• Clinical Research •

A clinicopathological study on IgG4-related ophthalmic disease

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Abstract

• AIM: To investigate clinicopathological features of immunoglobulin G4-related ophthalmic disease (IgG4-ROD), and analyze the recurrence rates following systemic corticosteroid administration.

• METHODS: We retrospectively searched clinical features, laboratory and histological findings based on the medical records of 21 patients with IgG4-ROD. All the patients examined in this study underwent surgical resection in the ocular adnexal lesions and underwent histological evaluation. This study further investigated clinical and histopathological features of 15 patients who received systemic corticosteroid after the resection.

• RESULTS: The mean age of the patients consisting of 7 males (33%) and 14 females (67%) was 61y. Fourteen patients were diagnosed as definitive, and 2 and 5 patients were probable and possible IgG4-ROD, respectively. Eyelid swelling was an initial symptom in 11 patients (52%) who did not show systemic involvements at a diagnosis. Fifteen patients received systemic corticosteroid administration, and all showed remission of inflammation. Among them, 10 patients did not recur, whereas 5 patients (33%) recurred during tapering. There were no significant difference between patients with or without recurrence in clinicopathological features.

• CONCLUSION: In this study, female patients are more predominant in IgG4-ROD. While inflammation recurs in one-third of patients, this study do not identify factors associated with recurrence after systemic corticosteroid administration.

• KEYWORDS: IgG4-related ophthalmic disease; corticosteroid; histopathology; recurrence

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INTRODUCTION

Immunoglobulin G4-related ophthalmic disease (IgG4-ROD) is characterized by enlargement of orbital tissues, infiltration of IgG4-positive plasma cells, and elevated serum IgG4 levels. The Japanese IgG4-related Ophthalmic Disease Study Group further revealed that the prevalence of IgG4-ROD among the orbital lymphoproliferative disorders was 22%[1]. IgG4-ROD can be found within the spectrum of systemic IgG4-related diseases (IgG4-RD) involving various systemic organs such as not only the orbit, but also pancreas, hepatobiliary tract, lung, kidney, retroperitoneum, and lymph nodes[2-6]. Systemic administration of corticosteroid is effective, and many patients have a good response to prednisolone (PSL)[5,7]. Although the inflammation recurs while PSL was tapered in selected patients[5,7], the mechanisms underlying the recurrence and risk factors remain unknown. Furthermore, there are no studies elucidating the relationship between pathological findings and clinical courses. In this study, we investigated the clinicopathological features of IgG4-ROD, and analyzed the recurrence rates following systemic corticosteroid administration.

SUBJECTS AND METHODS

This was a retrospective observational study. Institutional Review Board of Hokkaido University Hospital for clinical research approved this study (IRB number: 011-0319). Patients with IgG4-ROD treated in Hokkaido University Hospital from February 2006 to December 2014 were enrolled in this study. This study retrospectively investigated clinical features, laboratory and histological findings based on the medical records of 21 patients. Inclusion criteria were that the enlargements of orbital tissues were surgically resected, and that the patients followed the diagnostic criteria of IgG4-ROD published in 2015[2]. Briefly, the criteria included enlargement of tissues, high IgG4-positive plasma cell infiltration in the tissues (ratio of IgG4-positive cells to IgG-positive cells of 40% or above, or more than 50 IgG4-positive cells per high-power field with magnification of 400×), and elevated serum

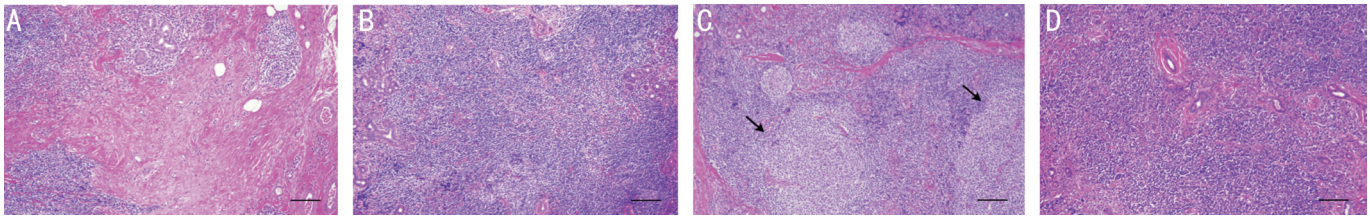

Figure 1 Histopathological evaluation of IgG4-ROD A: We defined 'fibrosis-positive ' when fibrosis occupied 30% or over of a low power field (hematoxylin and eosin, magnification: 40×); B: We defined 'fibrosis-negative' when fibrosis occupied less than 30% of a low power field (hematoxylin and eosin, magnification: 40×); C: We defined 'lymphoid follicle-positive', when at least one clearly configured lymphoid follicle (arrows) was observed in a whole field (hematoxylin and eosin, magnification: 40×); D: We defined 'lymphoid follicle-negative', when any lymphoid follicle was not observed in a whole field (hematoxylin and eosin, magnification: 40×). Scale bar=100 μm.

IgG4 concentration (≥135 mg/dL). Diagnoses were classified as 'definitive' when all of them were satisfied, 'probable' when enlargement of tissues and histopathologic criteria were satisfied, and 'possible' when enlargement of tissues and elevated serum IgG4 concentration were satisfied[2]. Patients with Sjögren syndrome, malignant lymphoma, sarcoidosis, Wegener granulomatosis, thyroid-related orbitopathy, idiopathic orbital inflammation, and dacryoadenitis or orbital cellulitis caused by bacteria or fungi infection were excluded in this study (UMIN registration number: R000033834). Informed consent was obtained from the patients according to the IRB recommendation.

This study examined the clinical course and pathological differences in the excised orbital tissues between the patients with and without recurrence following systemic corticosteroid therapy. The patients were evaluated as recurrence when the organs enlarged again.

Pathological Evaluation Twenty patients underwent surgical resection of tissues in the lacrimal gland enlargements and one patient underwent surgical resection of the nodule in the palpebral conjunctiva. The isolated tissues were fixed in formalin, and embedded in paraffin. Sections were submitted for hematoxylin and eosin staining and immunohistochemistry with anti-IgG4 and IgG antibodies to make histological diagnoses based on the IgG4-ROD diagnostic criteria. To evaluate the pathological difference between patients with and without recurrence following corticosteroid treatments, we analyzed IgG4:IgG ratio in infiltrating plasma cells, and the presence of fibrosis and lymphoid follicles in the excised tissues. As shown in Figure 1, this study defined 'fibrosis-positive' when fibrosis occupied 30% or over of the tissues under a low power field (magnification: 40×) (Figure 1A). Further this study defined 'lymphoid follicle-positive' (Figure 1C, arrows), when we observed at least one clearly configured lymphoid follicle in each section. If not, the cases were evaluated as fibrosis and/or lymphoid follicle-negative (Figure 1B, 1D).

Statistical Analysis We analyzed clinical and histological differences between patients with recurrence and without recurrence using the Mann-Whitney *U* test/Chi-square test. $P<0.05$ was considered significant. We performed all statistical analyses using statistical analyses software, Ver. 2.0, for Macintosh (Statistics Survey System-development, Esumi Corporation, Tokyo, Japan: http://www.esumi.co.jp).

RESULTS

Clinical Features We reviewed twenty-one patients with IgG4-ROD, and summarized their clinical features in Table 1. All patients except Case 6 underwent surgical resection of tissues in the lacrimal gland enlargements. Case 6 underwent surgical resection of the nodule in the palpebral conjunctiva. The patients consisted of 7 males (33%) and 14 females (67%). Mean age of the onset in all the patients was 61y, and those of males and females were 67y (range 56-80) and 58y (range 36-78), respectively. The mean presumed clinical symptom duration of the disease was 12mo (2-91mo). Serum IgG4 levels elevated more than 135 mg/dL in 20 patients (95%). Mean serum IgG4 concentration was 658.2 mg/dL. Fourteen patients were diagnosed as definitive, 2 patients probable, and 5 patients possible IgG4-ROD. Sixteen patients (76%) had bilateral periocular involvements. Eyelid swelling was an initial symptom in 11 patients (52%) who did not show systemic involvements at a diagnosis.

Ten patients (48%) had extraorbital involvements such as submandibular and parotid gland swelling (6 patients, 29%), lymphadenopathy (4 patients, 19%), and autoimmune pancreatitis (1 patient, 5%). Six patients (29%) had a medical history of bronchial asthma.

Treatments Among 21 patients, 15 patients received systemic corticosteroid administration. Case 1 received steroid pulse therapy (methylprednisolone at 1 g per day for 3d, followed by PSL at 40 mg per day, with tapering thereafter) because of deteriorated visual acuity caused by retrobulber optic perineuritis. Oral PSL was administered to 14 patients (Cases 2-15). The initial dose of PSL was 30 mg or 40 mg per day, which was gradually tapered. Cases 17 and 18 were given topical corticosteroid treatment including nasal and inhaled corticosteroid by an otolaryngologist and a physician, because they have allergic rhinitis and bronchial asthma, respectively.

Table 1 Clinical profiles of IgG4-ROD examined in this study

Case	Sex (y)	Age (y)	Side	Systemic involvement	Past medical history	Serum IgG4 (mg/dL)	Serum IgG (mg/dL)	Serum IgG4/IgG	Diagnosis	Treatment
1	M	56	B	Lymphadenopathy, pleural lesion	BA, DM	1370	2387	0.57	D	Systemic corticosteroids
2	F	52	L	Not found	Not found	305	2071	0.15	D	Systemic corticosteroids
3	M	73	B	Not found	HBV carrier	2010	4221	0.48	D	Systemic corticosteroids
4	F	58	B	Submandibular gland swelling, increased FDG uptake in the pancreas in PET	Not found	977	2497	0.39	D	Systemic corticosteroids
5	M	69	B	Not found	Benign prostatic hyperplasia, HL	875	2348	0.37	Po	Systemic corticosteroids
6	F	56	L	Not found	BA, herpes zoster	133	1193	0.11	Pr	Systemic corticosteroids
7	M	80	B	Not found	BA, HT	1500	4073	0.37	Po	Systemic corticosteroids
8	F	61	B	Submandibular gland swelling, lymphadenopathy	HT, HL	219	1411	0.16	Po	Systemic corticosteroids
9	M	65	B	Not found	Not found	573	2060	0.28	Po	Systemic corticosteroids
10	F	78	B	Not found	Sinusitis, spinal stenosis, herniated disc	811	1861	0.44	D	Systemic corticosteroids
11	F	72	B	Not found	Not found	201	1844	0.11	D	Systemic corticosteroids
12	F	56	B	Submandibular gland swelling	Thyroid cancer	396	1711	0.23	D	Systemic corticosteroids
13	F	55	L	Hashimoto's thyroiditis	BA, HT, HL, cardiac hypertrophy	494	1764	0.28	D	Systemic corticosteroids
14	F	72	B	Submandibular and parotid gland swelling, lymphadenopathy, autoimmune pancreatitis	BA	329	1639	0.20	D	Systemic corticosteroids
15	F	49	L	Not found	DM	94.2	ND	ND	Pr	Systemic corticosteroids
16	F	36	B	Thyromegaly	Not found	143	ND	ND	D	Total excision of the lacrimal gland tumor
17	F	65	B	Not found	Allergic rhinitis, hypertrophic cardiomyopathy	498	1918	0.26	D	Nasal corticosteroid
18	F	46	B	IgG4-related disease of paranasal sinus	BA, HBV carrier, sudden sensorineural hearing loss, synovitis	537	1462	0.37	Po	Inhaled corticosteroid
19	F	52	B	Submandibular gland swelling	Macular hole	398	1483	0.27	D	Observation
20	M	60	B	Not found	Not found	460	1957	0.24	D	Unknown
21	M	64	R	Parotid gland swelling, lymphadenopathy, wall thickening of bronchia, renal calyces and ureters, peritoneal fibrosis	Not found	1500	ND	ND	D	PSL (already given before biopsy)

B: Bilateral; L: Left; R: Right; BA: Bronchial asthma; DM: Diabetes mellitus; FDG: Fludeoxyglucose; PET: Positron emission tomography; HL: Hyperlipidemia; HT: Hypertension; HBV: Hepatitis B virus; ND: No data; D: Definitive; Pr: Probable; Po: Possible; mPSL: Methylprednisolone; PSL: Prednisolone.

Case 19 was observed without any treatment. Total excision of the lacrimal gland tumor was done in Case 16. Lacrimal gland enlargement was resected after PSL was initiated in the other hospital in Case 21. Case 20 stopped follow-up before treatment (Table 1).

Outcomes of Systemic Corticosteroid Table 2 summarized clinicopathological features and outcomes of systemic corticosteroid. Each case number of Table 2 corresponds to that of Table 1. A mean follow-up period was 39.9mo. All of 15 patients who were given systemic corticosteroid showed response and remission of inflammation after treatments. Ten patients (67%) eventually did not recur, while 5 patients

Table 2 Clinicopathological profiles in IgG4-related ophthalmic disease patients treated with systemic corticosteroids

Case	Treatment	Follow up (mo)	Recurrence	The dose of PSL at the recurrence	Fibrosis	Lymphoid follicles
1	mPSL 1 g/d for 3d, followed by PSL 40 mg/d	14	No	Na	+	+
2	PSL 30 mg/d	72	No	Na	-	-
3	PSL 30 mg/d	60	No	Na	+	+
4	PSL 30 mg/d	32	No	Na	+	-
5	PSL 30 mg/d	17	No	Na	+	-
6	PSL 30 mg/d	16	No	Na	-	-
7	PSL 30 mg/d	13	No	Na	+	-
8	PSL 30 mg/d	9	No	Na	+	+
9	PSL 40 mg/d	14	No	Na	-	-
10	PSL 30 mg/d	37	No	Na	+	+
11	PSL 30 mg/d	75	Yes	0	-	+
12	PSL 40 mg/d	77	Yes	0	+	+
13	PSL 30 mg/d	26	Yes	0	+	+
14	PSL30 mg/d	115	Yes	0	+	+
15	PSL40 mg/d	22	Yes	10	+	+

mPSL: Methylprednisolone; PSL: Prednisolone; Na: Not applicable, +: Positive, -: Negative.

Table 3 Factors associated with recurrence after administration of systemic corticosteroid *n* (%)

Factors	Non-recurrence (*n*=10)	Recurrence (*n*=5)	*P* (Mann-Whitney/Chi-square test)
Age (y)[a]	64.8±9.8	60.8±10.6	>0.05
Serum IgG4 levels (mg/dL)[a]	877±609	303±158	>0.05
Serum IgG levels (mg/dL)[a]	2412±1004	1740±86[b]	>0.05
Serum IgG4/IgG (%)[a]	33.1±15.4	20.5±7.2[b]	>0.05
Female	5 (50)	5 (100)	>0.05
Bilateral	8 (80)	3 (60)	>0.05
Involvement of other organs	3 (70)	3 (60)	>0.05
Definitive/Probable/Possible	5/1/4	4/1/0	
Following pathological criteria (definitive and probable)	6 (60)	5 (100)	>0.05
Fibrosis	7 (70)	4 (80)	>0.05
Lymphoid follicles	4 (40)	5 (100)	>0.05

[a]Mean±SD; [b]Not determined in 1 patient.

(33%) recurred during tapering PSL. The dose of PSL when inflammation recurred was 0 mg in 4 patients, and 10 mg in 1 patient. Systemic severe adverse effects did not occur in any of 15 cases. The patients with recurrence needed to increase the dose of PSL. At the recurrence, Cases 11-14 and Case 15 received 30 mg and 15 mg of PSL per day, respectively. All 5 patients showed response to the treatment, and the dose of PSL was gradually tapered. All five patients did not recur after that; however, Case 12 developed autoimmune pancreatitis and the dosage of PSL increased to 30 mg per day, which was gradually being tapered.

Factors Associated with Recurrence After Systemic Corticosteroid Administration We compared 10 patients without recurrence and 5 patients with recurrence concerning clinical and pathological features to investigate factors related to recurrence after administration of corticosteroids (Table 3). All clinicopathological factors such as age, gender, laterality, systemic involvement, serum IgG4 levels, duration of the disease, and serum IgG4:IgG ratio, lymphoid follicles and fibrosis in the tissues, and diagnostic classification (definitive, probable or possible) were not associated with the recurrence.

DISCUSSION

IgG4-RD is a collection of disorders with unknown etiology that are characterized by an infiltrate of IgG4-immunopositive plasma cells accompanied by enlargement of various organs in the body. IgG4-ROD is characterized by enlargement of orbital and periocular tissues, including the lacrimal glands, extraocular muscles, infraorbital and supraorbital nerves, sclera and lacrimal sac[8-11]. IgG4-ROD can be found in a part of IgG4-RD involving systemic organs[2-6], which is commonly associated with bronchial asthma and allergic rhinitis[12]. In this study, more than half of patients suffering from eyelid swelling showed no systemic involvements at a diagnosis, suggesting that periocular enlargement can be early manifestation in

IgG4-RD. The mean age of IgG4-ROD in our series was 61y, concurrent with other studies within the range of 51-61y[5,13-15]. Previous study reported that IgG4-RD has a male-gender predilection[16], whereas Andrew *et al*[17] addressed that IgG4-ROD affected men and women equally. In this study, female patients were more predominant in IgG4-ROD examined.

The optimal therapeutic strategy for IgG4-ROD has yet to be established. Because IgG4-ROD rarely manifests spontaneous remission without any treatment[18], steroid therapy is often used as a primary therapy for IgG4-ROD[13]. Most patients show response to the systemic corticosteroid therapy; however, Yu *et al*[13] reported that 2 of 8 patients with IgG4-ROD had poor response to systemic corticosteroid. The recurrence rates after steroid therapy ranged from 18%-58%[7,14-15,19]. In this study, all patients showed good response to steroid therapy and one-third of the patients eventually recurred following the treatment.

There are some previous reports investigating the risk factors of relapse after systemic corticosteroid administration. Recent study reported that the extraophthalmic involvement is a risk factor for frequent orbital relapse after corticosteroid treatment[14]. Another study reported the incidence of patients who were positive for rheumatoid factor before corticosteroid treatment was higher in the recurrence group[19]. In this study, the presence of systemic involvement was not related to the recurrence, and the serum rheumatoid factor levels were not available, the latter of which are future issues to be resolved.

To our knowledge, there are no studies elucidating the correlation between histological findings and activity of the disease in IgG4-ROD. In this study, the histological findings on lymphoid follicle and fibrosis were different in each patient. Therefore, we focused on the relationship between the histological findings and the clinical course of IgG4-ROD patients treated with systemic corticosteroids. However, there was no significant difference in the presence of lymphoid follicles and the extent of fibrosis between patients with or without recurrence. Further pathological studies are needed to elucidate the factors associated with recurrence after systemic corticosteroid administration.

We observed female patients more frequently in IgG4-ROD. Moreover, this study demonstrated that many of them were postmenopausal females. Recently, Jiang *et al*[20] reported that estrogen and its receptor might inhibit inflammation in the rat tissues, suggesting that estrogen may become a new therapeutic target for inflammatory diseases. Therefore, we speculate one of reasons why female patients were more observed in this study might be decreased estrogen levels in post-menopause, facilitating development of orbital inflammation. Further studies are needed to examine the expression of estrogen receptor in IgG4-ROD tissues to prove estrogen in the regulation of inflammation as a first step.

Serial changes in serum IgG4 levels are reported to reflect the activity of IgG4-RD[21]. Yu *et al*[13] reported that patients with poor response for systemic corticosteroid administration showed significantly lower serum IgG4 levels and IgG4:IgG ratio, suggesting that lower serum IgG4 levels reflected lower disease activity. In this study, all patients had good response to systemic corticosteroid regardless of serum IgG4 levels and serum IgG4:IgG ratio at an initial presentation. In addition, there is no significant difference in serum IgG4 levels or serum IgG4:IgG ratio between the patients with or without recurrence. Therefore, serum IgG4 levels did not predict the response to steroid treatment for IgG4-ROD nor the recurrence after steroid treatment in this study.

There are limitations in this study. First, the number of patients who underwent surgical resections of enlarged orbital tissues is limited. Second, because this is a retrospective study, the treatment, the follow-up periods, and the amount of information about systemic diseases differed among patients. Third, since there is lack of standardized treatment protocol, it is difficult to identify factors associated with recurrence after systemic corticosteroid administration. Forth, significant differences in the lengths of the follow-up period also may let analyze difficult regarding factors associated with recurrence after systemic corticosteroid administration. Fifth, the most of biopsy specimens were collected by partial resection, which may not have reflected the pathology of entire lesions.

In conclusion, female patients might be more predominant in IgG4-ROD. Although inflammation recurred in one-third of patients, this study did not identify clinicopathological factors associated with recurrence after systemic corticosteroid administration.

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REFERENCES

1 Japanese study group of IgG4 ophthalmic disease. A prevalence study of IgG4-related ophthalmic disease in Japan. *Jpn J Ophthalmol* 2013;57(6):573-579.

2 Goto H, Takahira M, Azumi A, Japanese Study Group for IgG4-Related Ophthalmic Disease. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Opthalmol* 2015;59(1):1-7.

3 Plaza JA, Garrity JA, Dogan A, Ananthamurthy A, Witzig TE, Salomão DR. Orbital inflammation with IgG4-positive plasma cells: manifestation of IgG4 systemic disease. *Arch Ophthalmol* 2011;129(4):421-428.

4 Wallace ZS, Deshpande V, Stone JH. Ophthalmic manifestations of IgG4-related disease: single-center experience and literature review. *Semin Arthritis Rheum* 2014;43(6):806-817.

5 Kubota T, Moritani S, Katayama M, Terasaki H. Ocular adnexal IgG4-related lymphoplasmacytic infiltrative disorder. *Arch Ophthalmol* 2010;128(5):577-584.

6 Divatia M, Kim SA, Ro JY. IgG4-related sclerosing disease, an emerging entity: a review of a multi-system disease. *Yonsei Med J* 2012;53(1):15-34.

7 Min HK, Lee YS, Yang SW, Lee J, Kwok SK, Ju JH, Kim WU, Park SH. Clinical outcomes and pathological characteristics of immunoglobulin G4-related ophthalmic disease versus orbital inflammatory pseudotumor. *Korean J Intern Med* 2017.

8 Ohshima K, Sogabe Y, Sato Y. The usefulness of infraorbital nerve enlargement on MRI imaging in clinical diagnosis of IgG4-related orbital disease. *Jpn J Ophthalmol* 2012;56(4):380-382.

9 Sogabe Y, Ohshima K, Azumi A, Takahira M, Kase S, Tsuji H, Yoshikawa H, Nakamura T. Location and frequency of lesions in patients with IgG4-related ophthalmic diseases. *Graefes Arch Clin Exp Ophthalmol* 2014;252(3):531-538.

10 Kase S, Suzuki Y, Shinohara T, Kase M. IgG4-related lacrimal sac diverticulitis. *Orbit* 2014;33(3):217-219.

11 Reynolds GL, Norris JH, Aslam S, Sharma S. IgG4-related disease presenting as posterior scleritis and vitritis, progressing to multifocal orbital involvement. *BMJ Case Rep* 2017:bcr-2017-219568.

12 Matsui S, Taki H, Shinoda K, Suzuki K, Hayashi R, Tobe K, Tokimitsu Y, Ishida M, Fushiki H, Seto H, Fukuoka J, Ishizawa S. Respiratory involvement in IgG4-related Mikulicz's disease. *Mod Rheumato*l 2012;22(1):31-39.

13 Yu WK, Kao SC, Yang CF, Lee FL, Tsai CC. Ocular adnexal IgG4-related disease: clinical features, outcome, and factors associated with response to systemic steroids. *Jpn J Ophthalmol* 2015;59(1):8-13.

14 Park J, Lee MJ, Kim N, Kim JE, Park SW, Choung HK, Khwarg SI. Risk factors for extraophthalmic involvement and treatment outcomes in patients with IgG4-related ophthalmic disease. *Br J Ophthalmol* 2017; 102(6):736-741.

15 Ebbo M, Patient M, Grados A, *et al*. Ophthalmic manifestations in IgG4-related disease: clinical presentation and response to treatment in a French case-series. *Medicine (Baltimore)* 2017;96(10):e6205.

16 Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012;366(6):539-551.

17 Andrew N, Kearney D, Selva D. IgG4-related orbital disease: a meta-analysis and review. *Acta Ophthalmologica* 2013;91(8):694-700.

18 Kase S, Yamamoto T, Ishijima K, Noda M, Ishida S. Spontaneous regression of IgG4-related dacryoadenitis. *Mod Rheumatol* 2013;23(5): 1018-1021.

19 Kubota T, Katayama M, Moritani S, Yoshino T. Serologic factors in early relapse of IgG4-related orbital inflammation after steroid treatment. *Am J Ophthalmol* 2013;155(2):373-379.el.

20 Jiang Q, Li WX, Sun JR, Zhu TT, Fan J, Yu LH, Burnstock G, Yang H, Ma B. Inhibitory effect of estrogen receptor beta on P2X3 receptors during inflammation in rats. *Purinergic Signal* 2017;13(1):105-117.

21 Tabata T, Kamisawa T, Takuma K, Egawa N, Setoguchi K, Tsuruta K, Obayashi T, Sasaki T. Serial changes of elevated serum IgG4 levels in IgG4-related systemic disease. *Intern Med* 2011;50(2):69-75.