

Clinical features of IgG4-related dacryoadenitis

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Abstract

Background To elucidate the clinical characteristics of IgG4-related dacryoadenitis.

Methods Clinical features, laboratory findings, radiological findings, associated diseases, treatment, and prognosis were prospectively examined in 12 patients (seven men, five women; mean age, 60.9±15.1 years) with IgG4-related dacryoadenitis.

Results In addition to eyelid swelling, other ophthalmologic symptoms were observed in seven patients, including diplopia ($n=4$), ptosis ($n=2$), visual field disturbance ($n=2$), eye pain ($n=2$), decrease of visual acuity ($n=2$), eye-movement disturbance ($n=1$), dry eye ($n=1$), corneal ulcer ($n=1$), and epiphora ($n=1$). Swelling of the lacrimal glands was bilateral in half of the patients. Other IgG4-related diseases were present in nine patients, including sialadenitis ($n=5$), autoimmune pancreatitis ($n=4$), retroperitoneal fibrosis ($n=2$), and lymphadenopathy ($n=8$). Serum IgG4 levels were significantly higher in patients with other IgG4-related disease (1070 ± 813 mg/dl) than in those without (197 ± 59 mg/dl, $p=0.017$). Allergic histories and elevated serum IgE levels were each detected in six

patients. Eight patients showed inflammatory extension beyond the lacrimal gland, such as thickened rectus muscle ($n=6$), inflammation of the optic nerve ($n=2$), and retrobulbar inflammation ($n=3$). Steroid therapy was effective in seven patients, but dacryoadenitis relapsed in two patients with markedly higher serum IgG4 levels and autoimmune pancreatitis.

Conclusions IgG4-related dacryoadenitis showed various ophthalmologic symptoms due to extensive inflammation beyond the lacrimal gland, frequent association with other IgG4-related disease or allergic phenomena, and steroid responsiveness.

Keywords IgG4 · IgG4-related dacryoadenitis · Lacrimal gland · Mikulicz's disease · Autoimmune pancreatitis

Introduction

IgG4-related disease is a recently emerged systemic condition characterized by unique pathological features that affect a wide variety of organs [1–3]. In 2003, we reported multiple extrapancreatic lesions with common histological features consisting of abundant infiltration of IgG4-positive plasma cells and lymphocytes with fibrosis in patients with autoimmune pancreatitis, and proposed a new systemic entity of IgG4-related systemic disease [4]. Salivary gland swelling is reportedly present in 14 % [5] to 36 % [6] and lacrimal gland swelling in 4 % [5] to 13 % [6] of patients with autoimmune pancreatitis.

Mikulicz's disease refers to idiopathic, bilateral, painless, and symmetrical swelling of the lacrimal, parotid, and submandibular glands [7]. This disease was recently recognized as a salivary gland (IgG4-related sialadenitis) and lacrimal gland (IgG4-related dacryoadenitis) manifestation of IgG4-related disease [1–3, 8]. The involvement of orbital tissues in IgG4-related disease is termed IgG4-related ophthalmic disease [1], ocular adnexal IgG4-related disease [9, 10], or IgG4-related orbital inflammation [11], as various orbital or periorbital regions are

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affected, such as the lacrimal glands, extraocular muscles, uveal tract, optic nerve sheath, superior orbital fissure and cavernous sinus, and orbital fatty tissues. This includes the conditions that have been labeled chronic sclerosing dacryoadenitis and inflammatory orbital pseudotumor [1, 2]. Several studies have examined orbital adnexal IgG4-related disease or IgG4-related orbital inflammation [9–12], but studies focusing on IgG4-related dacryoadenitis are rare [13–15]. We conducted the current study to describe the clinical, laboratory, and radiological presentations of histologically confirmed IgG4-related dacryoadenitis at a single center, using data collected in a prospective fashion.

Patients and methods

Diagnostic criteria for IgG4-related dacryoadenitis

By considering the diagnostic criteria for definite cases in the comprehensive clinical diagnostic criteria for IgG4-related disease [3] and histological criteria for IgG4-related ocular adnexal lymphoplasmacytic infiltrative lesions [10], IgG4-related dacryoadenitis was diagnosed when all three of the following criteria were fulfilled:

1. Swelling of the lacrimal gland on computed tomography (CT) and/or magnetic resonance imaging (MRI),
2. Elevation of serum IgG4 levels (≥ 135 mg/dl), and
3. Abundant infiltration of IgG4-positive plasma cells (>10 IgG4-positive plasma cells/high power field (HPF) and ratio of IgG4-positive cells/IgG-positive cells (IgG4/IgG%) ≥ 30 %) in the lacrimal gland.

Study patients

Between January 2008 and July 2012, a total of 12 patients were diagnosed with IgG4-related dacryoadenitis at Tokyo Metropolitan Komagome Hospital. All 12 patients underwent biopsy of the lacrimal gland on suspicion of lacrimal gland tumor such as lymphoma. All 12 patients underwent systemic CT (head to pelvis) and MRI of the orbital region and abdomen, including magnetic resonance cholangiopancreatography (MRCP). Nine patients underwent ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET). All patients provided written informed consent to undergo examinations. This study was approved by the Institutional Review Board of Tokyo Metropolitan Komagome Hospital.

Data analysis

The following data were analyzed: (1) clinical findings including age, sex, initial symptoms, and allergic history, (2) laboratory findings, (3) radiological findings, (4) associated diseases, (5) treatment, and (6) prognosis. Continuous variables

were compared using Student's *t*-test and the Mann–Whitney *U* test. Values of $p < 0.05$ were considered statistically significant.

Results

Clinical features

Twelve patients, seven men and five women, were included in the study. Mean age ($\pm$ SD) at diagnosis was 60.9 ± 15.1 years (range, 25–74 years). Diabetes mellitus and history of myocardial infarction were present in four and two patients respectively. Six patients had allergic histories such as allergic rhinitis. Eyelid swelling was observed in all patients, and other ophthalmologic symptoms were observed in seven patients, including diplopia ($n=4$), ptosis ($n=2$), visual field disturbance ($n=2$), eye pain ($n=2$), decrease of visual acuity ($n=2$), eye-movement disturbance ($n=1$), dry eye ($n=1$), corneal ulcer ($n=1$), and epiphora ($n=1$). Swelling of the lacrimal glands was in six patients, left-sided in five and right-sided in one. Other IgG4-related diseases were present in nine patients, including sialadenitis ($n=5$, synchronous), autoimmune pancreatitis ($n=4$: synchronous, $n=2$; metachronous, $n=2$), and retroperitoneal fibrosis ($n=2$, synchronous). Lymph node swelling was detected in eight patients (mediastinal lymph nodes ($n=6$: simultaneous, $n=4$; metachronous, $n=2$), abdominal lymph nodes ($n=3$, simultaneous), and cervical lymph nodes ($n=2$: simultaneous, $n=1$; metachronous, $n=1$). The mean interval from initial symptom to diagnosis of IgG4-related dacryoadenitis was 60.9 ± 15.1 months (range, 7–105 months) (Table 1).

Serological features

Mean serum IgG4 level was 779 ± 777 mg/dl (range, 145–2,490 mg/dl). Serum IgG levels were elevated in six patients, and IgG4/IgG% was elevated in all patients. Serum IgG4 levels were higher in male patients ($1,197 \pm 787$ mg/dl) than in female patients (193 ± 41 mg/dl, $p=0.018$). Serum IgG4 levels and IgG4/IgG% were significantly higher in patients with other IgG4-related disease (982 ± 805 mg/dl, 61.3 %) than in those without (170 ± 27 mg/dl, $p=0.013$; 12.3 %, $p=0.021$). Eosinophilia and elevated serum IgE levels were detected in two and six patients respectively. Serum IgE levels were significantly higher in patients with allergic histories ($1,981$ IU/ML) than in those without (334 IU/ML, $p=0.037$). Autoantibodies were detected in seven patients (antinuclear antigen, $n=6$; rheumatoid factor, $n=1$) (Table 2).

Imaging features

CT and/or MRI showed bilateral lacrimal gland swelling in six patients (Fig. 1) and unilateral swelling in six patients (Fig. 2).

Table 1 Clinical features of IgG4-related dacryoadenitis

Case	Age (years)	Sex	Past history	Allergy	Ophthalmologic symptoms	Swelling of lacrimal gland	Other IgG4-RD	Period to diagnosis (months)
1	60	F	none	allergic rhinitis	SEL	bilateral	none	unknown
2	74	F	DM	none	SEL	Left	sialadenitis, AIP ^a , LN	9
3	58	M	none	none	SEL, diplopia visual field disturbance	bilateral	AIP ^b , LN	36
4	25	F	none	allergic rhinitis	SEL, diplopia eye movement disturbance, eye pain	Left	none	20
5	36	F	none	allergic rhinitis	SEL, ptosis dry eye, corneal ulcer	right	none	4
6	71	M	DM, MI	none	SEL, diplopia decrease of visual acuity	Left	sialadenitis, AIP, LN	19
7	73	M	none	none	SEL	bilateral	RF, LN	105
8	67	M	none	mite	SEL	bilateral	sialadenitis, AIP, LN	7
9	68	M	DM, MI	allergic rhinitis	SEL, diplopia	bilateral	LN	24
10	67	M	none	none	SEL	Left	sialadenitis	12
11	64	M	DM angina	drug	SEL, visual field disturbance epiphora, eye pain, decrease of visual acuity	Left	RF, LN	96
12	68	F	breast cancer	none	SEL, ptosis	bilateral	sialadenitis, LN	12

IgG4-RD IgG4-related disease; *DM* diabetes mellitus; *MI* myocardial infarction; *SEL* swelling of eyelid; *AIP* autoimmune pancreatitis; *LN* lymph node; *RF* retroperitoneal fibrosis; *F* female; *M* male

^a 13 years before dacryoadenitis

^b 32 months after dacryoadenitis

Eight patients exhibited inflammatory extension beyond the lacrimal gland, such as thickened rectus muscle ($n=6$, Fig. 3a), displaced optic nerve in two patients (Fig. 3b), inflammation of the optic nerve ($n=2$) and retrobulbar tissue ($n=3$) (Fig. 3c), and four patients showed exophthalmos (Fig. 3c). Sinusitis was detected in six patients (patients 3, 5, 6, and 9-11) (Table 3).

Treatment and prognosis

Steroid therapy was performed for seven patients who did not display or decreased eyelid swelling after biopsy surgery. Steroid was also administered for autoimmune pancreatitis ($n=4$) and retroperitoneal fibrosis ($n=1$). The initial oral prednisolone dose (about 0.6 mg/kg/day) was administered

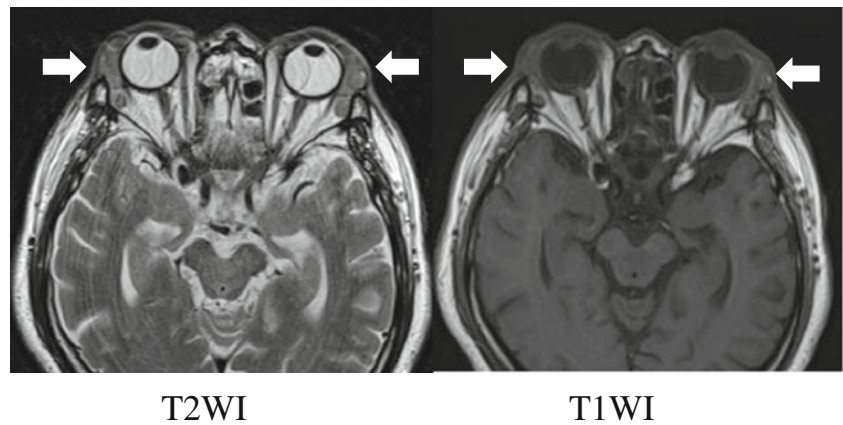
Table 2 Serological features of IgG4-related dacryoadenitis

N Case	WBC (/μl)	CRP (mg/dl)	Eosinophils (/μl)	Serum IgG4 (mg/dl)	Serum IgG (mg/dl)	IgG4/IgG (%)	IgE (IU/ml)	ANA	RF	SS-A	SS-B
*N	<7,700 ^a	0–0.3	<600	<135	<1,800	5–6	<580	<40	<5	-	-
1	6,500	0	300	198	1,461	13.5	2,752	640	<5	-	-
2	3,400	0.1	141	202	1,539	13.1	431	320	<5	-	-
3	6,200	2.5	180	1910	2,601	73.4	92	<40	<5	-	-
4	8,100	0	930	145	1,270	11.4	4,816	<40	<5	-	-
5	11,000	0	170	167	1,482	11.2	279	<40	<5	-	-
6	5,200	0.2	700	2,490	4,135	60.2	386	40	<5	-	-
7	5,100	0	10	1,270	2,869	44.2	736	40	<5	-	-
8	8,300	0	150	872	2,092	41.6	2,154	<40	<5	-	-
9	4,500	0	240	1,130	2,161	52.2	777	40	<5	-	-
10	6,400	0	80	280	1,591	17.6	58	<40	160	-	-
11	7,600	0.2	300	433	1,865	23.2	1,109	40	<5	-	-
12	6,200	0	330	255	1,491	17.1	298	<40	<5	-	-

ANA antinuclear antibody; *RF* rheumatoid factor

^a normal range

Fig. 1 MRI showing bilateral lacrimal gland swelling (arrows)



for 2–4 weeks, with the intention of gradual tapering to a maintenance dose (average 5 mg/day) over 2–3 months. Remission was achieved in all seven patients, and maintenance therapy was performed in six patients. During follow-up (mean duration, 24 ± 15 months), IgG4-related dacryoadenitis relapsed in two patients, at 7 and 8 months after starting steroid treatment. At relapse, one patient had been continuing maintenance therapy, but the other had discontinued steroid treatment. Re-administration or increased dose of steroid was effective in treating relapsed dacryoadenitis. Currently, six patients are still on maintenance therapy (Table 4).

Discussion

No diagnostic criteria for IgG-related dacryoadenitis currently exist. Based on the diagnostic criteria for definite cases in the comprehensive clinical diagnostic criteria for IgG4-related disease [3] and histological criteria for IgG4-related ocular adnexal lymphoplasmacytic infiltrative lesions [10], we created diagnostic criteria for IgG4-related dacryoadenitis in the present study. These criteria comprise typical radiological features of swelling of the lacrimal glands, elevated serum

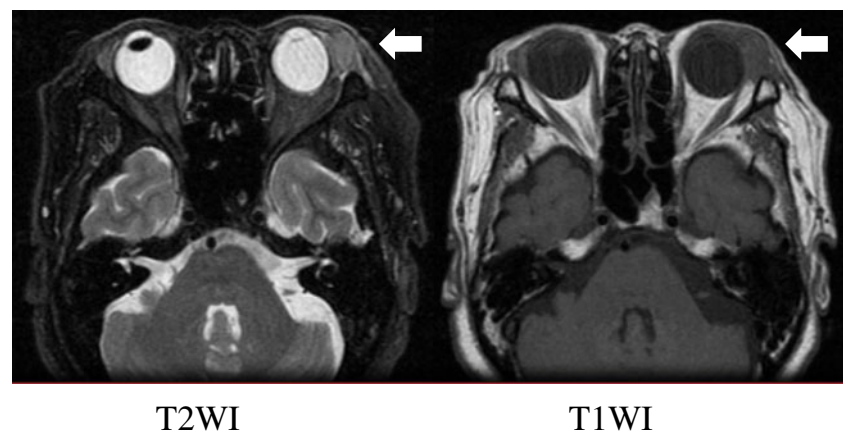
IgG4 levels, and histological findings of abundant infiltration of IgG4-positive plasma cells.

We gathered clinical data from 58 cases of IgG4-related dacryoadenitis reported in the literature, which were diagnosed based on swelling of the lacrimal glands with elevated serum IgG4 levels and/or abundant infiltration of IgG4-positive plasma cells in biopsied or resected lacrimal gland specimens [9–15] (Table 5).

In the present study, mean age at diagnosis was 60.9 years, not significantly different from the 56.6 years reported in the literature. The male-to-female ratio in our patients was 1:0.7, compared to 1:1.5 in the literature. Similarly to autoimmune pancreatitis [16, 17], IgG4-related dacryoadenitis tended to occur in middle-aged individuals, but unlike autoimmune pancreatitis which showed male preponderance [16, 17], IgG4-related dacryoadenitis showed no sex preponderance.

In terms of symptoms, in addition to eyelid swelling, various ophthalmologic symptoms (double vision, ptosis, visual field disturbance, eye pain, decrease of visual acuity, eye-movement disturbance, dry eye, corneal ulcer, and epiphora) were observed with inflammatory extension beyond the lacrimal gland, such as extraocular muscle, optic nerve, and the retrobulbar region. In the literature, changes in

Fig. 2 MRI showing unilateral lacrimal gland swelling (arrows)



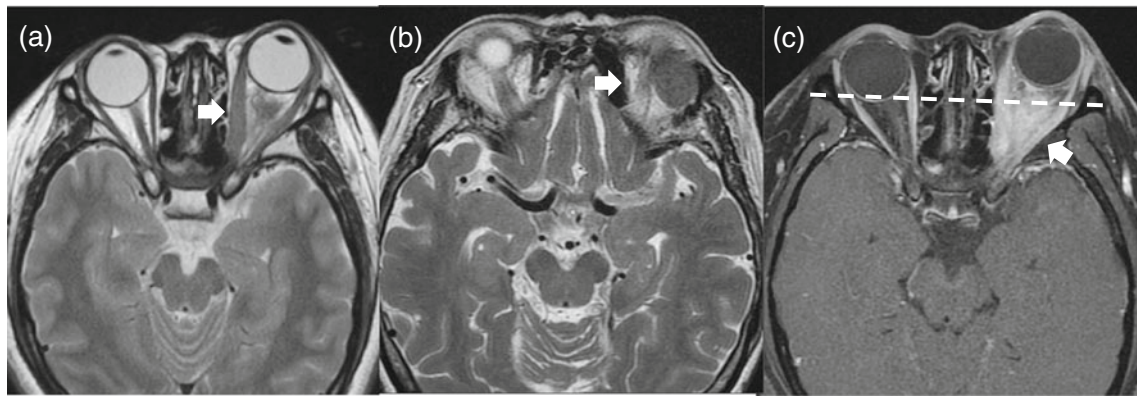


Fig. 3 MRI showing inflammatory extension beyond the lacrimal gland such as **a** thickened rectus (*arrow*), **b** displacement of optic nerve (*arrow*), and **c** retrobulbar inflammation (*arrow*) and exophthalmos (*dotted line*)

extraocular muscle and optic nerve were detected in eight (23 %) and six (17 %) of 35 patients with IgG4-related dacryoadenitis respectively. Swelling of the lacrimal glands was bilateral in half of our cases, compared to 71 % in the literature.

IgG4-related disease frequently affects more than one organ system concurrently or metachronously [1–3], and 75 % of IgG4-related dacryoadenitis patients showed other IgG4-related diseases, such as IgG4-related sialadenitis ($n=5$), autoimmune pancreatitis ($n=4$), IgG4-related retroperitoneal fibrosis ($n=2$), and lymphadenopathy ($n=8$). On FDG-PET, uptake of FDG was observed in many lesions involved in IgG4-related disease. Other IgG4-related diseases associated with

IgG4-related dacryoadenitis in the literature include sialadenitis ($n=21$), lymphadenopathy ($n=8$), autoimmune pancreatitis ($n=2$), retroperitoneal fibrosis ($n=1$), and pseudotumor of the liver ($n=1$). All patients visited ophthalmologists complaining of eyelid swelling, and underwent biopsy of the lacrimal gland on suspicion of orbital tumor. The mean interval from onset to diagnosis of IgG4-related dacryoadenitis was relatively long (60.9 months). Organ enlargements in addition to lacrimal gland swelling suggest IgG4-related dacryoadenitis, and measurement of serum IgG4 levels will lead to an early diagnosis.

In the present study, serum IgG4 levels were significantly higher in patients with other IgG4-related disease than in those without. In our previous studies, autoimmune pancreatitis

Table 3 Imaging features of IgG4-related dacryoadenitis

Case	Swelling of lacrimal gland	Extraocular muscle change	Optic nerve change	Retrobulbar change	Uptake of FDG on PET
1	bilateral	none	none	none	none
2	left	none	none	none	NE
3	bilateral ^a	none	none	none	right salivary gland, LN ¹
4	left ^a	thickened left rectus (external, medial, inferior)	inflammation (left)	inflammation	NE
5	right	thickened right rectus (external)	none	none	right orbit
6	left	thickened left rectus (external, medial, superior, inferior)	inflammation of optic nerve sheath (left)	inflammation	bilateral orbits, bilateral salivary glands, LN ²
7	bilateral ^a	none	none	none	bilateral orbits, LN ³
8	bilateral	thickened right (external, medial, inferior), left (external) rectus	none	none	bilateral orbits, pancreas, LN ^{1,3}
9	bilateral	none	none	none	bilateral orbits, LN ^{2,3}
10	left	thickened both rectus (inferior)	none	none	NE
11	left ^a	thickened both rectus (inferior)	space occupying lesion (bilateral)	orbital tumor (left) tuber outward medial rectus (right)	bilateral orbits, retroperitoneum, LN ^{1,3}
12	bilateral	none	none	none	bilateral orbits and salivary gland, LN ^{1,2}

LN lymph node; NE not examined; LN¹ cervical lymph node; LN² mediastinal lymph node; LN³ abdominal lymph node

^a With exophthalmos

Table 4 Treatment and prognosis of IgG4-related dacryoadnitis

Case	Steroid therapy PSL (mg/day) ^a	Remission	Maintenance PSL (mg/day)	Relapse	PSL (mg/day) at relapse	Follow-up period (months)
1	-	-		-		15
2	40	+	5	-		50
3	28	+	5	+ (7 months)	5	50
4	30	+	6.5	-		16
5	40	+	-	-		24
6	30	+	5	+ (8 months)	-	42
7	-	-		-		21
8	30	+	5	-		16
9	-	-		-		16
10	-	-		-		11
11	35	+	6.5	-		11
12	-	-		-		13

^a Initial dose of prednisolone

patients with serum IgG4 levels ≥ 220 mg/dl frequently exhibited other organ involvement [18], and serum IgG4 levels were significantly higher in patients with both autoimmune pancreatitis and Mikulicz's disease (median, 970 mg/dl) than in those with only autoimmune pancreatitis (267 mg/dl, $p < 0.01$) (19). Autoimmune pancreatitis patients with organ involvement of three other organs also reportedly show significantly higher IgG4 levels than those with no lesions [6, 19]. Somewhat unsurprisingly, serum IgG4 levels appear to reflect disease activity in IgG4-related disease. In the present series, serum

IgG4 levels were higher in male patients than in female patients, which might be attributable to the finding that three of the five female patients had no other IgG4-related disease.

In the present series, six patients had allergic histories, and eosinophilia and elevated serum IgE levels were detected in two and six patients respectively. Serum IgE levels were significantly higher in patients with allergic histories than in those without. In a series by Plaza et al., bronchial asthma was detected in four of ten patients (40 %) with IgG4-related dacryoadenitis [12]. In a series by Kubota et al., four of eight patients (50 %) with IgG4-related dacryoadenitis had allergic history (allergic rhinitis, $n = 3$; bronchial asthma, $n = 1$) [10]. Serum IgE levels were reportedly elevated in 56–75 % of patients with IgG4-related dacryoadenitis. In autoimmune pancreatitis, 22 % of cases had a history of allergic disease, and these patients frequently showed elevated serum IgE levels and peripheral eosinophilia, so allergic mechanisms are suspected to be implicated in AIP [20]. Some cases of IgG4-related dacryoadenitis may also be related to allergic phenomena. Antinuclear antigen and rheumatoid factor were positive in 44 % and 16 % of patients with autoimmune pancreatitis in the literature [17], and in 50 % and 8 % of IgG4-related dacryoadenitis patients in the present series, respectively.

In the present series, seven symptomatic patients received steroid therapy. Remission was achieved in all of them, but two patients relapsed: one after stopping steroid and one during maintenance therapy. In the literature, nine of 25 patients (36 %) with IgG4-related dacryoadenitis who were treated with steroid relapsed. According to a multicenter survey of treatment of autoimmune pancreatitis in Japan [21], the relapse rate for autoimmune pancreatitis patients treated with steroid was 24 % (110/451), and elevated serum IgG4 levels were one predictor of relapse. Serum IgG4 levels for the two relapsed patients were markedly elevated, at 1,910 mg/dl and 2,490 mg/dl, and were associated

Table 5 Clinical findings of IgG4-related dacryoadenitis reported in the literature

Age at diagnosis (years, mean $\pm$ SD)	56.6 $\pm$ 17.2 ($n = 58$)
Male:female	23:35 ($n = 58$)
Laterality	($n = 41$)
Bilateral	29 (71 %)
Right	7
Left	5
Other IgG4-related diseases	($n = 58$)
Sialadenitis	21
Lymphadenopathy	8
Autoimmune pancreatitis	2
Retroperitoneal fibrosis	1
Pseudotumor of the liver	1
Inflammatory extension beyond the lacrimal gland	($n = 35$)
Extraocular muscle	8
Optic nerve	6
Treatment	($n = 58$)
Steroid	25 (relapse $n = 9$)
Observation	13
Excision	8
Radiation	7
Rituximab	5

with autoimmune pancreatitis. In IgG4-related dacryoadenitis patients with markedly elevated serum IgG4 levels, steroids might need to be tapered more slowly, and longer maintenance therapy with a relatively high dose of prednisolone might be necessary.

The present study was undertaken focusing on clinicopathologically confirmed IgG4-related dacryoadenitis. Several limitations to this study must be considered. First, although the number of patients with IgG4-related dacryoadenitis analyzed represents the largest such series in the literature, further studies that include larger numbers of cases and longer follow-up are needed to confirm the clinical findings, treatment outcomes, and predictive factors of relapse. Second, definitive diagnostic criteria for IgG4-related dacryoadenitis are needed. A third limitation is that FDG-PET was performed in only nine patients. If more patients had undergone FDG-PET, a higher prevalence of systemic disease might have been identified.

In summary, IgG4-related dacryoadenitis exhibits a unique clinical appearance with various ophthalmologic symptoms due to extensive inflammation beyond the lacrimal gland, frequent association with other IgG4-related diseases or allergic phenomena, and steroid responsiveness. IgG4-related dacryoadenitis patients with other IgG4-related disease showed higher IgG4 levels and an increased risk of relapse. Further studies are needed to confirm the present observations.

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Conflict of Interest The authors state that they have no conflict of interest.

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