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Original Article

Immunoglobulin G4 (IgG4)-Positive or -Negative Ocular Adnexal Benign Lymphoid Lesions in Relation to Systemic Involvement

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The purpose of this study is to determine the relationship of ocular adnexal benign or reactive lymphoid hyperplasia, including orbital pseudotumor, with immunoglobulin G4 (IgG4)-related diseases. Medical charts of 9 consecutive patients with ocular adnexal benign lymphoid lesions, seen in the Department of Ophthalmology, Okayama University Hospital, were reviewed, and pathological sections were restained immunohistochemically for IgG4-, IgG-, and CD138-positive plasma cells. The diagnosis of IgG4-positive lesions was based on 10 or more IgG4-positive plasma cells in a high-power field and greater than 40% ratios of IgG4-positive plasma cells/CD138-positive plasma cells and IgG4-positive plasma cells/IgG-positive plasma cells. IgG4-positive lesions were determined as absent in 5 patients (4 with bilateral lacrimal/orbital lesions and one with a unilateral conjunctival lesion), none of whom showed systemic manifestations. In contrast, IgG4-positive lesions were present in 4 patients (3 with bilateral lacrimal/orbital lesions and one with a unilateral lacrimal/orbital lesion), who showed systemic manifestations : one with Hashimoto thyroiditis, one with IgG4-positive bilateral interstitial lung disease and hepatic inflammatory pseudotumor, one with bilateral interstitial lung disease, and one with systemic lymphadenopathy and antiphospholipid syndrome. In conclusion, IgG4-positive ocular adnexal benign lymphoid lesions might be used as a benchmark for the probable presence of other systemic lymphoid lesions. 〔*J Clin Exp Hematopathol 50(2) : 129-142, 2010*〕

Keywords: IgG4-related disease, ocular adnexal benign (reactive) lymphoid hyperplasia (lesion), orbital pseudotumor, fluorodeoxyglucose (FDG) positron emission tomography fused with computed tomography (PET/CT), interstitial lung disease

INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease is an evolving concept of clinicopathological entity that has not yet been fully established.[1-6] The entity is characterized clinically by high levels of serum IgG4 or pathologically by predominant infiltration of plasmacytic cells with IgG4 expression. The entity includes autoimmune pancreatitis, sclerosing cholangitis, Mikulicz disease (chronic sclerosing dacryoadenitis with sialadenitis),[7-11] Küttner tumor (chronic sclerosing sialadenitis),[12] and retroperitoneal fibrosis. Systemic lymphadenopathy,[13,14] lung and liver inflammatory pseudotumors,[15] interstitial lung disease,[16-18] and tubulointerstitial nephritis[19-21] are also considered as part of IgG4-related disease.

Ocular adnexa is a term to indicate eye globe-supporting tissues in the orbit and includes eyelids, conjunctiva, lacrimal glands, lacrimal sacs, and extraocular muscles. Lymphoproliferative lesions, including both malignant lymphoma and benign lymphoid hyperplasia, frequently involve the ocular adnexa, and present diagnostic challenges to ophthalmologists. Several diagnostic terms, orbital inflammatory pseudotumor,[22,23] sclerosing dacryoadenitis (as part of Mikulicz disease),[7-11] idiopathic orbital inflammation,[24-26] idiopathic extraocular myositis,[27] and reactive lymphoid hyperplasia, have been used to describe benign lymphoproliferative lesions in the orbit. The clinical and pathological differences among these entities remain obscure at the moment. To obtain insight into the pathogenesis of orbital benign lympho-

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proliferative lesions and hence to obtain clinical guidance on such diseases, we reviewed a series of ocular adnexal benign lymphoid lesions from the viewpoint of IgG4 expression in the tissue and clinical characteristics.

PATIENTS AND METHODS

This study included 9 consecutive patients (Table 1) who were seen in the Department of Ophthalmology, Okayama University Hospital, and diagnosed pathologically with benign lymphoproliferative lesions in the ocular adnexa in 7 years from 2003 to 2009. The 9 patients were 3 men and 6 women, with an age ranging from 21 to 91 (mean, 45) years.

Bilateral lacrimal gland masses with or without orbital extension were found in 7 patients : 3 patients without orbital extension and 4 with orbital extension, while a unilateral lacrimal gland mass with orbital extension was found in one patient (Case 3) and a unilateral conjunctival lesion in one patient (Case 8). Of 8 patients with bilateral or unilateral lacrimal and orbital masses, excisional biopsy was approached from the conjunctiva in 3 patients and from eyelid skin incision in 5 patients.

Pathological diagnoses were based on hematoxylin-eosin staining and immunohistochemical staining of 4-μm-thickness sections from the excised tissues fixed with 10% formalin and embedded in paraffin. Immunohistochemistry was performed using an automated slide stainer (BenchMark XT, Ventana Medical Systems, Inc., Tucson, Arizona, USA). Tissue sections were processed by standardized heating pretreatment for antigen retrieval prior to entering the usual immunohistochemical procedures.[14,28] The standard primary antibodies used in this study were CD20 (1:200 dilution, Novocastra, Newcastle, UK), CD3 epsilon (1:50 dilution, Novocastra), CD5 (1:100, Novocastra), and CD10 (1:50 dilution, Novocastra).

Immunohistochemical staining for IgG4 (1:1,000 dilution, mouse monoclonal antibody against human IgG4, Binding Site, Birmingham, UK), IgG (1:10,000 dilution, polyclonal rabbit antibody against human IgG, Dako, Glostrup, Denmark), and CD138 (1:100 dilution, mouse monoclonal antibody against CD138, Dako) was repeated or additionally performed for this study in older cases. Heating at 100˚C for 30 min was carried out as the pretreatment for IgG4 and CD138 staining while digestion with protease 1 for 4 min was performed for IgG staining. For all cases, immunoglobulin light chain restrictions were examined by immunohistochemical staining for the κ and λ chains [mouse monoclonal antibody against human κ (1:100 dilution) and λ (1:200 dilution), Novocastra]. The diagnosis of benign lymphoid lesions was based on immunohistochemical features such as the equal distribution of CD20-positive B cells and CD3-positive T cells, and no light chain restriction to the κ or λ chain.

The number of IgG4-positive plasma cells in the areas with the highest density of IgG4-positive plasma cells was counted in a high-power field with a ×10 eyepiece lens and a ×40 objective lens under a light microscope. The mean number of IgG4-positive plasma cells in 5 high-power fields was calculated for each specimen and scored as follows : less than 10 positive cells/high-power field as negative and 10 or more cells as positive. The positive results were further subdivided into mildly positive (10-29 positive cells/high-power field), moderately positive (30-99 positive cells/high-power field), and markedly positive (more than 100 positive cells/high-power field). In addition, the mean ratio of IgG4-positive plasma cells/CD138-positive plasma cells and the mean ratio of IgG4-positive plasma cells/IgG-positive plasma cells were calculated for 5 high-power fields in each specimen, and a ratio over 40% was interpreted as positive.[14,28]

RESULTS

Pathological features (Table 2)

In the bilateral lacrimal gland tissues in 3 patients (Cases 2, 4, and 6 ; Fig. 1), the unilateral lacrimal gland tissue in one patient (Case 1 ; Fig. 1), and the unilateral conjunctival tissue in one patient (Case 8 ; Fig. 1), the mean number of IgG4-positive plasma cells in a high-power field was 9 or less in the most aggregated areas with IgG4-positive plasma cells, and in addition, both the mean ratio of IgG4-positive plasma cells/CD138-positive plasma cells and the mean ratio of IgG4-positive plasma cells/IgG-positive plasma cells were smaller than 40%. These 5 patients were determined to have IgG4-negative ocular adnexal benign lymphoid lesions. Three (Cases 2, 4, and 6) of the 4 patients with IgG4-negative lacrimal gland lesions showed well-preserved glandular structures with no fibrosis, often accompanied by lymphoid follicle formation (Fig. 1). In contrast, the remaining one (Case 1) of the 4 patients with IgG4-negative lacrimal gland lesions showed fibrosis and glandular tissue destruction with lymphoid follicle formation (Fig. 1). One patient (Case 8) with the IgG4-negative conjunctival lesion showed diffuse infiltration with plasma cells and eosinophils in the subconjunctival regions without lymphoid follicle formation (Fig. 1).

In the bilateral lacrimal gland tissues in 3 patients (Cases 5, 7, and 9 ; Figs. 1, 2, and 3) and the unilateral lacrimal gland tissue in one patient (Case 3 ; Fig. 4), the mean number of IgG4-positive plasma cells in a high-power field was 10 or greater in the most aggregated areas with IgG4-positive plasma cells, and in addition, both the mean ratio of IgG4-positive plasma cells/CD138-positive plasma cells and the mean ratio of IgG4-positive plasma cells/IgG-positive plasma cells were greater than 40%. These 4 patients were determined to have IgG4-positive ocular adnexal benign lymphoid lesions. Three (Cases 3, 7, and 9) of the 4 patients showed marked plasmacytic infiltration, dense fibrosis, lymphoid fol-

Table 1. Clinical characteristics of 9 consecutive patients with ocular adnexal benign lymphoid lesions

Case No./ Sex/Age*	Ophthalmic presentation	Time of orbital biopsy	Method of biopsy	Treatment	Preceding biopsy at another hospital	Systemic manifestations	Serum IgG4 level (% of total IgG)	Other abnormal laboratory findings
1/Female/ 21	Bilateral orbital/lacrimal gland masses	November 2003	Right orbital excisional biopsy	Radiation 20 Gy to right orbital mass	Renal biopsy in 1999, diagnosing IgA nephropathy	IgA nephropathy in 1999 Gallium scan abnormal uptake only in bilateral lacrimal glands in 2003	N.D.	None
2/Male/ 21	Bilateral lacrimal gland masses	May 2006	Bilateral lacrimal excisional biopsy	None	None	None	N.D.	None
3/Male/ 60	Right orbital/lacrimal gland mass	June 2007	Right orbital excisional biopsy	Radiation 20 Gy	None	Hashimoto thyroiditis in December 2007 Abnormal uptake in right orbit and bilateral thyroids on PET/CT	N.D.	None
4/Female/ 45	Bilateral orbital/lacrimal gland masses	December 2007	Complete extirpation of bilateral masses	None	None	None	N.D.	None
5/Male/ 48	Bilateral lacrimal gland masses	March 2008	Bilateral lacrimal excisional biopsy	Oral prednisolone tapered from 30 mg daily	Right axillary lymph node and right pleural biopsy, and transbronchial lung biopsy, showing non-specific inflammation CT-guided left upper lobar mass biopsy, showing adenocarcinoma (All biopsy done in February 2008)	Hepatic inflammatory pseudotumors and bilateral interstitial lung disease IgG4-positive lesion at liver biopsy in March 2008 Adenocarcinoma and IgG4-positive lesions at left upper lobar resection in April 2008 Abnormal uptake in the liver and lung on PET/CT	2,570 mg/dL (47%)	Hyper-γ-globulinemia (3,623 mg/dL) Eosinophilia
6/Female/ 29	Bilateral lacrimal gland masses	July 2008	Bilateral lacrimal excisional biopsy	None	None	None	N.D.	None
7/Female/ 32	Bilateral orbital/lacrimal gland masses	October 2008	Bilateral orbital excisional biopsy	Oral prednisolone tapered from 30 mg daily	Transbronchial lung biopsy at another hospital in August 2008, showing plasma cell infiltration (less than 10% the ratio of IgG4-positive cells/CD138-positive cells)	Cervical and mediastinal lymphadenopathy Bilateral interstitial lung disease Gallium scan abnormal uptake in bilateral lacrimal glands and lungs	233 mg/dL	Hyper-γ-globulinemia (IgG, 4,794 mg/dL)
8/Female/ 91	Right lower bulbar conjunctival mass	December 2008	Right conjunctival excisional biopsy	None	None	Temporary right parotid gland swelling in December 2008	N.D.	None
9/Female/ 60	Bilateral orbital/lacrimal gland masses	August 2009	Bilateral orbital excisional biopsy	None	None	Antiphospholipid syndrome Bilateral inguinal and axillary lymphadenopathy Gallium scan abnormal uptake in bilateral lacrimal glands and trunk	120 mg/dL (7.41%)	Anti-ssDNA Ab Anti-dsDNA Ab Anti-cardiolipin Ab Antinuclear Ab

N.D., not determined ; anti-ssDNA Ab, anti-single-stranded DNA antibody ; anti-dsDNA Ab, anti-double-stranded DNA antibody.
*Age at ophthalmic presentation

Table 2. Histopathology and IgG4 immunohistochemistry in biopsy or excised tissues in 9 consecutive patients with ocular adnexal benign lymphoid lesions

Case No./ Sex/Age	Location of lesions	Surgical approach	Presence of fibrosis	Lacrimal glandular destruction	Presence of follicles	Eosinophilic infiltration	Number of IgG4-positive cells in a high-power field	IgG4-positive cells/ CD138-positive cells ratio (%)	IgG4-positive cells/ IgG-positive cells ratio (%)	IgG4 immunostain determination*
1/Female/ 21	Right orbital/lacrimal gland lesion	Skin incision	Yes	Yes	Yes	Yes	8	12%	12%	Negative
2/Male/21	Right lacrimal gland lesion	Conjunctival incision	No	No	No	No	4	9%	10%	Negative
	Left lacrimal gland lesion	Conjunctival incision	No	No	No	No	4	8%	10%	Negative
3/Male/60	Right orbital/ lacrimal gland lesion	Skin incision	Yes	Yes	Yes	No	41	75%	82%	Positive
4/Female/ 45	Right orbital/ lacrimal gland lesion	Skin incision	No	No	Yes	No	9	10%	13%	Negative
	Left orbital/ lacrimal gland lesion	Skin incision	No	No	Yes	No	9	12%	12%	Negative
5/Male/48	Right lacrimal gland lesion	Conjunctival incision	No	No	No	No	90	89%	90%	Positive
	Left lacrimal gland lesion	Conjunctival incision	No	No	No	No	95	80%	83%	Positive
	Liver	Liver needle biopsy	Yes	Hepatocyte destruction	No	Yes	72	84%	85%	Positive
	Lung	Left upper lobar resection	Yes	Alveolar destruction	No	Yes	56	92%	94%	Positive
6/Female/ 29	Right lacrimal gland lesion	Conjunctival incision	No	No	Yes	No	1	5%	5%	Negative
	Left lacrimal gland lesion	Conjunctival incision	No	No	Yes	No	0	0%	0%	Negative
7/Female/ 32	Right orbital/ lacrimal gland lesion	Conjunctival incision	Yes	Yes	Yes	No	2	4%	5%	Negative
	Left orbital/ lacrimal gland lesion	Conjunctival incision	Yes	Yes	Yes	No	3	6%	5%	Negative
	Right orbital/ lacrimal gland lesion	Skin incision	Yes	Yes	Yes	No	25	52%	55%	Positive
	Left orbital/ lacrimal gland lesion	Skin incision	Yes	Yes	Yes	No	29	56%	55%	Positive
8/Female/ 91	Right conjunctival lesion	Conjunctival incision	No	Not applicable	No	Yes	7	8%	9%	Negative
9/Female/ 60	Right orbital/ lacrimal gland lesion	Skin incision	Yes	Yes	Yes	No	62	92%	92%	Positive
	Left orbital/ lacrimal gland lesion	Skin incision	Yes	Yes	Yes	No	75	89%	90%	Positive

*This is based on both the number of IgG4-positive plasma cells in a high-power field (less than 10 cells as negative and 10 or more cells as positive, mean of 5 counts) and the ratios of IgG4-positive plasma cells/CD138-positive plasma cells and of IgG4-positive plasma cells/IgG-positive plasma cells (over 40%, mean of 5 counts) in a high-power field.

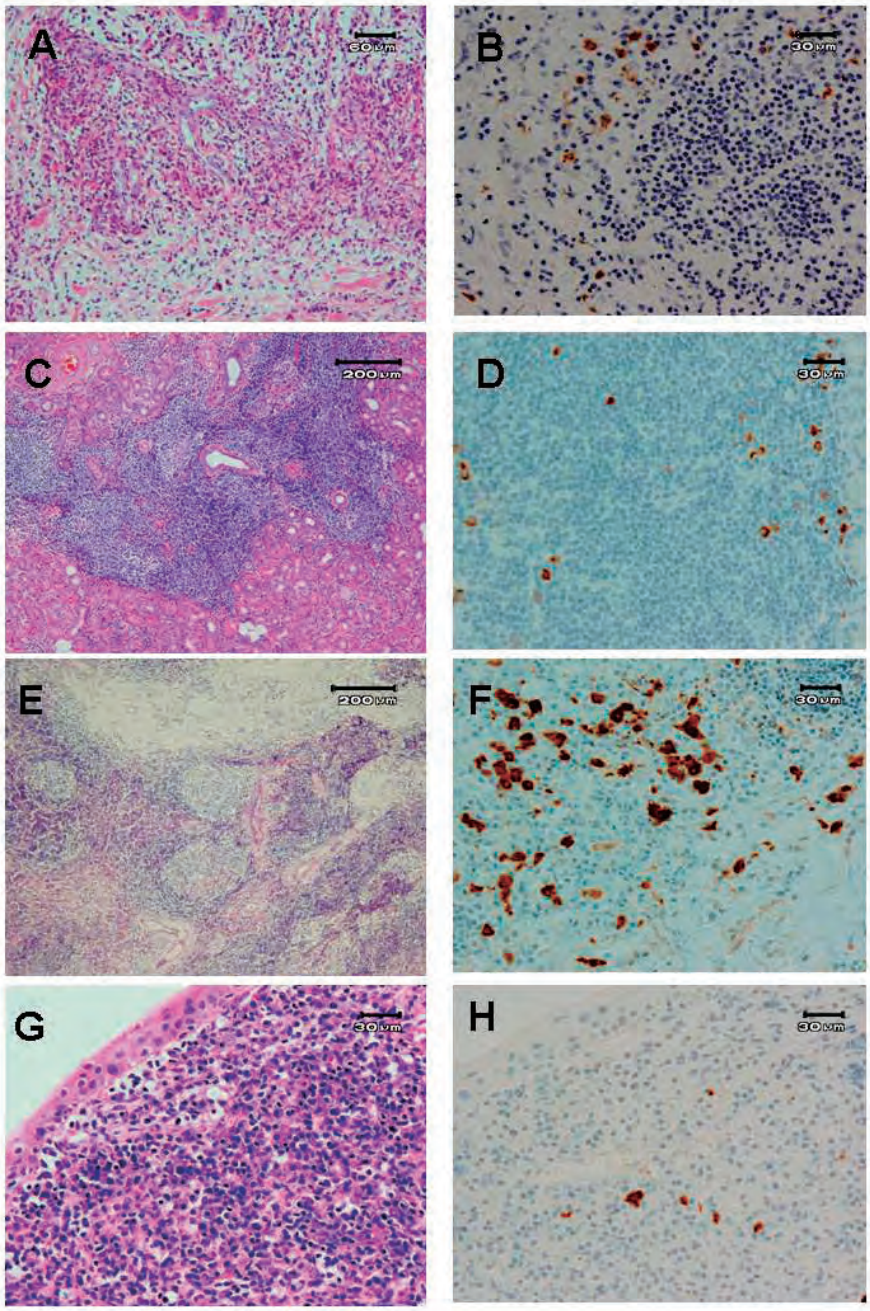

Fig. 1. Hematoxylin-eosin stain (*left column*) and immunohistochemical IgG4 stain (*right column*). Case 1 (right lacrimal gland in *1A* and *B*) : a 21-year-old woman with bilateral lacrimal gland masses and IgA nephropathy, Case 4 (left lacrimal gland in *1C* and *D*) : a 45-year-old woman with bilateral lacrimal gland masses, Case 7 (right lacrimal gland in *1E* and *F*) : a 32-year-old woman with bilateral interstitial lung disease and bilateral lacrimal gland masses, and Case 8 (*1G* and *H*) : a 91-year-old woman with the right unilateral conjunctival mass with temporary right parotid gland enlargement. IgG4-positive plasma cell infiltration is determined as negative in the 3 patients (Cases 1, 4, and 8 ; *1B*, *D*, and *H*). Note fibrosis and lymphoid follicle formation with IgG4-positive plasma cells mainly distributed in the interfollicular areas in Case 7 (*1F*), determined as an IgG4-positive lesion. *Bar* = 30 μm (*1B*, *D*, *F*, *G*, and *H*), 60 μm (*1A*), and 200 μm (*1C* and *E*).

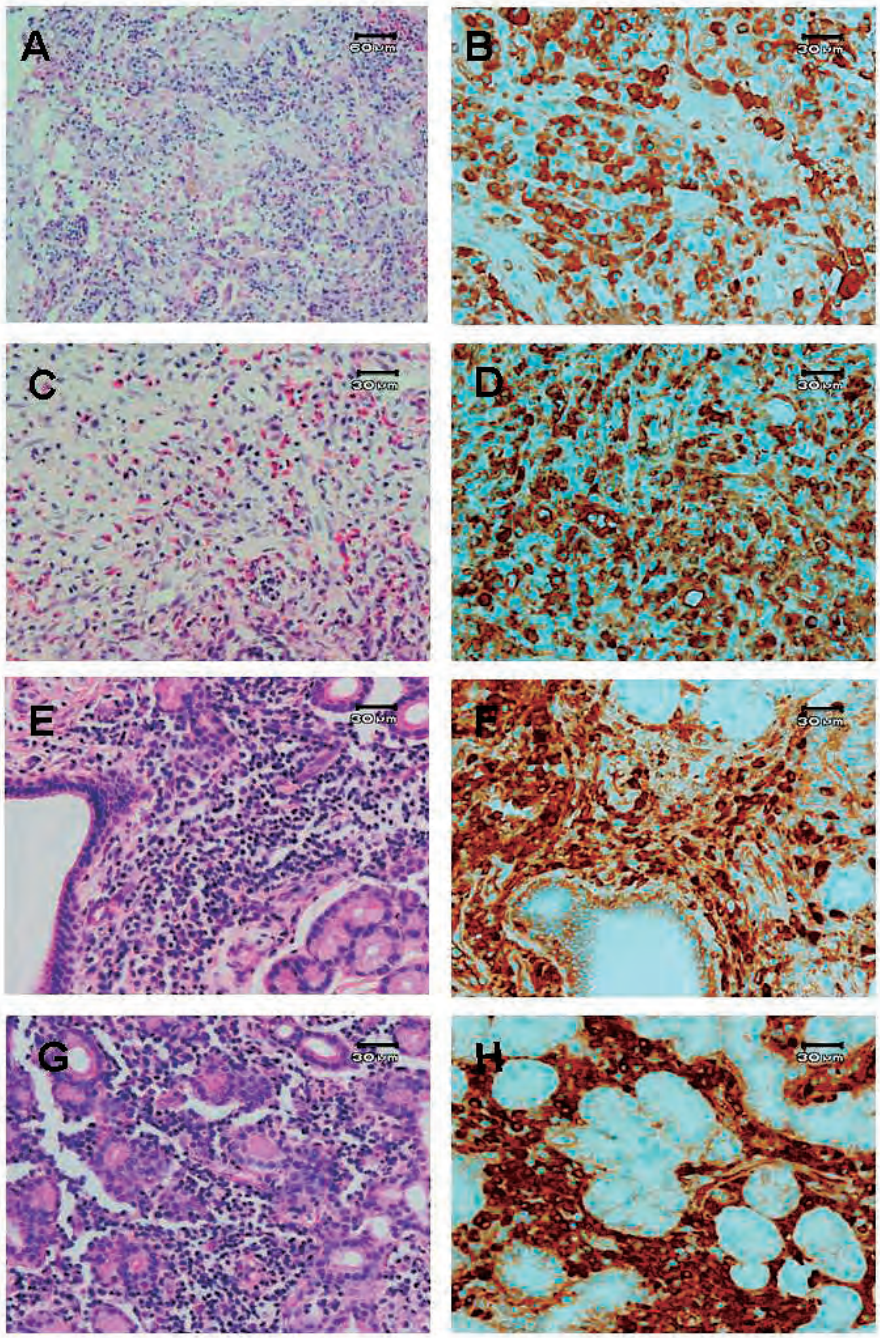

Fig. 2. Case 5, a 48-year-old man with bilateral interstitial lung disease with left upper lobe adenocarcinoma, hepatic inflammatory pseudotumor, and bilateral lacrimal gland masses. Hematoxylin-eosin stain (*left column*) and IgG4 immunohistochemical stain (*right column*). Marked infiltration with IgG4-positive plasma cells in the resected left upper lung lobe (*2A* and *B*), liver needle biopsy specimen (*2C* and *D*), the right lacrimal gland (*2E* and *F*), and the left lacrimal gland (*2G* and *H*). Note eosinophils in the lung (*2A*) and liver biopsy specimen (*2C*) and preservation of the lacrimal glandular structures without fibrosis or lymphoid follicle formation (*2E* and *G*). *Bar* = 60 μm (*2A*) and 30 μm (*2B-H*).

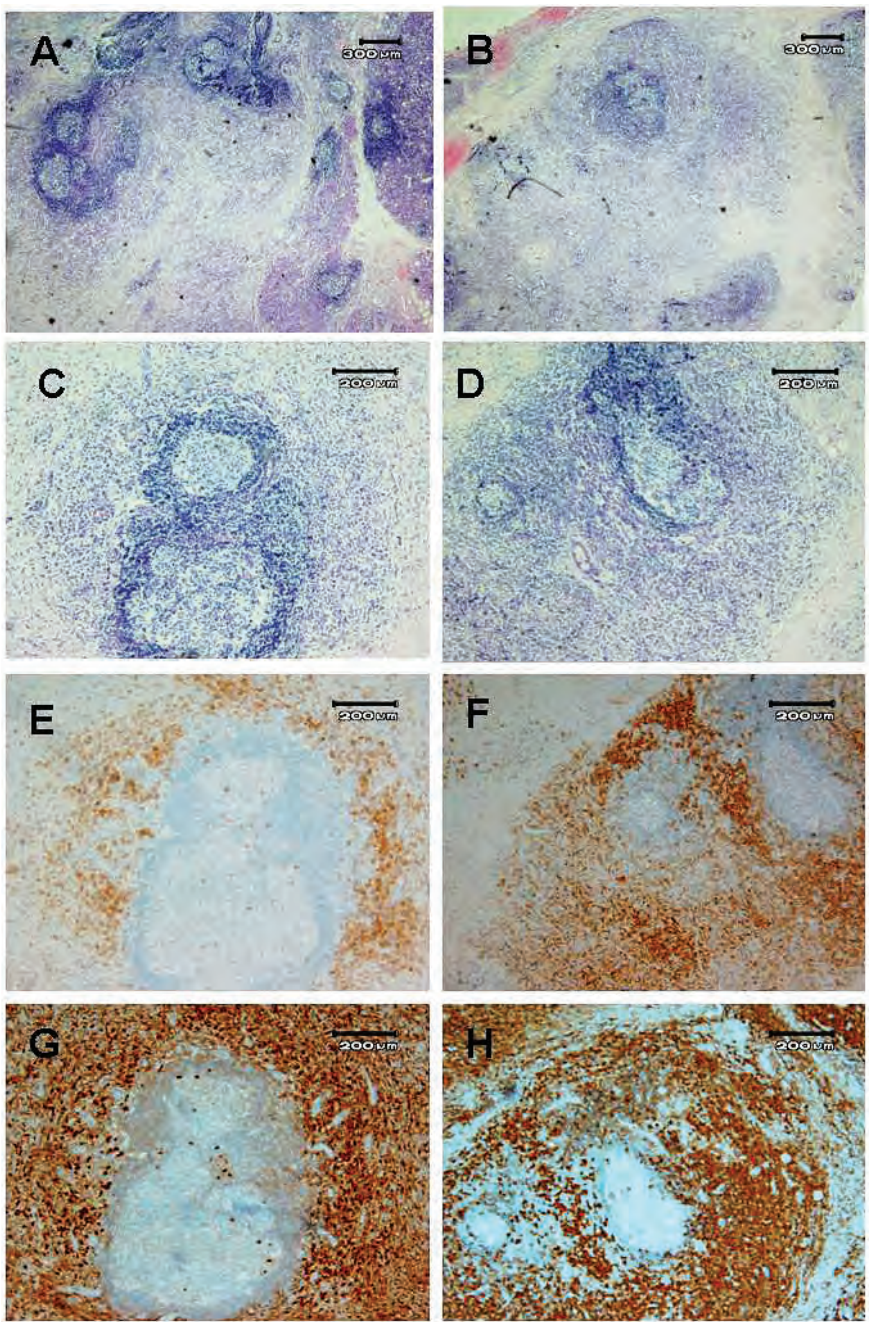

Fig. 3. Case 9, a 60-year-old woman with bilateral lacrimal gland masses, systemic lymphadenopathy, and antiphospholipid syndrome. The right lacrimal gland (*left column*) and the left lacrimal gland (*right column*). Hematoxylin-eosin stain in lower magnification (*3A* and *B*) and higher magnification (*3C* and *D*), immunohistochemical CD138 stain (*3E* and *F*) and IgG4 stain (*3G* and *H*). Note fibrosis and lymphoid follicle formation with IgG4-positive plasma cells mainly distributed in the interfollicular areas. *Bar* = 300 μm (*3A* and *B*) and 200 μm (*3C-H*).

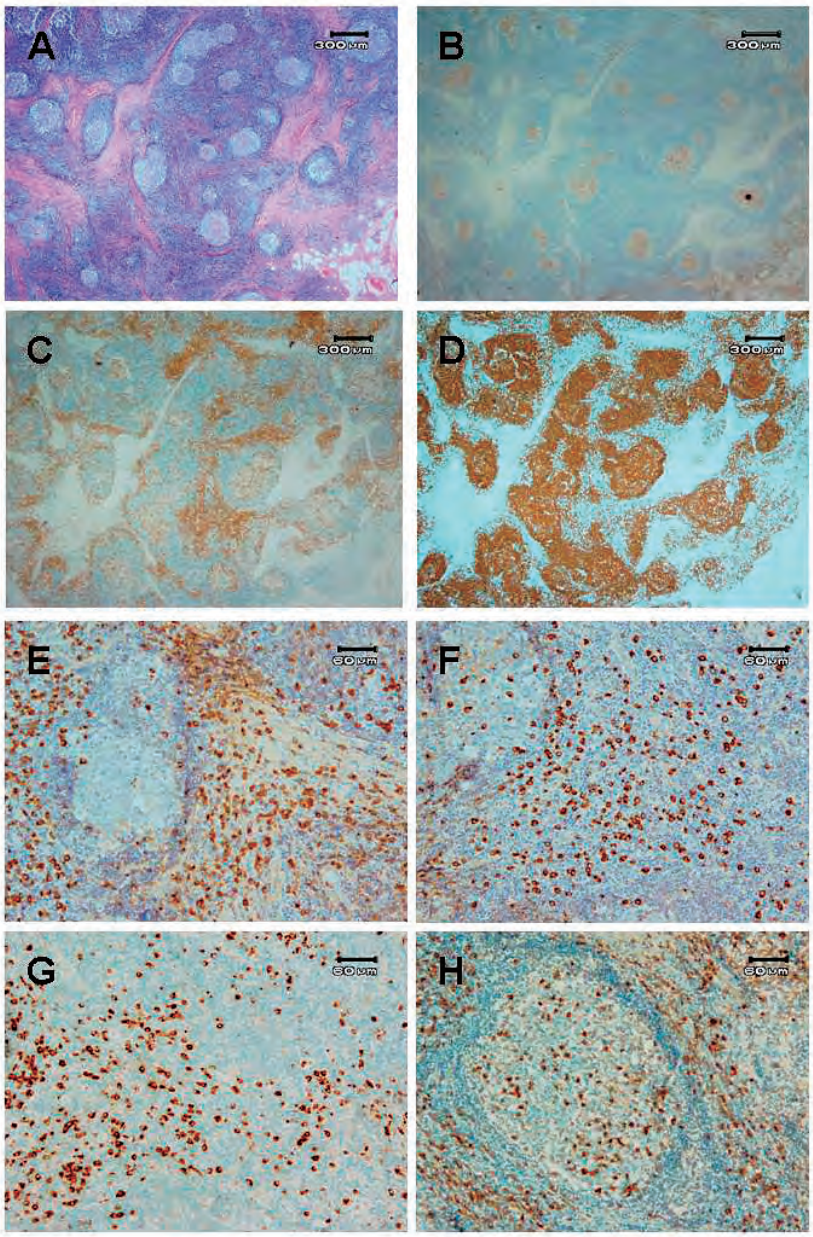

Fig. 4. Case 3, a 60-year-old man with right unilateral lacrimal gland mass and Hashimoto thyroiditis. Hematoxylin-eosin stain (*4A*), immunohistochemical CD10 stain (*4B*), CD3 (*4C*), CD20 (*4D*), κ light chain (*4E*), λ light chain (*4F*), IgG4 (*4G*), and IgG (*4H*). CD20-positive B cells and CD3-positive T cells are found in equal numbers. κ or λ light chain restriction is not observed. Note fibrosis and lymphoid follicle formation with IgG4-positive plasma cells mainly distributed in the interfollicular areas (follicles positive for CD10 ; *4B*). *Bar* = 300 μm (*4A-D*) and 60 μm (*4E-H*).

licle formation, and destruction and atrophy of the lacrimal glandular tissues while the remaining one patient (Case 5 ; Fig. 2) showed marked plasmacytic infiltration around the well-preserved lacrimal glandular structures without fibrosis or lymphoid follicle formation. The IgG4-positive plasma cells were aggregated mainly in the interfollicular areas, but found sparsely inside the follicles in the 3 patients (Cases 3, 7, and 9), while the IgG4-positive plasma cells infiltrated densely around the lacrimal glands in one patient (Case 5 ; Fig. 2). Lymphoepithelial lesions or obliterative phlebitis was not noted in any tissues.

One patient (Case 5 ; Fig. 2) with IgG4-positive benign lymphoid lesions of the bilateral lacrimal glands also had other tissues obtained by lung lobar resection and liver needle biopsy. In both lung and liver tissues, the mean number of IgG4-positive plasma cells in a high-power field was 10 or greater in the most aggregated areas with IgG4-positive plasma cells, and in addition, both the mean ratio of IgG4-positive plasma cells/CD138-positive plasma cells and the mean ratio of IgG4-positive plasma cells/IgG-positive plasma cells were greater than 40%. The lung and liver tissues showed destruction of the alveolar structures and the hepatocytes, respectively, and were replaced by fibrosis in some areas (Fig. 2). Eosinophilic infiltration was found in the lung and liver tissues but lymphoid follicle formation was not noted in either tissue.

Clinical features (Table 1)

Of the 9 patients, 5 patients were determined pathologically to have IgG4-negative ocular adnexal benign lymphoid lesions. Three patients (Cases 2, 4, and 6) showed bilateral lacrimal gland masses without systemic manifestations. These 3 patients were followed without treatment after the pathological diagnosis of benign lymphoid lesions. One patient (Case 1 ; Fig. 5) developed bilateral lacrimal gland masses with orbital extension in the 4-year course of IgA nephropathy under oral prednisolone at 5 mg daily. One patient (Case 8 ; Fig. 6) showed a unilateral conjunctival mass with temporary parotid gland enlargement on the same side.

In contrast, the remaining 4 patients were determined pathologically to have IgG4-positive ocular adnexal benign lymphoid lesions. The first patient (Case 3 ; Fig. 6) showed a unilateral orbital mass extending posteriorly from the lacrimal gland and also developed Hashimoto thyroiditis. He

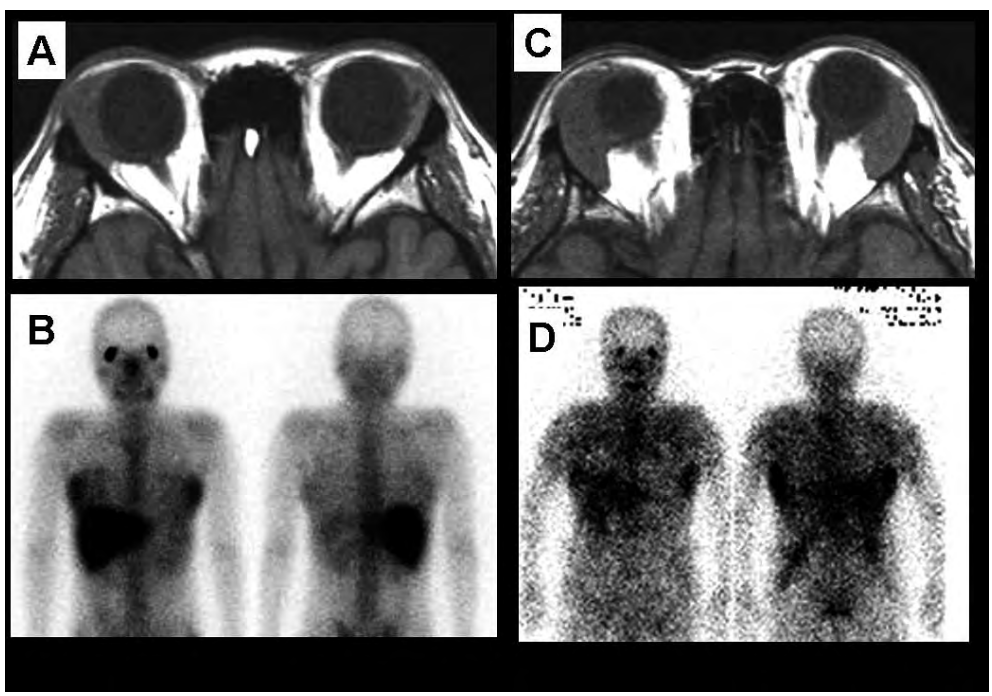

Fig. 5. Case 1 (*left column*) and Case 9 (*right column*). A 21-year-old woman (Case 1) presents bilateral lacrimal gland masses on T1-weighted magnetic resonance imaging (*5A*) in the 4-year-course of IgA nephropathy. Gallium scan shows abnormal uptake only in the bilateral lacrimal glands (*5B*). A 60-year-old woman (Case 9) presents bilateral lacrimal gland masses on T1-weighted magnetic resonance imaging (*5C*) and abnormal gallium scan uptake not only in the bilateral lacrimal glands but also in the body areas corresponding to systemic lymphadenopathy (*5D*).

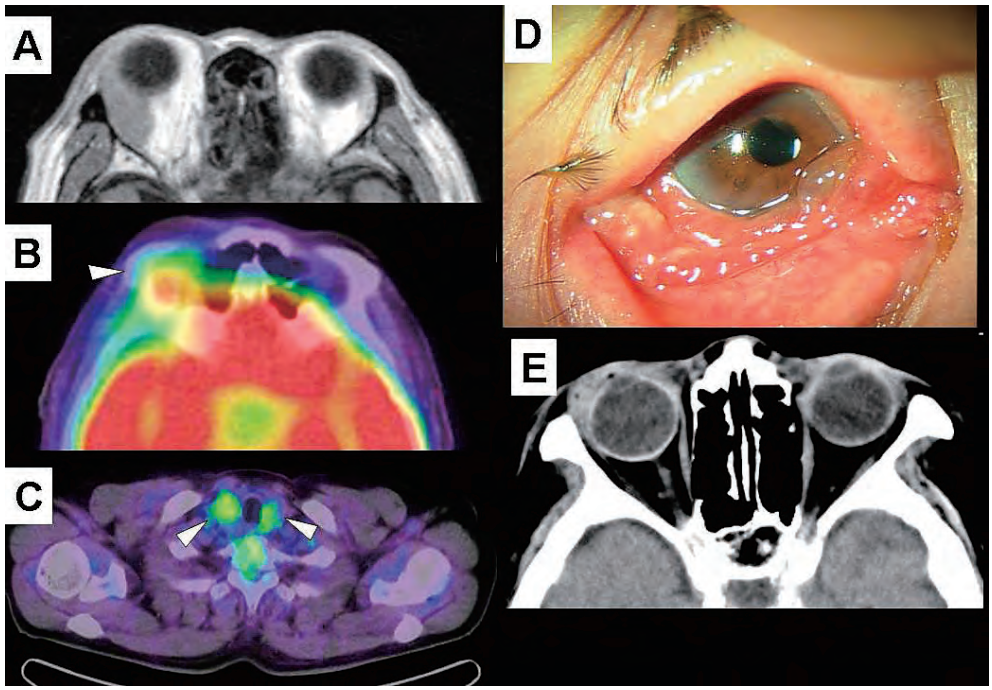

Fig. 6. Case 3 (*left column*) and Case 8 (*right column*). A 60-year-old man presents with a right orbital mass on T1-weighted magnetic resonance imaging (*6A*) and Hashimoto thyroiditis. Fluorodeoxyglucose positron emission tomography fused with computed tomography shows high uptake in the right orbit (*arrowhead* in *6B*, the maximum standardized uptake value : SUVmax = 7.38) and bilateral thyroids (*arrowheads* in *6C*, SUVmax = 3.69). A 91-year-old woman develops right bulbar conjunctival mass (*6D*), which is localized superficially on computed tomographic scan (*6E*).

preferred to undergo 20 Gy radiation for the orbital lesion rather than to take oral steroids. The right orbital residual lesion (the maximum standardized uptake value : SUVmax = 7.38) and the bilateral thyroids (SUVmax = 3.69) showed abnormal uptake in whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography fused with computed tomography (PET/CT) (Fig. 6).

The second patient (Case 5 ; Fig. 7) developed bilateral lacrimal gland masses in the course of liver inflammatory pseudotumors and bilateral interstitial lung disease coupled with lung adenocarcinoma. Before the surgical resection of the left upper lung lobe, FDG-PET/CT demonstrated abnormal uptake in the liver (SUVmax = 3.0), the left upper lung field (SUVmax = 2.2), bilateral hilar and mediastinal regions (SUVmax = 2.8-3.5), corresponding to hepatic pseudotumors, lung adenocarcinoma, hilar and mediastinal lymphadenopathy, respectively. Conjunctivally approached bilateral lacrimal gland biopsy, liver needle biopsy, and lung lobar resection all showed IgG4-positive lesions, leading to the diagnosis of IgG4-related disease. After the lobar resection for lung adenocarcinoma and pathological confirmation of no lymph node metastasis, oral prednisolone, tapered from 30 mg daily, led to the subsidence of symptoms such as fever and cough.

The third patient (Case 7 ; Fig. 7) showed bilateral lacrimal gland masses with orbital extension in association with bilateral interstitial lung disease. Transbronchial lung biopsy at a previous hospital and the initial biopsy of lacrimal gland tissues by the conjunctival approach at this hospital did not prove IgG4-related disease. Consequently, excisional biopsy of the bilateral lacrimal masses by skin incision led to the diagnosis of IgG4-related disease, and oral prednisolone, tapered from 30 mg daily and maintained at 20 mg daily, resulted in recovery from cough and fever caused by the lung disease.

The fourth patient (Case 9 ; Fig. 5) showed bilateral orbital masses in the course of axillary and inguinal lymphadenopathy with antiphospholipid syndrome. Excisional biopsy of the bilateral lacrimal masses led to the diagnosis of IgG4-related disease, and the patient chose observation after the biopsy. Two of 3 patients (Cases 5, 7, and 9), as far as serum IgG4 levels were measured, showed elevated levels of serum IgG4, based on the preliminary criteria (Table 1).[6]

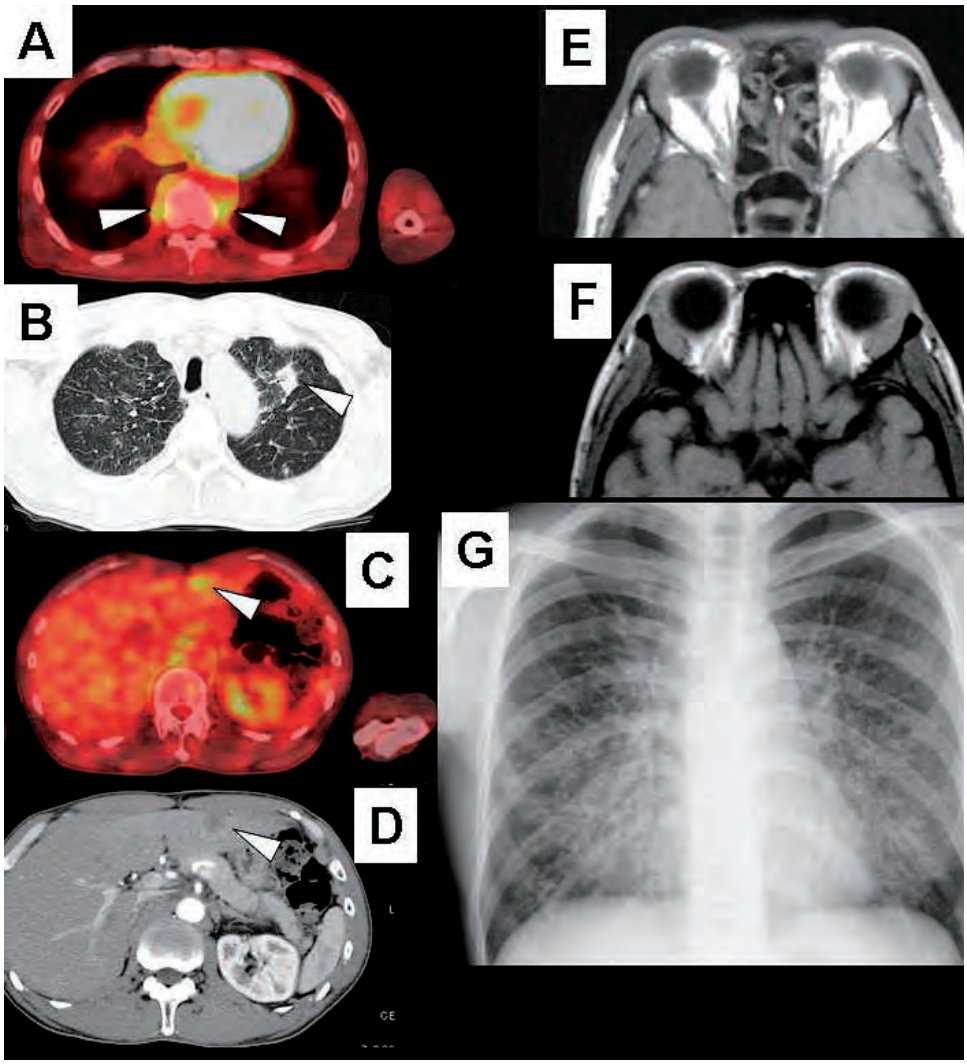

Fig. 7. A 48-year-old man (Case 5) presents a left upper pulmonary lobe mass (*7B*, *arrowhead*), proven to be adenocarcinoma, together with bilateral interstitial lung disease (*7B*), and liver lesions (*7D*, *arrowhead*) on computed tomographic scans. Fluorodeoxyglucose positron emission tomography fused with computed tomography shows high uptake on bilateral hilar and mediastinal regions (*7A*, *arrowheads*, the maximum standardized uptake value : SUVmax = 2.8-3.5) and in the liver (*7C*, *arrowhead*, SUVmax = 3.0). He also shows bilateral lacrimal gland masses on T1-weighted magnetic resonance imaging (*7E*). A 32-year-old woman (Case 7) shows bilateral lacrimal gland masses on T1-weighted magnetic resonance imaging (*7F*) and bilateral interstitial lung disease on plain chest X-ray film (*7G*).

DISCUSSION

The goal of this study is to review clinical characteristics of ocular adnexal benign lymphoid lesions from the standpoint of IgG4-related disease. The ocular adnexa is one of the main sites in the body to develop idiopathic inflammatory lesions referred to by several diagnostic names : orbital inflammatory pseudotumor, idiopathic orbital sclerosis, idiopathic orbital inflammation, and benign or reactive lymphoid hyperplasia.[22-27] These clinical entities do not necessarily have concrete diagnostic bases and are used interchangeably. The established entity of IgG4-related disease involving the ocular adnexa is Mikulicz disease, which refers to idiopathic, bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands.[7-11]

In the present study involving 9 patients with ocular adnexal benign lymphoid lesions, 4 patients with bilateral or unilateral lacrimal gland masses often with posterior orbital extension met the immunohistochemical diagnostic criteria for IgG4-positive lesions. The common clinical features

among these 4 patients were the presence of systemic manifestations in addition to the ocular adnexal lesions : bilateral interstitial lung disease in two patients, hepatic inflammatory pseudotumors in one patient, Hashimoto thyroiditis in one patient, and lymphadenopathy with antiphospholipid syndrome in one patient. Until now, IgG4-related interstitial lung disease,[16-18] IgG4-related hepatic inflammatory pseudotumors,[15] and IgG4-related systemic lymphadenopathy[13,14] have been documented clinically and histopathologically. Hashimoto thyroiditis has also been reported to be associated with IgG4-related retroperitoneal fibrosis,[29,30] and might be classified into IgG4-positive and -negative thyroid lesions on the basis of immunohistochemistry.[31,32] Thus, the 4 patients could be diagnosed with IgG4-related disease with the involvement of bilateral or unilateral lacrimal gland.

In contrast, 5 patients, who did not meet the immunohistochemical diagnostic criteria for IgG4-positive lesions of the ocular adnexa, had no systemic manifestations except for one patient with preceding IgA nephropathy. Until now, tubulointerstitial nephritis has been reported as a renal complication of IgG4-related disease.[19-21] The association of IgA nephropathy with benign lymphoid lesions of the bilateral lacrimal glands in this patient might have only occurred by chance since she has developed no other systemic manifestations during the 6-year follow-up.

Histopathological characteristics among the present series of 9 patients could not provide a simple divide between the 4 patients with IgG4-related disease and the other 5 patients without the disease. Fibrosis, lacrimal glandular destruction, and lymphoid follicle formation as common histopathological features of the bilateral or unilateral lacrimal gland lesions were found in 3 of the 4 patients with the diagnosis of IgG4-related disease. These histopathological points have been described as uniform features of IgG4-related ocular adnexal disease.[28,33] Frequent involvement of bilateral lacrimal glands is also consistent with the uniform clinical features. Eosinophilic infiltration was not a constant finding in either IgG4-positive or -negative ocular adnexal lesions.

In contrast, the remaining one patient (Case 5) with IgG4-related disease showed well-preserved lacrimal glandular structures with marked plasma cell infiltration but without fibrosis or lymphoid follicle formation. These features are not consistent with the previously described uniform pathology of IgG4-related ocular adnexal disease.[28,33] Such discrepancy might be explained by different approaches of the biopsy and different locations of the tissue obtained : the bilateral lacrimal tissues in this patient were excised from the conjunctiva, and thus, might not include the main portion of the disease. Such rationale is supported further by another patient (Case 7) who underwent transconjunctival tissue resection on the initial biopsy and lacrimal gland resection with skin incision on the second biopsy. Only the second excisional biopsy, but not the initial transconjunctival biopsy, proved IgG4-related ocular adnexal disease.

Of the four patients with bilateral lacrimal gland lesions who were not diagnosed histopathologically with IgG4-related disease, three patients showed no fibrosis or lacrimal glandular destruction, often associated with lymphoid follicle formation, while one patient (Case 1) with IgA nephropathy showed fibrosis, glandular destruction, and lymphoid follicle formation. Two patients underwent conjunctival approach for bilateral lacrimal gland biopsy while the other two, including this Case 1 patient, underwent skin incision for lacrimal gland resection. Thus, the present pathological findings are not related to the difference in surgical approaches, either conjunctival or skin incision.

The diagnostic role of whole-body FDG-PET/CT in IgG4-related disease, including Mikulicz disease, has been advocated by recent reports.[34-36] In this study, two patients underwent FDG-PET/CT. One patient (Case 3) showed abnormal uptake, not only in the unilateral lacrimal gland where the biopsy was performed, but also in the bilateral thyroids to reveal such systemic foci. Another patient (Case 5) underwent PET/CT to evaluate the metastasis of lung adenocarcinoma for the purpose of staging. The liver showed foci of abnormal uptake, which were later proven to be IgG4-related hepatic inflammatory pseudotumors. On the basis of the limited number of patients experienced in this study, FDG-PET/CT appears to be useful to disclose certain systemic foci of involvement with IgG4-related disease.

A major limitation in this study is the immunohistochemical diagnostic criteria that we adopted to determine the IgG4-positive or -negative lesions : less than 10 IgG4-positive cells/high-power field as negative and 10 or more cells as positive for the first criterion, the ratio of IgG4-positive plasma cells/CD138-positive plasma cells over 40% as positive for the second criterion, and the ratio of IgG4-positive plasma cells/IgG-positive plasma cells over 40% as positive for the third criterion.[14,28] The most recommended criterion at the moment is the ratio of IgG4-positive plasma cells/IgG-positive plasma cells over 40%.[14] CD138 antigen is a membrane protein, syndecan-1, which belongs to the heparan sulfate proteoglycan family, and is used as a specific marker for plasma cells.

In the present study, the number of IgG-positive plasma cells in a certain field was smaller than the number of CD 138-positive plasma cells in all the lesions of 9 patients, suggesting that the plasma cells produce different types of immunoglobulins other than IgG. Under the circumstances, the ratio of IgG4-positive plasma cells/IgG-positive plasma cells becomes greater than the ratio of IgG4-positive plasma cells/CD138-positive plasma cells. Overall, the three criteria for immunohistochemical diagnosis of IgG4-positive lesions appear to be appropriate since a clear-cut divide between the positive lesions and the negative lesions was obtained for all

the three criteria in this study. Simple counting of IgG4-positive plasma cells in a high-power field or the ratio of IgG4-positive plasma cells/CD138-positive plasma cells could be used for convenience in place of the ratio of IgG4-positive plasma cells/IgG-positive plasma cells as the most recommended for use. Of course, the number of positive plasma cells in a high-power field and both the ratio of IgG4-positive plasma cells/CD138-positive plasma cells and the ratio of IgG4-positive plasma cells/IgG-positive plasma cells would vary from area to area in a lesion and would also change in the evolving course of the disease. The long-term follow-up of patients and further recruitment of additional patients are necessary to obtain a more definite answer to the role of IgG4 in the ocular adnexal and other systemic lymphoid lesions.

In conclusion, IgG4-positive ocular adnexal benign lymphoid lesions involving unilateral or bilateral lacrimal glands were complicated by other systemic manifestations. The histopathology of the ocular adnexal lesions, frequently, but not always, shows fibrosis, destruction of lacrimal glandular tissue, and lymphoid follicle formation as described previously.[28,33] IgG4 immunostaining in the ocular adnexal benign lymphoid lesions would be recommended as a routine procedure, and hence, the detection of the IgG4-positive ocular adnexal lesions might be used as a benchmark for the probable presence of systemic diseases. Long-term follow-up of patients with IgG4-positive lesions is mandatory since malignant lymphoma would occur in the setting of IgG4-related disease,[28] and also IgG4-producing cells by themselves might be neoplastic.[37]

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