Clinical observation of orbital IgG4-related diseases

NA WU[1] and FENG YUAN SUN[2]

[1]Department of Ophthalmology, Tianjin First Central Hospital, Tianjin 300192;
[2]Department of Ophthalmology, Tianjin Medical University Eye Hospital, Tianjin 300384, P.R. China

Received March 21, 2018; Accepted November 7, 2018

DOI: 10.3892/etm.2018.7002

Abstract. The aim of the present study was to observe the histopathological changes of immunoglobulin G4-related orbital diseases (IgG4-RODs), summarize the clinical manifestations and imaging features of the IgG4-RODs of the eyelids and explore the early diagnosis of IgG4-RODs. Between June 2011 and May 2015, 23 patients with non-specific orbital inflammation in the Department of Ophthalmology at the First Central Hospital of Tianjin were recruited. The serum IgG4 titer in 9 patients ranged from 4.58 to 46.70 g/l (reference value, 0.03-2.01 g/l), with an average value of 21.93±2.18 g/l. Notably, the degree of increase in the 9 patients with IgG4-RODs was different, but all were >1.35 g/l. A total of 6 cases of infraorbital nerve thickening were observed. In addition, there were 3 cases of extraocular muscle thickening and 1 patient with IgG4-ROD had an orbital tissue lesion extending along the inferior temporal septum to the left pterygopalatine fossa, with left sacral fissure widening and involvement of the left maxillary sinus. The study revealed that the thickening of the inferior orbital nerve may be a characteristic of IgG4-ROD. Therefore, on the basis of biopsy and serological examination in the clinic, early diagnosis can be combined with imaging examination, clinical manifestation and laboratory examination, so as to reduce misdiagnosis and missed diagnosis.

Introduction

Idiopathic orbital inflammation (IOI) is a type of cryptogenic, non-infectious, inflammatory infiltrating orbital disease that can involve any tissue in the orbit (1). The diagnosis of IOI requires the exclusion of tumors, infections and systemic inflammatory diseases. Due to the large number of non-specific inflammatory diseases and how complex the diseases are (2), the clinical diagnosis and the pathological diagnosis require further regulation. Different types of inflammatory pseudotumors vary greatly, and each has a different response to treatment (3). Notably, orbital inflammatory pseudotumor is a chronic non-specific inflammatory proliferative disease that originates in the eyelids (4). Clinically, it has been demonstrated that the clinical manifestations of inflammatory pseudotumors are diverse and may be similar to various other diseases, including lymphoma or systemic connective tissue inflammation (5). Its diagnosis and treatment difficulties, etiology and pathogenesis are unknown, and it is a challenge for ophthalmologists (4).

At present, the majority of studies have identified that non-specific eyelid inflammation is associated with systemic immune diseases, including IgG4-related systemic diseases (6). Immunoglobulin G4-related orbital disease (IgG4-ROD) is an autoimmune disease characterized by infiltration of $IgG4^+$ plasma cells accompanied by tissue fibrosis of multiple organs throughout the body and swelling or tumor-like, nodular or proliferative lesions (6).

The timely identification, and correct diagnosis and proper handling of IgG4-ROD are essential for the diagnosis and treatment of IOI, in which patients typically experience painless swelling of both eyes as the first symptom (7). The majority of newly diagnosed patients are diagnosed with non-specific inflammation, such as lacrimal gland or orbital inflammatory pseudotumor (8). In the treatment of patients requiring hormone therapy based on the condition, poor treatment or relapse of patients through tissue biopsy, a number of $IgG4^+$ plasma cells have been identified to infiltrate tissues, and the possibility of eyelid IgG4-RODs should be considered.

Materials and methods

Participants. Pathological eyelid specimens were collected from 23 patients with non-specific orbital inflammation in the Department of Ophthalmology at the Tianjin First Center Hospital (Tianjin, China) between June 2011 and May 2015. All patients underwent orbital lesion resection and histopathological examinations 2 weeks after admission. Patients with lymphocyte and plasmacyte infiltration of the orbital region as the main pathological features on their pathological records were included in the study. A total of 9 patients with IgG4-ROD (6 males and 3 females) and 14 patients without IgG4-ROD (8 males and 6 females) were recruited to the present study. The mean age of the patients with IgG4-ROD was 53.2±11.8 years and patients without IgG4-ROD was 49.5±9.3 years. The exclusion criteria of the IgG4-ROD group

Correspondence to: Dr Na Wu, Department of Ophthalmology, Tianjin First Center Hospital, 24 Fukang Road, Tianjin 300192, P.R. China
E-mail: wuna0312@126.com

Key words: orbital disease, immunoglobulin G, differential diagnosis, immunohistochemistry, IgG4-related eye disease

were as follows: Patients with lymphoma, a mesenchymal tumor, an epithelial tumor or a metastatic tumor. The present study was approved by the Ethics Committee of Tianjin First Center Hospital (Tianjin, China; approval no. 2016N056KY). All patients provided written informed consent.

Hematoxylin and eosin (H&E) staining. Eyelid specimens were sliced into 4-μm-thick sections. All sections were fixed with 4% formaldehyde solution at 4˚C for 24 h and embedded in paraffin. After rinsing with distilled water for 2 min the sections, the sections were placed in 95% ethanol for 2 min, hydrated for 5 min and stained with hematoxylin for 3 min at 40˚C. The sections were then wash with water for 30 sec and counterstained with eosin for 60 sec at 50˚C. The images were observed using a fluorescence microscope at a magnification of x100.

Serological tests. A week after enrollment, the blood from the patients was centrifuged at 1,000 x g for 7-10 min at 4˚C to extract serum. Serum IgG4 levels were measured by immunoturbidimetry using an automatic turbidimeter (Behring BN II Nephelometer) and N Latex IgG4 (both Siemens AG, Munich, Germany) at 10˚C for 15 min.

Immunohistochemical staining. Eyelid specimens were sliced into 3-4-μm-thick sections and fixed with 4% formaldehyde solution at 4˚C for 24 h and embedded in paraffin. The sections were stained with anti-IgG primary antiobodies from a immunohistochemistry kit (cat. no. ZA-0448; 1:500; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China) and anti-IgG4 primary antiobodies from a immunohistochemistry kit (cat. no. IM-0041; 1:500; Shanghai Jie Hao Biotechnology Co., Ltd., Shanghai, China) at 37˚C for 2 h and a enzyme-labeled sheep anti-mouse/rabbit IgG polymer (cat. no. PV-6000; 1:1,000; Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., Beijing, China) at 37˚C for 30 min. IgG and IgG4 were expressed in the cytoplasm, and were brownish yellow or dark brownish yellow particles when positively stained. The images were observed using a light microscope at a magnification of x400.

Routine visual inspection using a 5-meter logarithmic vision chart, slit lamp, computer intraocular pressure measurement, fundus examination, Hertel eyeball out of focus measurement of the eyeball and nine eye movements was performed 1 week prior to orbital lesion resection (9), in addition to computed tomography (CT) and magnetic resonance imaging (MRI).

The preoperative CT examination was performed using a Toshiba Aquilion 16-slice spiral CT scanner (Toshiba Corporation, Tokyo, Japan) with axial and coronal scanning. The patients undergoing axial scanning were in a supine position, the radiographic base line was perpendicular to the table and the spiral scans were conducted from the upper to the lower edge of the eyelid. The patients undergoing coronal scanning were in the prone position, the hearing line is parallel to the table, and the spiral scans were conducted from the front edge of the orbital crest to the posterior edge of the optic canal.

The MRI examination was performed using the Siemens ESSENZA 1.5T superconducting MRI scanner (Siemens AG, Munich, Germany). The scanning method was as follows: The conventional sequence of the scanning method consisted of the sagittal (T1WI, T2WI) and coronal (T: WI + pressure fat) plain scans.

Follow-up. A total of 19 patients were followed-up 6 months after enrollment; 9 patients with IgG4-ROD and 10 patients without IgG4-ROD.

Statistical analysis. SPSS 19.0 statistical software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. The χ^2 test was used to compare data for males and females. The difference in the age of onset between the two groups was compared using the two-sample t-test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical features and laboratory tests. No significant difference in the age at onset (P=0.26) or sex (P=0.53) was identified between the two groups. Serological tests were performed. Notably, the serum IgG4 titer in 9 patients ranged from 4.58 to 46.70 g/l (reference value, 0.03-1.35 g/l) (10), with an mean value of 21.93±2.18 g/l. Notably, the degree of increase was different regarding serological IgG4, but all were >1.35 g/l (Table I). These findings suggested that increased serological IgG4 levels were elevated (>1.35 g/l), which is an important serological feature to consider in IgG4-ROD. In IgG^+ plasma cells, the absolute value was ≤50 and the HPF-$IgG4/IgG^+$ plasma cell ratio was >40% (Fig. 1A-C).

Eye performance. A total of 16 patients out of 23 exhibited no significant vision loss. The ocular manifestations of patients with IgG4-ROD were primarily eyelid swelling (9 cases), ocular protrusion (4 cases) and limited eyeball movement (3 cases). The ocular manifestations of patients with non-IgG4-ROD were primarily eyelid swelling (8 cases), ocular protrusion (7 cases), limited eye movement (6 cases; Table II).

Imaging findings. CT and MRI scans from patients with IgG4-ROD revealed orbital tissue involvement and clear invasion of the lesion into the lacrimal gland tissue. A total of 9 out of 5 cases involved the lacrimal gland tissue, mostly predominantly with bilateral lacrimal gland diffuse symmetry. CT examinations indicated medium density changes, unclear boundaries, uniform density, no calcification and no destructive changes in the surrounding bone wall. There were 6 cases of infraorbital nerve thickening (Fig. 1D), 3 cases of extraocular muscle thickening and 1 patient with IgG4-ROD had an orbital tissue lesion extending along the inferior temporal septum to the left pterygopalatine fossa, with left sacral fissure widening and involvement of the left maxillary sinus. In 9 cases, IgG4-ROD CT scans indicated that the lesions were of moderate density and that there was no destructive change in the peripheral bone wall, suggesting that the disease was a less aggressive lesion. Of these cases, 3 had signs of limited eye movements. The examinations revealed that the corresponding extraocular muscles were invaded to different degrees, indicating that the functions of the extraocular muscles were affected when the extraocular muscles were affected.

Relevant examination of the patient's eye prior to and following sectioning demonstrated that the disease had little

Table I. Serum IgG4 levels in all patients 1 week after recruitment.

Variable	IgG4 (g/l)
Patients with IgG4-ROD	
Case 1	12.40
Case 2	15.19
Case 3	42.75
Case 4	5.72
Case 5	20.41
Case 6	39.05
Case 7	4.58
Case 8	46.70
Case 9	10.53
Mean ± standard deviation	21.93±2.18
Patients without IgG4-ROD	
Case 10	0.21
Case 11	0.37
Case 12	0.65
Case 13	0.05
Case 14	0.92
Case 15	0.07
Case 16	0.12
Case 17	0.14
Case 18	0.42
Case 19	1.08
Case 20	0.97
Case 21	0.03
Case 22	0.74
Case 23	0.38
Mean ± standard deviation	0.43±0.19

effect on vision. Furthermore, poor vision correction was primarily due to the opacity of the lens or fundus lesions.

Therapeutic effect. Of the 9 cases of IgG4-ROD, 7 had follow-up data, of which 5 were treated with glucocorticoids, which lead to symptoms being relieved and controlled, with only 1 patient experiencing symptom recurrence when glucocorticoids were reduced. Follow-up data were available for 10 of the 14 patients with non-IgG4-ROD. Symptoms were controlled in 1 case by treatment with glucocorticoids. Symptoms improved in 13 cases following surgery.

Discussion

The most common type of clinical non-specific orbital inflammation is orbital inflammatory pseudotumor (4). Orbital inflammatory pseudotumor occurs predominantly in young and middle-aged individuals with more than one eye (11). No significant difference regarding sex was observed in the present study. However, due to the small number of cases observed, it is necessary to increase the sample size in the future. Typical clinical manifestations of IgG4-ROD include hyperplasia of the eyelids, exophthalmos and eye movement (12). Chronic or severe cases of obstruction, eyelid and conjunctival congestion, edema, diplopia and vision loss

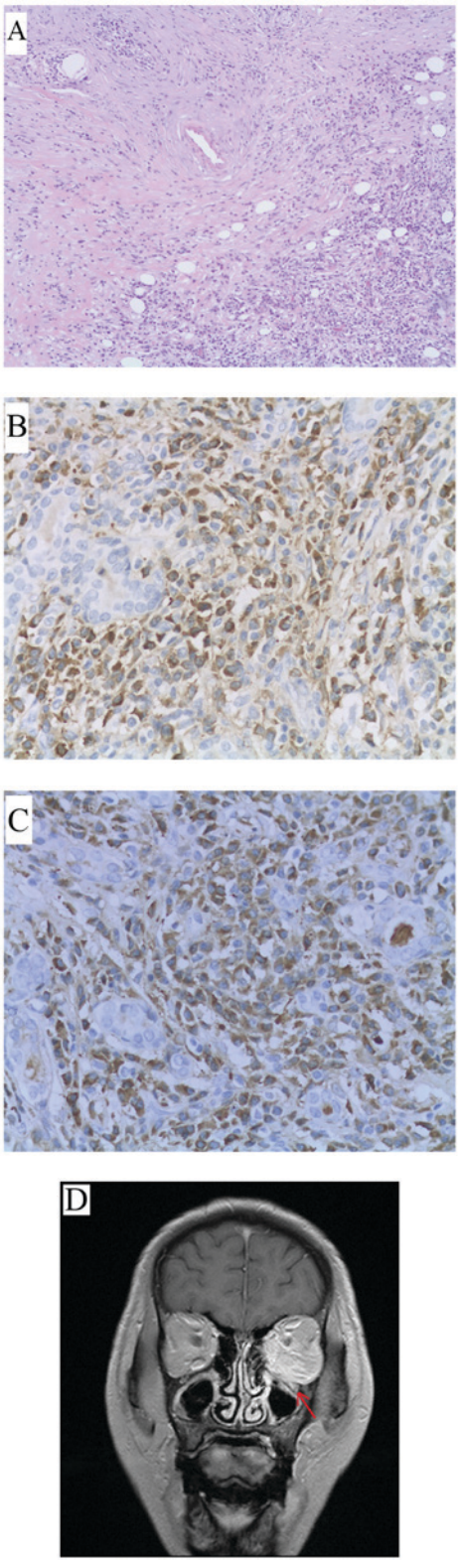

Figure 1. Evaluation of a patient with IgG4-ROD following orbital lesion resection. (A) A large amount of lymphocyte and cytoplasmic infiltration and cystia in the lesions were observed via hematoxylin and eosin staining (magnification, x50). (B) A large number of IgG^+ cells were indicated in the diseased tissue using EnVision (magnification, x400). (C) A large number of $IgG4^+$ cells were demonstrated in the diseased tissue (magnification, x400). (D) Nerve enlargement of left eye socket.

Table II. Symptom distribution in the IgG4-ROD and non-IgG4-ROD group assessed 1 week after recruitment.

Ocular symptoms	Number of cases	IgG4-ROD group (n=9)	Non-IgG4-ROD group (n=14)
Eyelid swelling	17	9 (100.0)	8 (57.1)
Exophthalmia	11	4 (44.4)	7 (50.0)
Eye pain	5	2 (22.2)	3 (21.4)
Vision loss	7	3 (33.3)	4 (28.6)
Eye itching	1	0 (0.0)	1 (7.1)
Tears	3	1 (11.1)	2 (14.3)
Eye congestion	1	0 (0.0)	1 (7.1)
Diplopia	1	1 (11.1)	0 (0.0)
Eye movement restriction	11	3 (33.3)	6 (42.9)

Data are presented as n (%) of the each group. IgG4-ROD, related orbital disease.

may appear outside of the eye content protruding from the chalazion (13). In the present study, by clinically observing eyelid IgG4-ROD, it was revealed that the clinical imaging examination exhibited a characteristic imaging change of submental nerve thickening, which may aid in early and correct diagnosis. In addition to histopathological examination, the ability to perform an early diagnosis from outside the eye enabled the standardization of treatment and the avoidance of blind repeated surgery. According to previously published studies, infraorbital nerve enlargement, referring to the coronal position, is a characteristic imaging change of IgG4-ROD when the infratemporal nerve is thicker than the optic nerve (14). In the present study, the IgG4-ROD lesion exhibited a high signal in the T1-weighted and T2-weighted images, but a low signal in MRI, as well as a homogeneous enhancement in contrast-enhanced MRI with iliac crest. Usually, no bone destruction was observed. Therefore, the present study aimed to encourage clinicians to focus on to imaging examinations for recurrent eyelid circumferences. In patients with lumps or swelling, by observing and summarizing the clinical and imaging characteristics of IgG4-ROD a better diagnosis basis and treatment plan could be selected as soon as possible in order to achieve an improved prognosis.

Simple inflammatory pseudotumor occurs in multiple directions, which may cause the extraocular muscles of the eyelid, lacrimal ducts, hernia sac and meninges to occur around the optic nerve and adjacent tissues (15). It has been reported that orbital inflammatory pseudotumor and benign orbital lymphoid hyperplasia (OBLH) are benign and idiopathic, accounting for 30-70% of all eyelid biopsies (16,17). In eyelid disease, the lesion starts in a supercellular lymph plasma cytoplasm with a morphology that is not like OBLH. Over time, lesions may gradually harden and are similar to IOI (18,19). If IgG4 staining is not performed to reveal the diagnosis, the case may be misdiagnosed as OBLH or IOI (8,20).

IgG4-related diseases have recently been considered to be autoimmune diseases in almost every organ and tissue in the body (21-23). A total of 4-13% of patients with IgG4-related diseases exhibit eyelid involvement, which becomes IgG4-ROD (24). The majority of these patients present with enlarged lacrimal glands, prominent eyeballs, orbital masses and blindness (13). IgG4-ROD involving the extraocular muscles is primarily associated with lacrimal gland enlargement, submental neuropathy or periorbital soft tissue lesions (9). In the cases of extraocular muscle involvement, the majority of the patients experienced unrestricted eye movement, there was no clear regularity in extraocular muscle hypertrophy and there was usually multiple muscle involvement (6,25).

IgG4-ROD can affect a variety of eyelid tissues and organs (13). Non-specific eyelid inflammation is a type of eyelid disease reported in fewer studies than IgG4-ROD, of which the majority are case reports, with only one large sample multi-center randomized controlled study (26). It is expected that the association between eyelid diseases and IgG4-related disease will be fully elucidated, and only through IgG4-related studies is it possible to identify the specific role of IgG4 in IgG-ROD and its mechanisms in order to fundamentally improve the diagnosis, treatment effect and prognosis of these diseases.

In conclusion, the present findings suggest the clinical feature of IgG4-ROD is bilateral lacrimal gland enlargement with thickening of the inferior tibial nerve, extraocular myositis and oppressive optic neuropathy. The disease is characterized by tumor-like hyperplasia, fibrosis, $IgG4^+$ plasma cell infiltration and markedly elevated blood IgG4 levels. The present study demonstrated that submaxillary nerve enlargement is a characteristic imaging change of IgG4-ROD. Since IgG4-ROD is a recurrent progressive disease, early diagnosis and early intervention therapy are of great importance in preventing the progression of the disease to irreversible fibrosis.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the present study available from the corresponding author on reasonable request.

Authors' contributions

NW and FYS participated in the literature search, study design, writing and critical revision. NW primarily participated in data collection, data analysis and data interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tianjin First Center Hospital (Tianjin, China; approval no. 2016N056KY). All patients provided written informed consent.

Patient consent for publication

The patient has provided consent for publication.

Competing interests

The authors declare that they have no competing interests.

References

1. McNab AA and McKelvie P: IgG4-related ophthalmic disease. Part I: Background and pathology. Ophthal Plast Reconstr Surg 31: 83-88, 2015.
2. Patnana M, Sevrukov AB, Elsayes KM, Viswanathan C, Lubner M and Menias CO: Inflammatory pseudotumor: The great mimicker. AJR Am J Roentgenol 198: W217-W227, 2012.
3. Sato Y, Ohshima K, Ichimura K, Sato M, Yamadori I, Tanaka T, Takata K, Morito T, Kondo E and Yoshino T: Ocular adnexal IgG4-related disease has uniform clinicopathology. Pathol Int 58: 465-470, 2008.
4. Jin R, Zhao P, Ma X, Ma J, Wu Y, Yang X, Zhang J, Zhong R and Zeng Y: Quantification of Epstein-Barr virus DNA in patients with idiopathic orbital inflammatory pseudotumor. PLoS One 8: e50812, 2013.
5. Mombaerts I, Goldschmeding R, Schlingemann RO and Koornneef L: What is orbital pseudotumor? Surv Ophthalmol 41: 66-78, 1996.
6. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Sumida T, Mimori T, Tanaka Y, *et al*: A novel clinical entity, IgG4-related disease (IgG4RD): General concept and details. Mod Rheumatol 22: 1-14, 2012.
7. Wallace ZS, Khosroshahi A, Jakobiec FA, Deshpande V, Hatton MP, Ritter J, Ferry JA and Stone JH: IgG4-related systemic disease as a cause of 'idiopathic' orbital inflammation, including orbital myositis, and trigeminal nerve involvement. Surv Ophthalmol 7: 26-33, 2012.
8. Andrew N, Kearney D and Selva D: IgG4-related orbital disease: A meta-analysis and review. Acta Ophthalmoi 9l: 694-700, 2013.
9. Higashiyama T, Nishida Y, Ugi S, Ishida M, Nishio Y and Ohji M: A case of extraocular muscle swelling due to IgG4-related sclerosing disease. Jpn J Ophthalmol 55: 315-317, 2011.
10. Takahashi Y, Kitamura A and Kakizaki H: Bilateral optic nerve involvement in immunoglobulin G4-related ophthalmic disease. J Neuroophthalmol 34: 16-19, 2014.
11. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, *et al*: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 22: 21-30, 2012.
12. Paulus YM, Cockerham KP, Coekerham GC and Gratzinger D: IgG4-positive sclerosing orbital inflammation involving the conjunctiva: A case report. Ocul Immunol Inflamm 20: 375-377, 2012.
13. Morel N, Rigolet A, Schleinitz N, Garnier A and Costedoat-Chalumeau N: Bilateral enlargement of the lacrimal glands from IgG4-related systemic disease. Ann Intern Med 156: 669-670, 2012.
14. Ohshima K, Sogabe Y and Sato Y: The usefulness of infraorbital nerve enlargement on MRI imaging in clinical diagnosis of IgG4-related orbital disease. Jpn J Ophthalmol 56: 380-382, 2012.
15. Strehl JD, Hartmann A and Agaimy A: Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. J Clin Pathol 64: 237-243, 2011.
16. von Holstein SL, Therkildsen MH, Prause JU, Stenman G, Siersma VD and Heegaard S: Lacrimal gland lesions in Denmark between 1974 and 2007. Acta Ophthalmol 91: 349-354, 2013.
17. Shields CL, Shields JA, Eagle RC and Rathmell JP: Clinicopathologic review of 142 cases of lacrimal gland lesions. Ophthalmology 96: 431-435, 1989.
18. Jakobiec FA: Ocular adnexal lymphoid tumors: Progress in need of clarification. Am J Ophthalmol 145: 941-950, 2008.
19. Cheuk W, Yuen HK and Chan JK: Chronic sclerosing dacryoadenitis: Part of the spectrum of IgG4-related Sclerosing disease? Am J Surg Pathol 31: 643-645, 2007.
20. Andrew N, Sladden N, Kearney D, Crompton J and Selva D: Sequential biopsies from immunoglobulin G4-related orbital disease demonstrate progressive fibrosis. Clin Experiment Ophthalmol 42: 789-791, 2014.
21. Frulloni L and Lunardi C: Serum IgG4 in autoimmune pancreatitis: A marker of disease severity and recurrence? Dig Liver Dis 43: 674-675, 2011.
22. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V and Stone JH: The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. Ann Rheum Dis 74: 14-18, 2015.
23. Dua P, Shinder R, Laskar DB, Lazzaro DR and Rizzuti AE: A case of hypertrophic herpes simplex virus affecting the eyelid and cornea masquerading as IgG4-related disease. Am J Ophthalmol Case Rep 9: 68-71, 2017.
24. Mulay K, Aggarwal E, Jariwala M and Honavar SG: Orbital immunoglobulin-G4-related disease: Case series and literature review. Clin Exp Ophthalmol 42: 682-687, 2014.
25. Wallace ZS, Deshpande V and Stone JH: Ophthalmic manifestations of IgG4-related disease: Single-center experience and literature review. Semin Arthritis Rheum 43: 806-817, 2014.
26. Kubota T and Mofitani S: Orbital IgG4-related disease: Clinical features and diagnosis. ISRN Rheumatol 2012: 412896, 2012.