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Original Article

Follow-up with serum IgG4-monitoring in 8 patients with IgG4-related disease diagnosed by a lacrimal gland mass

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The diagnostic criteria for IgG4-related disease were previously published and serum IgG4 measurement has been reimbursed by national health insurance in Japan since 2012. Eight patients diagnosed with IgG4-related disease based on lacrimal gland masses were retrospectively reviewed. The 8 patients were 3 men and 5 women ranging in age from 52 to 77 (median, 63) years at the initial visit and their follow-up period ranged from 0.25 to 11 (median, 7) years. Bilateral and unilateral involvement were noted in 4 patients each; 2 on the right side and 2 on the left side in those with unilateral involvement. Serum IgG4 was high in 5 of 8 patients at the initial visit. Five patients with no systemic signs were followed without treatment, whereas oral steroids were administered and tapered in the other 3 patients who exhibited systemic signs. One patient with a history of radiation for MALT lymphoma in bilateral lacrimal glands developed IgG4-related disease in the left lacrimal gland 10 years later and was followed without treatment. Nine years later, her serum IgG4 level increased to 1500 mg/dL and paracardiac lesions, found on positron emission tomography, were confirmed to be MALT lymphoma by needle biopsy, leading to systemic chemotherapy. The other 7 patients had neither local recurrence nor additional systemic signs. Serum IgG4 monitoring may be useful to detect systemic complications in IgG4-related ophthalmic disease and markedly high serum IgG4 levels may indicate new lymphoma at other sites.

Keywords: IgG4-related disease, lacrimal gland, serum IgG4, prednisolone, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

INTRODUCTION

Immunoglobulin G4 (IgG4)-related disease is a recently established clinical entity characterized by infiltration or mass formation with IgG4-producing plasma cells and lymphocytes often accompanied by fibrosis in multiple organs.[1] The 2011 comprehensive diagnostic criteria for IgG4-related disease in Japan were published by the Government-sponsored taskforce of Japanese clinicians and pathologists in January 2012,[2] and the measurement of serum IgG4 became covered by reimbursement of national health insurance in Japan in December 2012. In January 2020, towards worldwide recognition of the entity, the 2019 classification criteria for IgG4-related disease were published by American College of Rheumatology and European League Against Rheumatism.[3,4] The pathological criteria remain key for the diagnosis of IgG4-related disease and an increase in serum IgG4 levels supports the clinical diagnosis.[5]

In the field of ophthalmology, the diagnostic criteria for IgG4-related ophthalmic disease were published in 2015,[6] together with the criteria in other organs such as autoimmune pancreatitis and sclerosing cholangitis. We previously reported a series of patients with IgG4-related disease in the ocular adnexa in 2010[7] and demonstrated IgG4-related disease in the background of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) in the lacrimal gland in 2011.[8] In this study, we reviewed an additional series of patients with IgG4-related disease diagnosed in the lacrimal gland and examined their follow-up by monitoring serum IgG4 levels in the era after

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the establishment of the diagnostic criteria. The clinical question in this study was whether serum IgG4-monitoring aided in deciding the treatment for IgG4-related disease.

METHODS

Eight consecutive patients with lacrimal gland lesions who were diagnosed with IgG4-related disease between 2009 and 2020 were retrospectively reviewed (Table 1). Case 1 in this study was reported in part as Case 9 in our previous study,[7] and Case 2 was reported in our previous case report.[8] The follow-up of these two patients is described in this study. The study was performed according to the Declaration of Helsinki and was approved as a retrospective study by the ethics committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital. All 8 patients, except one (Case 5) who declined surgery, underwent excisional biopsy of the lacrimal gland lesions by a single surgeon (TM) at Okayama University Hospital and were diagnosed with IgG4-related disease by immunostaining of paraffin sections at the Department of Pathology.

Data collected from medical records were gender, age at the initial presentation and surgery, laterality of lacrimal gland involvement, pathological findings, prednisolone treatment, follow-up period, serum IgG4 and soluble interleukin-2 receptor (sIL-2R) levels at each visit, magnetic resonance imaging and whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) findings, and systemic signs other than orbital signs throughout the course.

Immunohistochemical staining was based on the protocol recommended for the Bond Polymer Refine Detection Kit in the Bond-III Fully Automated IHC and ISH Stainer system (Leica Biosystems, Welzlar, Germany). Primary antibodies used were: mouse monoclonal antibodies against CD3 (Leica NCL-L-CD3-565, Leica Biosystems Novocastra), CD20 (Leica NCL-L-CD20-L26), IgG4 (MBL BS-MCO11, Medical & Biological Laboratories, Nagoya), and IgG (Leica NCL-L-IgG). Both κ light chain and λ light chain were detected by *in situ* hybridization using Bond Ready-to-Use ISH Kappa Probe (PBO0645, Leica Biosystems) and Lambda Probe (PBO0669).

RESULTS

Clinical findings

The 8 patients comprised 3 men and 5 women ranging in age from 52 to 77 (median, 63) years at the initial visit to the Department of Ophthalmology (Table 1). The follow-up period ranged from 0.25 to 11 (median, 7) years. Bilateral and unilateral involvement was noted in 4 patients each: 2 on the right side and 2 on the left side in those with unilateral involvement (Fig. 1, Fig. 2). Excisional biopsy was scheduled within one month after the initial visit for 7 patients. The 4 patients with bilateral lacrimal gland lesions underwent bilateral excisional biopsy. Histopathology with immunostaining confirmed IgG4-related disease in the lacrimal gland lesions. One patient (Case 5) declined excisional biopsy. The clinical diagnosis in this patient was thus based on the increase in serum IgG4, and clinical exclusion of lymphoma and sarcoidosis in the course of the disease.

The serum IgG4 level was high in 5 of 8 patients at the initial visit based on the diagnostic criteria of 135 mg/dL or higher (Table 1). The serum sIL-2R level was high in 5 of 8 patients at the initial visit. During follow-up, 7 of the 8 patients exhibited a relative increase in serum IgG4 at the last visit compared with the initial visit (Fig. 3). The serum IgG4 level decreased after surgery in only two patients (Cases 7 and 8, Fig. 3). Another patient (Case 5) with no surgery also had a decrease in serum IgG4 in response to oral prednisolone (Fig. 3) compared with the level at the initial visit. Five patients with no systemic signs were followed without treatment. In contrast, oral prednisolone at an initial dose ranging from 10 to 30 mg daily was administered to the other 3 patients (Cases 4, 5, and 7) who exhibited systemic signs on FDG-PET and later tapered. The systemic signs were prostatic and lung lesions in Case 4, mediastinal lesions (Fig. 1I) in Case 5, and pancreatic (Fig. 2H) and bilateral submandibular gland lesions (Fig. 2G) in Case 7. The lacrimal gland mass and mediastinal lesions resolved in response to oral prednisolone in one patient (Case 5) without a pathological diagnosis.

The patient (Case 2) with a history of radiation therapy for MALT lymphoma in the bilateral lacrimal glands developed IgG4-related disease (Fig. 1C, 1D) in the left lacrimal gland 10 years later and was followed without treatment after the pathological diagnosis of IgG4-related disease (Fig. 4A-4F).[8] Nine years after the diagnosis of lacrimal gland IgG4-related disease by the second excisional biopsy, her serum IgG4 level increased to 2090 mg/dL (Fig. 3), and paracardiac lesions were found by FDG-PET (Fig. 1E, 1F) and confirmed to be MALT lymphoma by needle biopsy (Fig. 4G-4L). In half a year, she underwent 5 courses of bendamustine (90 mg/m^2 on days 1 and 2) combined with rituximab (375 mg/m^2 on day 1) as systemic chemotherapy to achieve complete remission. She received oral mesalazine at 2400 mg daily throughout the course. At the final visit, half a year after chemotherapy, the serum IgG4 level decreased to 155 mg/dL from the highest value of 2090 mg/dL (Fig. 3) and serum sIL-2R level decreased to 438 U/mL from the highest value of 1527 U/mL. The other 7 patients did not have local recurrence or additional systemic signs.

Pathological findings

Lacrimal gland lesions in all 7 patients with excisional biopsy fulfilled the pathological criteria of IgG4-related disease: 10 or more IgG4-positive cells in a high-power field and 40% or higher ratio of IgG4-positive cells over IgG-positive cells (Table 1). In Case 2 with later development of paracardiac MALT lymphoma, the left lacrimal gland lesion diagnosed as IgG4-related disease contained lymphoid follicles with interfollicular fibrotic bundles (Fig. 4A, 4B), and

Table 1. Summary of 8 patients with IgG4-related disease in lacrimal glands

Case No./ Gender	Age at first visit and biopsy	Follow-up years#	Laterality	Excisional biopsy	IgG4/IgG-positive cells (%) in lacrimal gland lesion	Preceding or concurrent systemic lesions	Treatment	Serum IgG4 (mg/dL) Initial/Last visit	Serum sIL-2R (U/mL) Initial/Last visit	Later systemic lesions
1/Female	60	11 years	Bilateral	Yes	100% (Right side) 100% (Left side)	Antiphospholipid syndrome 3 years previously	No	104 / 39	374 / n.d.	No
2/Female	58	10 years (20 years)*	Left	Yes	100%	Ulcerative colitis 6 years previously 30 Gy of radiation to left and right lacrimal glands MALT lymphoma 10 and 7 years previously	No	376/ 155	756 / 438	Paracardiac MALT lymphoma 9 years later
3/Female	67	9.5 years	Bilateral	Yes	90% (Right side) 50% (Left side)	No	No	432 / 856	819 / 1102	No
4/Male	67	11 years	Left	Yes	95%	Prostatic lesion confirmed to be IgG4-related disease at prostatectomy 2 years previously	Prednisolone 10 mg	106/ 229	626 / n.d.	Pneumonitis confirmed to be IgG4-related disease by TBLB 1 year later
5/Male	77	5 years	Right	No	Not performed	Mediastinal lesion	Prednisolone 30 mg	279 / 360	493 / 340	No
6/Female	52	4 years	Bilateral	Yes	100% (Right side) 100% (Left side)	No	No	40 / 100	229 / 256	No
7/Female	76	3 years	Right	Yes	70%	Pancreatic lesion Bilateral submandibular gland lesions	Prednisolone 25 mg	273 / 689	421 / 866	No
8/Male	56	0.25 years	Bilateral	Yes	100% (Right side) 100% (Left side)	Pneumonitis (mild)	No	881 / 740	733 / 646	No

#Until November 2020. *20 years after the diagnosis of MALT lymphoma in the left lacrimal gland.
sIL-2R, soluble interleukin-2 receptor; TBLB, transbronchial lung biopsy; MALT lymphoma, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue; n.d., not determined.

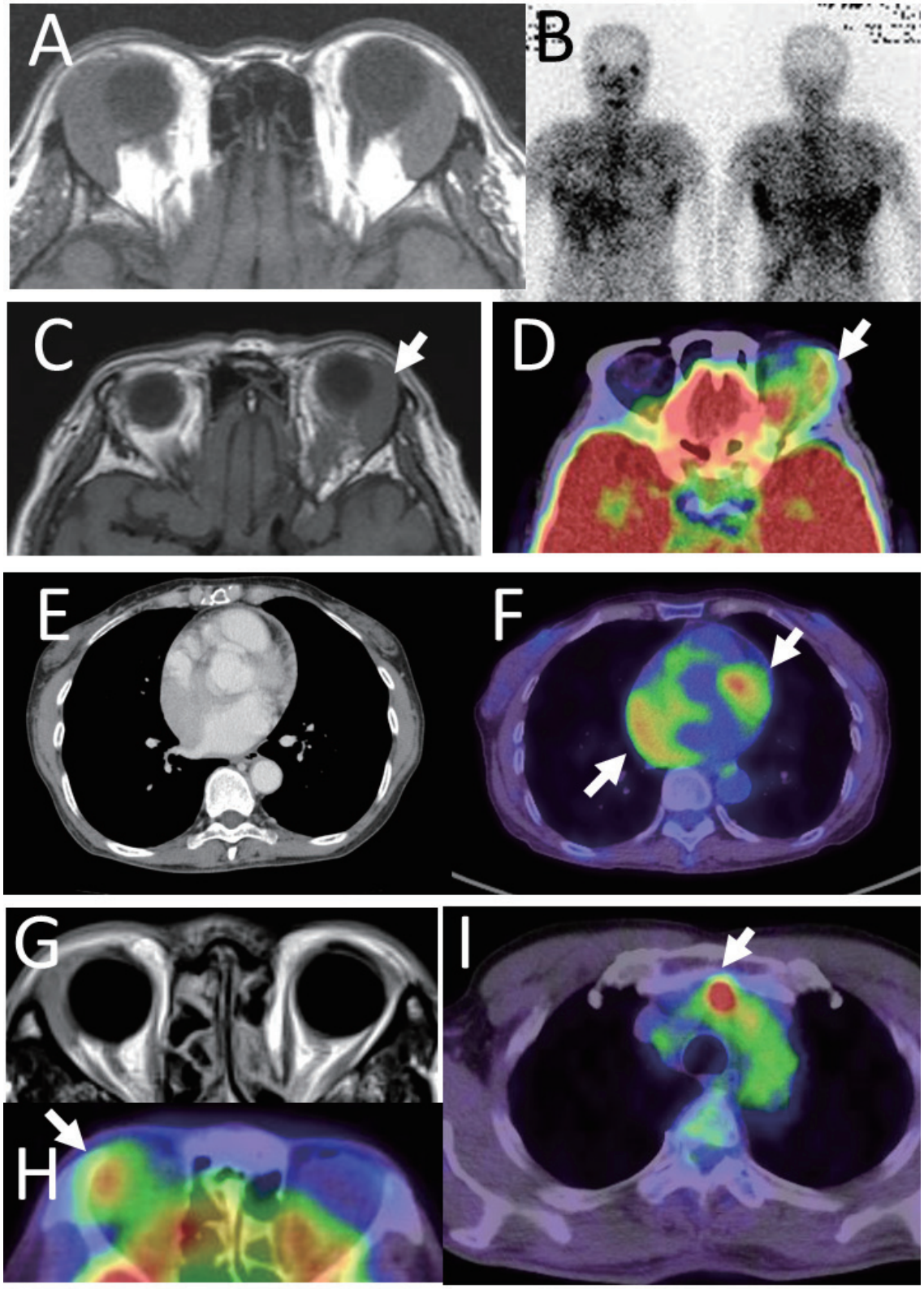

Fig. 1. Case 1. Bilateral lacrimal gland masses on magnetic resonance imaging (***A***) and high uptake by the bilateral lacrimal glands on gallium-67 scintigraphy (***B***). Case 2. Left lacrimal gland mass on magnetic resonance imaging (arrow, ***C***) and high uptake by the lacrimal gland mass on whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) (arrow, ***D***). Paracardiac lesions on computed tomography (***E***) and high uptake on FDG-PET (arrows, ***F***). Case 5. Right lacrimal gland mass on magnetic resonance imaging (***G***), and high uptake on FDG-PET by the right lacrimal gland (arrow, ***H***) and mediastinal lesion (arrow, ***I***).

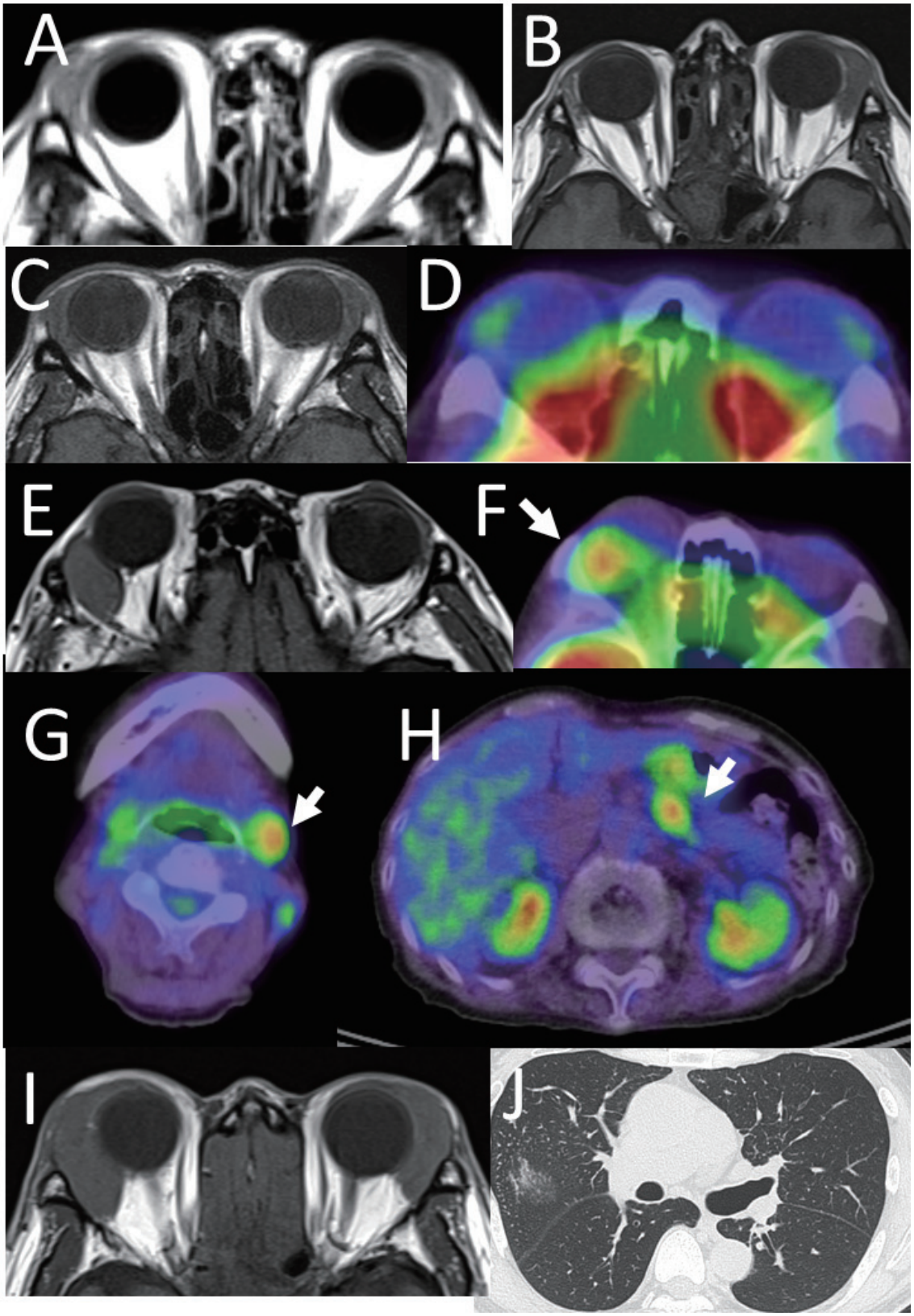

Fig. 2. Case 3. Bilateral lacrimal gland masses on magnetic resonance imaging (***A***). Case 4. Left lacrimal gland mass on magnetic resonance imaging (***B***). Case 6. Bilateral lacrimal gland masses on magnetic resonance imaging (***C***) and weak uptake by bilateral lacrimal gland masses on whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) (***D***). Case 7. Right lacrimal gland mass on magnetic resonance imaging (***E***) and high uptake on FDG-PET by the right lacrimal gland mass (***F***). High uptake on FDG-PET by bilateral submandibular glands (arrow, ***G***) and the pancreas (arrow, ***H***). Case 8. Bilateral lacrimal gland masses on magnetic resonance imaging (***I***) and granular shadows in the lung field (***J***).

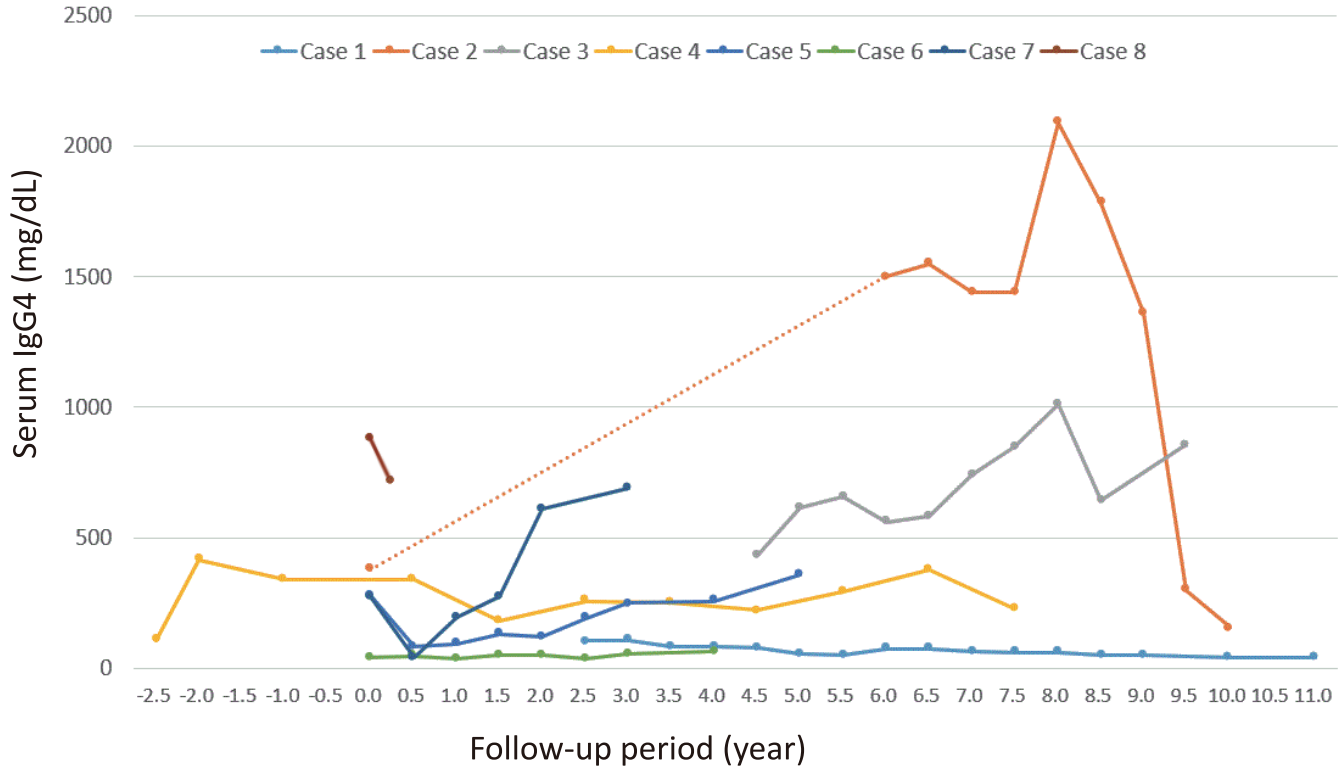

Fig. 3. Serum IgG4 levels during the follow-up periods of 8 patients. Measured values are shown as closed circles. The period with missing data in Case 2 is shown by a broken line. Zero point on the horizontal line (years) indicates the timing for excisional biopsy in all cases except for Case 5 without surgery at the initial visit. Case 8 had only two measurements in a short follow-up period of 3 months.

was infiltrated by plasma cells and lymphocytes. The ratio of IgG4/IgG-positive cells (Fig. 4C, 4D) was 100%, and κ light chain-positive cells (Fig. 4E) and λ light chain-positive cells (Fig. 4F) were similar in number. In contrast, the paracardiac lesion diagnosed as MALT lymphoma exhibited diffuse infiltration with medium-sized lymphoid cells (Fig. 4G, 4H). The ratio of IgG4/IgG-positive cells (Fig. 4I, 4J) was 30%, and κ light chain-positive cells (Fig. 4K) were more predominant than λ light chain-positive cells (Fig. 4L). IgG4-positive cells appeared as lymphoma cells because they overlapped with predominant κ light chain-positive cells.

In Case 2, left and right lacrimal gland lesions diagnosed as MALT lymphoma 10 and 7 years previously, respectively, before the diagnosis of IgG4-related disease in the left lacrimal gland, were reexamined by novel immunostaining (Fig. 5). The paraffin block containing the right lacrimal gland tissue was sufficiently large for re-sectioning to stain IgG, IgG4, κ light chain, and λ light chain (Fig. 5E-5H), but only IgG4 (Fig. 5B) was stained on a preserved paraffin section of the left lacrimal gland tissue because little tissue in the paraffin block remained after the previous sectioning. In MALT lymphoma of the left lacrimal gland 10 years previously, the number of IgG4-positive cells was 10 or greater in a high-power field (Fig. 5B). In MALT lymphoma of the right lacrimal gland 7 years previously, IgG-positive cells (Fig. 5E) were present in a small number, but IgG4-positive cells (Fig. 5F) were absent. In the lesion of the right lacrimal gland, κ light chain-positive cells (Fig. 5G) were more predominant than λ light chain-positive cells (Fig. 5H), which was consistent with κ chain predominance in the paracardiac lesion (Fig. 4K).

In 4 patients with bilateral lacrimal gland involvement with IgG4-related disease, the extent of fibrosis was basically the same between the bilateral lesions in 3 patients, whereas extent of fibrosis differed between the right-side and left-side lesions in the remaining one patient (Case 6). In Case 3 with a serum IgG4 level of 432 mg/dL, the extent of fibrosis was similar between the lesions on the right side (Fig. 6A-6D) and the left side (Fig. 6E-6H). In contrast, fibrosis was more marked in the right-side lesion (Fig. 7A-7D) than in the left-side lesion with better preservation of lacrimal gland acini (Fig. 7E-7H) in Case 6 with no increase in the serum IgG4 level at 40 mg/dL. In all lesions of the 7 patients who underwent excisional biopsy, IgG4-positive cells were found mainly in interfollicular spaces (Fig. 6D, 6H) and among lacrimal gland acini (Fig. 7H). There was also a small number of IgG4-positive cells infiltrating the follicles (Fig. 6H).

DISCUSSION

The clinical question in this study was the utility of serum IgG4-monitoring in follow-up of patients diagnosed with IgG4-related disease based on the lacrimal gland lesions in the era of the established disease criteria. Since the establishment of the comprehensive diagnostic criteria of IgG4-related disease,[2] there have been several reports of series of

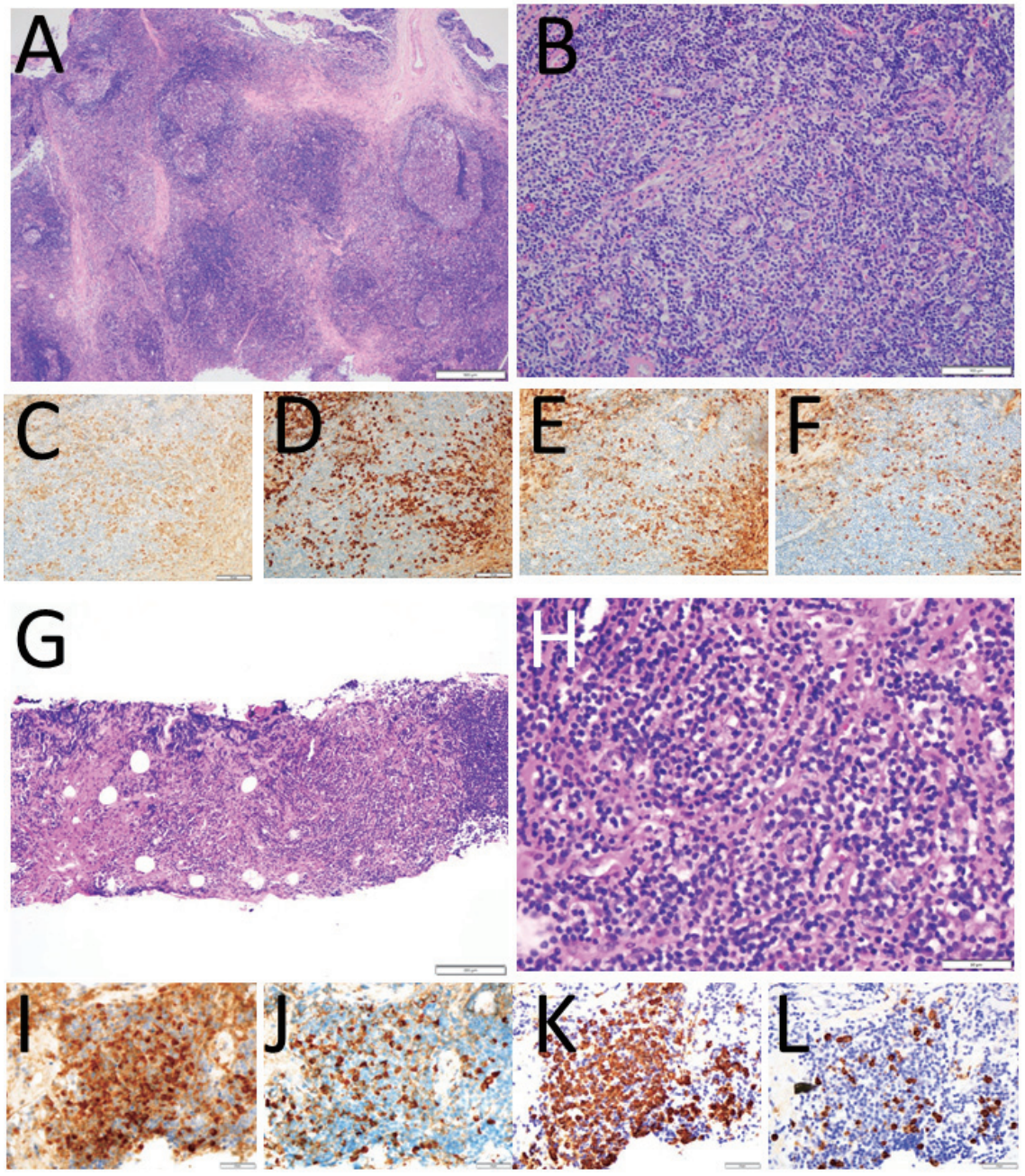

Fig. 4. Case 2. IgG4-related disease in the left lacrimal gland mass (***A-F***). Lymphoid follicles separated by fibrotic bundles (***A***), and infiltration of plasma cells and lymphocytes (***B***). IgG4 (***D***) / IgG (***C***) = 100%. κ chain (***E***) and λ chain (***F***) bitype. MALT lymphoma in a paracardiac mass (***G-L***). Diffuse infiltration of medium-sized lymphoid cells in the needle biopsy specimen (***G***, ***H***). IgG4 (***J***) / IgG (***I***) = 30%. Dominant κ chain (***K***) in comparison with λ chain (***L***). White scale bar = 500 μm in ***A***, bar = 100 μm in ***B-F***, bar =200 μm in G, and bar = 50 μm in ***H-L***.

patients with IgG4-related disease in the ocular adnexa, so-called IgG4-related ophthalmic disease.[9-13] The measurement of serum IgG4 may be used to detect relapse after prednisolone treatment in the follow-up of patients with pathologically confirmed IgG4-related ophthalmic disease.[13] In the present series of patients, serum IgG4 levels were monitored but not used as a guide for adjusting the dose of oral prednisolone in 3 patients with steroid therapy. The presence of symptoms and signs, revealed mainly by computed tomography, in addition to adverse events caused by prednisolone, were used to determine the tapering and discontinuation of prednisolone in these patients.

Lacrimal gland masses must be differentiated from inflammation and malignancy. Lymphoma is frequent in the lacrimal gland[14-17] compared with epithelial tumors such as benign and malignant pleomorphic adenoma. An increase in the serum sIL-2R level, as measured in the present series of patients, supports lymphoproliferative disorders, such as lymphoma, and sarcoidosis. IgG4-related disease is a common cause of inflammatory diseases in the lacrimal gland. In

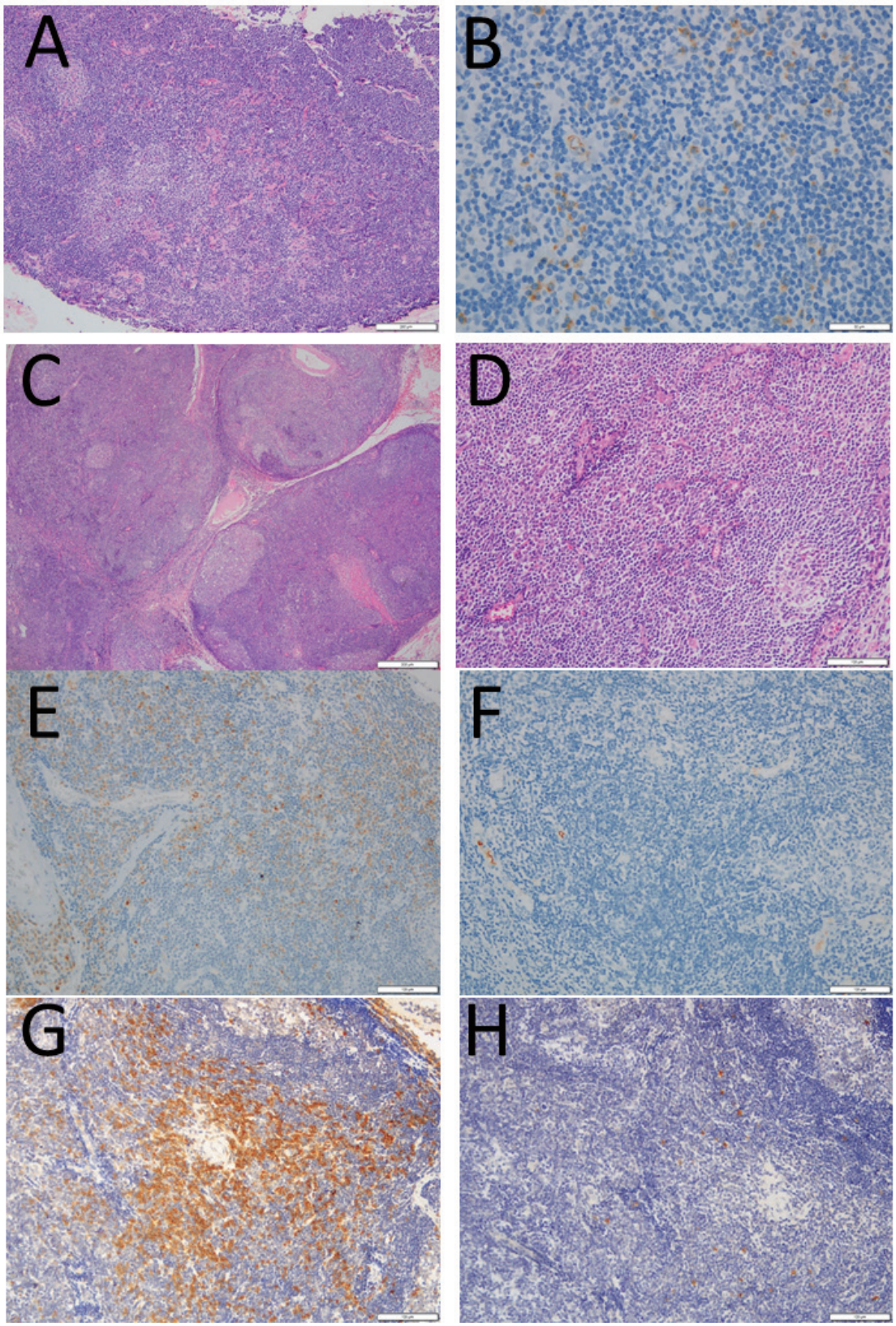

Fig. 5. Case 2. Re-immunostaining of left (***A***, ***B***) and right (***C***-***H***) lacrimal gland lesions diagnosed as MALT lymphoma 10 and 7 years previously, respectively, from the time point of diagnosis of IgG4-related disease in the left lacrimal gland mass. Obscured follicular structure, and diffuse infiltration of medium-sized lymphoid cells on the left (***A***) and right sides (***C***, ***D***). IgG4-positive cells are present (***B***) on the left side. IgG-positive cells are present (***E***) but IgG4-positive cells are absent (***F***) on the right side. Note dominant κ chain (***G***) in comparison with λ chain (***H***) on the right side. White scale bar = 200 μm in ***A***, bar = 50 μm in ***B***, bar =500 μm in ***C***, and bar = 100 μm in ***D***-***H***.

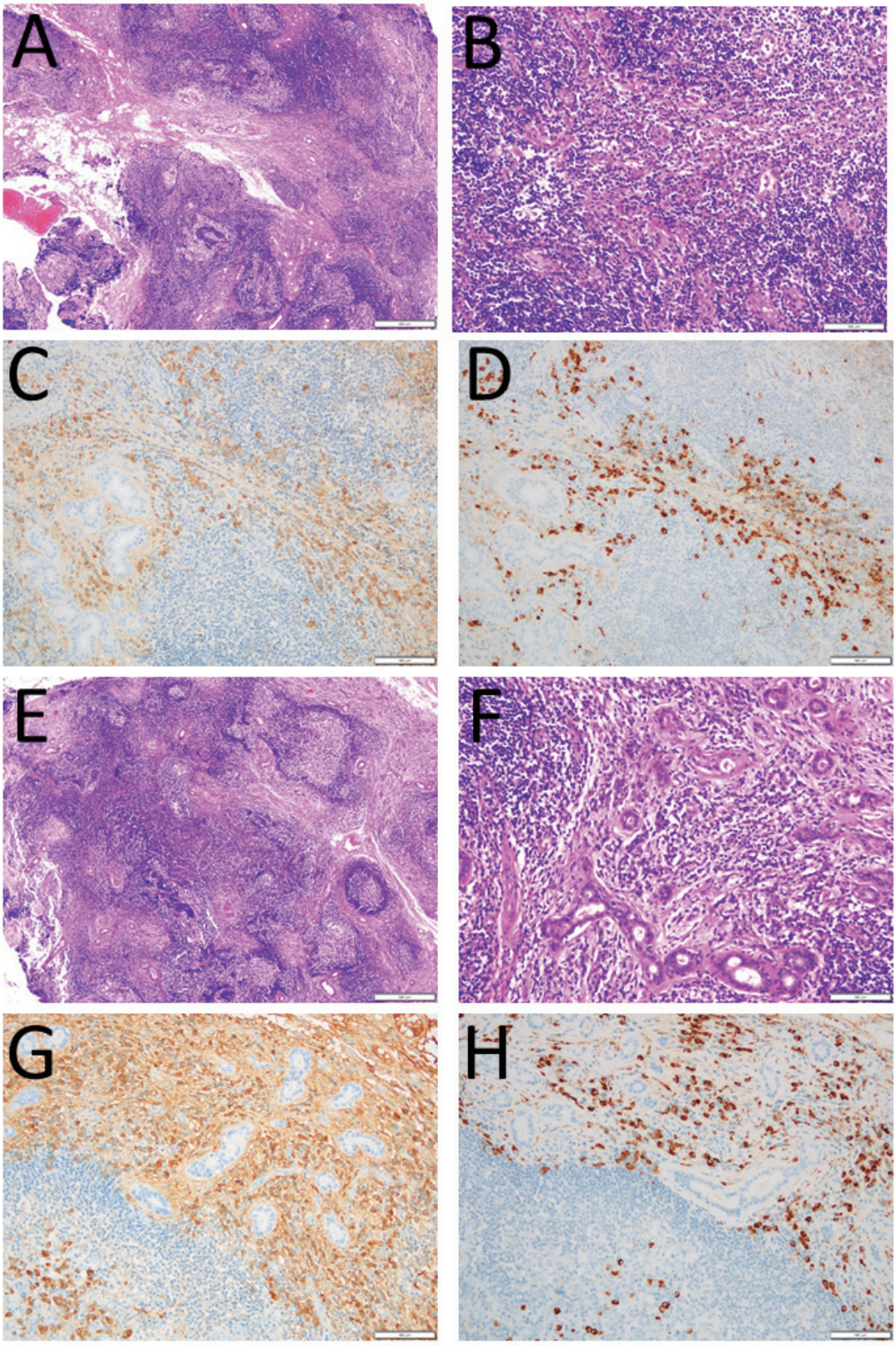

Fig. 6. Case 3. Lacrimal gland masses on the right (***A*-*D***) and left sides (***E*-*H***). Lymphoid follicles separated by fibrotic bundles (***A***, ***E***), and infiltration of plasma cells and lymphocytes (***B***, ***F***). Note lacrimal gland acini in ***F***. IgG4 (***D***) / IgG (***C***) = 90% on the right side and IgG4 (***H***) / IgG (***G***) = 50% on the left side. White scale bar = 500 μm in ***A*** and ***E***, bar = 100 μm in ***B*-*D*** and ***F*-*H***.

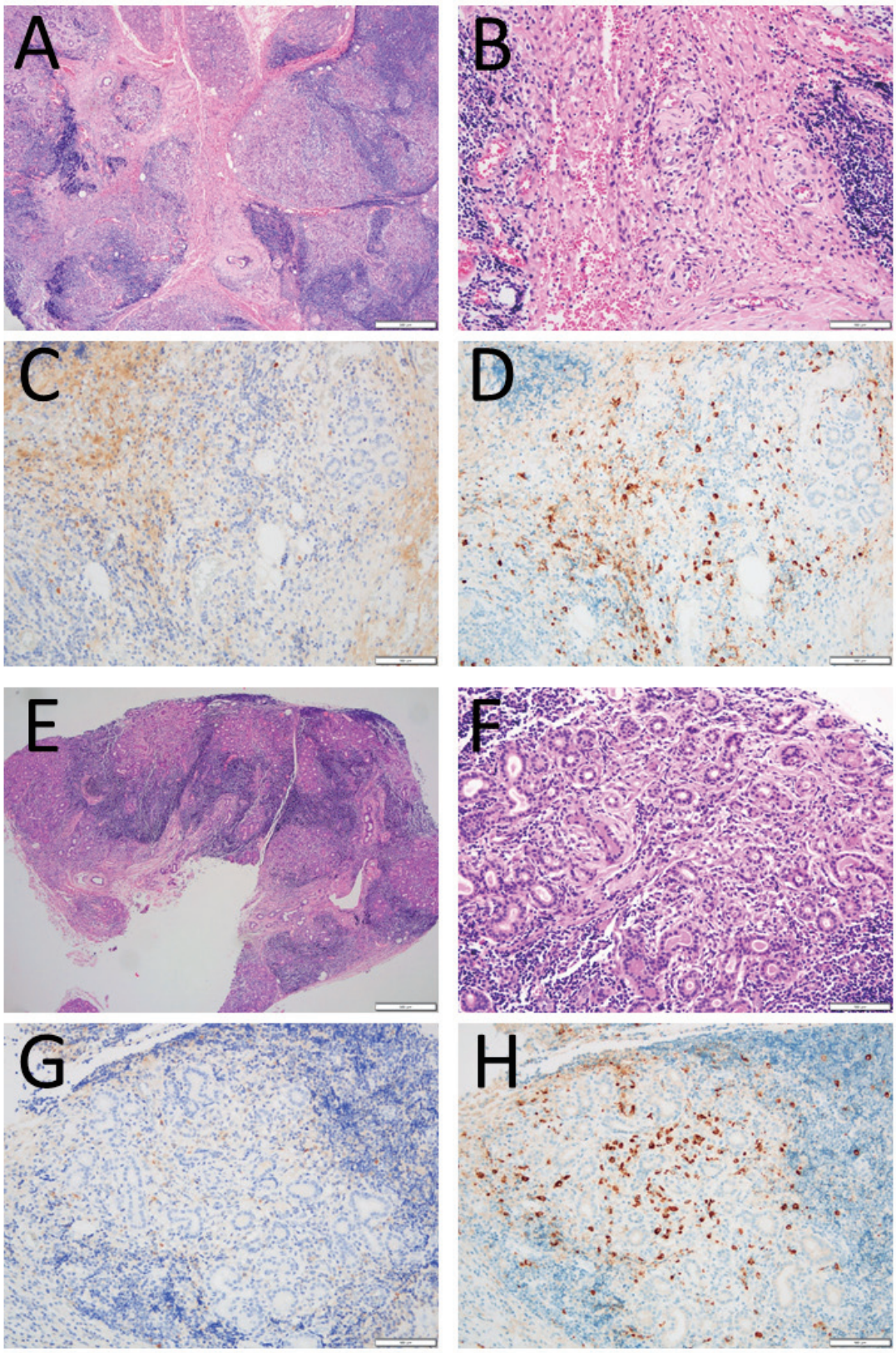

Fig. 7. Case 6. Lacrimal gland masses on the right (***A-D***) and left sides (***E-H***). Lymphoid follicles separated by fibrotic bundles (***A***), and infiltration of plasma cells and lymphocytes (***B***, ***F***). Note less fibrotic change and preservation of lacrimal gland acini on the left side (***E***, ***F***). IgG4 (***D***) / IgG (***C***) = 100% on the right side and IgG4 (***H***) / IgG (***G***) = 100% on the left side. White scale bar = 500 μm in ***A*** and ***E***, bar = 100 μm in ***B-D*** and ***F-H***.

addition, sarcoidosis and Kimura disease[18] have to be considered as other causes of inflammation in the lacrimal gland. There is also the entity of idiopathic orbital inflammation or orbital pseudotumor with non-specific inflammation, which does not satisfy the pathological criteria of IgG4-related disease.[19] Furthermore, MALT lymphoma can develop in the background of IgG4-related disease in the lacrimal gland.[20,21] The above strongly suggest that pathological diagnosis by biopsy is required in the case of lacrimal gland masses.

In the present series of patients, 3 (Cases 1, 4, and 6) did not fulfill the serum IgG4 level criteria of 135 mg/dL or higher at the initial visit. Indeed, all 7 patients with excisional biopsy demonstrated a typical pathology pattern for IgG4-related disease. There was no difference in pathological findings between the patients with and without an increase in serum IgG4 based on the diagnostic criteria. Furthermore, the presence of other systemic signs was unable to explain the higher serum IgG4 levels at the initial visit. In addition, oral prednisolone, which was prescribed to 3 patients (Cases 4, 5, and 7), did not necessarily lead to a stable reduction of serum IgG4 levels (Fig. 3). Therefore, regarding the clinical question in this study, it remains unclear whether serum IgG4 levels can be used to monitor the disease activity and systemic involvement of IgG4-related disease.

All 7 patients (Cases 1-7) in the present study with long-term follow-up, except for one (Case 1), exhibited a relative increase in serum IgG4 levels at the last visit compared with the initial visit, irrespective of prednisolone treatment. They did not have novel symptoms or signs on computed tomography or FDG-PET. As an exception, one patient (Case 2) with markedly high serum IgG4 levels over 1500 mg/dL had high-uptake lesions in the paracardiac area and was confirmed to have MALT lymphoma by biopsy. This patient had a low level of serum IgG4 at the last visit after systemic chemotherapy for MALT lymphoma. Overall, a relative increase in serum IgG4 levels over time is acceptable except for excessive increases over 1500 mg/dL. In the last patient (Case 8) with a short follow-up period (3 months), the increase in serum IgG4 at the initial visit supported IgG4-related disease as a probable cause for elastic-hard bilateral lacrimal gland masses.

In the sequence of events in Case 2, the patient first developed left lacrimal gland MALT lymphoma with λ light chain predominance and positive IgG4. Three years later, she developed right lacrimal gland MALT lymphoma with κ light chain predominance and negative IgG4, and left lacrimal gland IgG4-related disease with κ and λ chain bitype 7 years after that.[8] Nine years later, she developed paracardic MALT lymphoma with κ light chain predominance and positive IgG4. Re-staining of the preceding MALT lymphomas confirmed that IgG4-positive cells were present in the left lacrimal gland lesion 10 years previously but absent in the right lacrimal gland lesion 7 years prior to the time point of the diagnosis of IgG4-related disease in the left lacrimal gland.[8] Subsequently, IgG4-positive cells were present in a large number in the paracardiac lesion of MALT lymphoma 9 years after the diagnosis of IgG4-related disease in the left lacrimal gland. The shared κ light chain predominance suggests the same lineage of lymphoma cells in the preceding and later MALT lymphoma in different sites of the body. The increase in IgG4-positive cells in the later paracardiac lesion of MALT lymphoma may have played a role in the relapse of lymphoma, regardless of whether lymphoma cells produced IgG4.[22]

A major limitation in this retrospective study was that serum IgG4 measurements were not performed at each visit throughout the follow-up period. In Case 2, serum IgG4 data were missing for a long period after the initial measurement at excisional biopsy with the diagnosis of IgG4-related disease because the patient had ulcerative colitis and was followed by an internist at another hospital. The second limitation is that the present study included only patients with IgG4-related disease in lacrimal glands. Serum IgG4 monitoring, therefore, cannot be generalized to IgG4-related disease in other organs such as autoimmune pancreatitis. Even with these limitations, follow-up with serum IgG4 monitoring may be useful to detect new lymphoma in patients with IgG4-related disease when the serum IgG4 level markedly increases during the time course of IgG4-related disease in the lacrimal gland.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this study.

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