrangement (F, J). A: Tumor type 1 demonstrates cellular infiltration together with fibrosis and lymphoid follicle formation. B: At a high magnification, the tissue consists of an aggregation of small lymphocytes and plasma cells admixed with blood vessels and fibroblasts. C: Marked CD138-positive plasma cells infiltrate outside the lymphoid follicle (LF). D: IgG4 immunoreacitivity is strongly detected in the tissue. E: CD20-positive B-cell infiltration is observed. F: Orbital tissue from "tumor type 1 (T1)" shows no IgH gene rearrangement, determined by Southern blot analysis. G: Tumor 2 demonstrates marked cellular infiltration without fibrosis or lymphoid follicle formation. H: At a high magnification, there is an aggregation of small-sized atypical lymphoid cells. I: CD20-positive lymphoid cells are markedly observed in the tissue. J: Several IgG4-positive cells infiltrate the tissue. K: IgH gene rearrangement is detected in tumor type 2 (T2) tissues. (Original magnification: A, C, D, E, G, I, J ×40; B, H ×100).*

rearrangement as determined by Southern blot analysis (Figure 2 F). In contrast to tumor type 1, tumor type 2 histologically exhibited dense cellular infiltration without fibrosis or lymphoid follicle formation (Figure 2 G). At a high magnification, there was a collection of small-sized atypical lymphoid cells, which were CD20-positive (Figure 2 H and I), in the tissue. Several IgG4-positive plasma cells infiltrated the tissue (Figure 2 J). Southern blot analysis verified IgH gene rearrangement of the JH region in tumor type 2 tissues (Figure 2 K). Flow cytometry showed a large population of CD20-positive cells, comprising 52.1% in tumor 2 tissue compared to tumor type 1 (30.1%). Based on the pathological findings, tumor type 1 and 2 were diagnosed as IgG4-related inflammation and EMZL, respectively. A systemic survey showed no other lesions related to lymphoproliferative disorders except for ophthalmic regions. The patient initially received oral prednisolone at a dose of 30 mg/per day for three months, which was then tapered gradually. After starting oral prednisolone, a number of orbital masses were reduced; however, a few masses remained unchanged, being consistent with EMZL. The patient underwent 30-Gy X-ray irradiation in total to both eyes one month after starting prednisolone. After oral prednisolone at 5 mg had been administered, the bilateral tumors diminished. The patient is currently well with no recurrence or systemic involvement (Figure1 F).

Discussion

Recently, IgG4-related ophthalmic disease includes not only dacryoadenitis, but also other orbital tissue involvements such as the infraorbital nerve (6). In the present case, IgG4-related inflammation involved the orbit including the lacrimal gland adjacent to the orbicularis oculi muscle, which indicated that IgG4-related inflammation can develop in the massive orbital soft tissue. Previous reports demonstrated that EMZL can arise from IgG4-related dacryoadenitis (4, 5), based on the histopathology from one biopsy specimen of the lesions. This study also demonstrated typical histological IgG4-related inflammation in tumor type 1, containing IgG4-positive plasma cells and fibrosis together with CD20-positive small lymphocytes without *IgH* gene rearrangement. In contrast, tumor type 2 revealed marked CD20-positive atypical lymphoid cell infiltration with *IgH* gene rearrangement, admixed with IgG4-positive plasma cells. These findings suggest that the EMZL arose from massive IgG4-related orbital inflammation, verified by two biopsy samples.

In this case, IgG4-related inflammation presented with multiple nodular lesions in the orbit. In addition, there were two different kinds of tumors in the lesions based on MRI and surgical microscopy findings before biopsy. Therefore, we decided to partially remove each tumor, leading to correct diagnoses of IgG4-related inflammation and EMZL with typical pathological findings. However, if ophthalmologists or surgeons had removed only one tumor tissue, they might have missed the inflammation or malignancy. This would have led to insufficient treatment or overtreatment. Therefore, since IgG4-related orbital inflammation can represent multiple nodular lesions, biopsies from multiple sites within the lesions are required to make a correct diagnosis in selected cases.

Corticosteroids are known to be effective for treating patients with IgG4-related inflammatory diseases (7). In contrast, radiation therapy has been conducted in selected patients with IgG4-related ophthalmic inflammation, while the efficacy of the therapy varies in each case (8). Moreover, effective treatments for IgG4-related disease simulating malignant lymphoma have yet to be determined. Oyama *et al*. demonstrated a case of systemic multifocal EMZL expressing IgG4, which was treated with combination chemotherapy consisting of rutuximab, pirarubicin, cyclophosphamide, vincristine and prednisolone (9). This case showed massive IgG4-related inflammation as well as EMZL in the ophthalmic region, the former of which can potentially lead to the onset of malignant lymphoma. Therefore, we decided to treat the patient with initial oral prednisolone followed by radiotherapy to both eyes. After starting prednisolone, the volumes of the orbital and eyelid masses markedly decreased, which contributed to avoiding overexposure to irradiation. In fact, no recurrence has yet been noted, with a favorable cosmetic appearance. Oral prednisolone followed by radiotherapy may be a useful treatment for patients with IgG4-related ophthalmic disease simulating EMZL.

References

1 Yamamoto M, Takahashi H, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Shinomura Y and Imai K: A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. Mod Rheumatol *16*: 335-340, 2006.

2 Kawano M, Yamada K, Kakuchi Y, Ito K, Hamano R, Fujii H, Inoue R, Matsumura M, Takahira M, Zen Y, Yashie A, Nakashima A and Yamagishi M: A case of immunoglobulin G4-related chronic sclerosing sialadenitis and dacryoadenitis associated with tuberculosis. Mod Rheumatol *19*: 87-90, 2009.

3 Kase S, Yamamoto T, Ishijima K, Noda M and Ishida S: Spontaneous regression of IgG4-related dacryoadenitis. Mod Rheumatol 2012 Aug 11. [Epub ahead of print] doi: 10.1007/s10165-012-0728-4

4 Sato Y, Ohshima K, Takata K, Huang X, Cui W, Ohno K and Yoshino T: Ocular adnexal IgG4-producing mucosa-associated lymphoid tissue lymphoma mimicking IgG4-related disease. J Clin Exp Hematop *52*: 51-55, 2012.

5 Cheuk W, Yuen HK, Chan AC, Shih LY, Kuo TT, Ma MW, Lo YF, Chan WK and Chan JK: Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: A previously undescribed complication of IgG4-related sclerosing disease. Am J Surg Pathol *32*: 1159-1167, 2008.

6 Sogabe Y, Miyatani K, Goto R, Ishii G, Ohshima K and Sato Y: Pathological findings of infraorbital nerve enlargement in IgG4-related ophthalmic disease. Jpn J Ophthalmol *56*: 511-514, 2012.
7 Seki N, Yamazaki N, Kondo A, Nomura K and Himi T: Spontaneous regression of lung lesions after excision of the submandibular gland in a patient with chronic sclerosing sialadenitis. Auris Nasus Larynx *39*: 212-215, 2012.
8 Kubota T, Moritani S, Katayama M and Terasaki H: Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder. Arch Ophthalmol *128*: 577-584, 2010.
9 Oyama T, Takizawa J, Nakamura N, Aoki S, Aizawa Y and Abe H: Multifocal mucosa-associated lymphoid tissue lymphoma associated with IgG4-related disease: A case report. Jpn J Ophthalmol *55*: 304-306, 2011.

Received May 1, 2013
Revised May 21, 2013
Accepted May 22, 2013