• Clinical Research •

Clinicopathologic features of 89 patients with lacrimal gland prolapse

Yu-Yao Qu[1], Le Dong[1,3], Ya-Guang Hu[1], Ning Gao[1], Jing-Ming Li[1], Qiao-Chu Cheng[1], Shan Gao[1], Ting Wei[1], Jian-Min Ma[2], Wan-Hu Zhang[1]

[1]Department of Ophthalmology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China
[2]Beijing Ophthalmology and Visual Sciences Key Laboratory, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China
[3]Department of Ophthalmology, the Ninth Hospital of Xi'an, Xi'an 710054, Shaanxi Province, China
Co-first Authors: Yu-Yao Qu and Le Dong
Correspondence to: Wan-Hu Zhang. Department of Ophthalmology, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi Province, China. wanhuzhang@163.com
Received: 2024-06-03 Accepted: 2024-10-16

Abstract

● **AIM:** To analyze the clinical and pathological features of 89 patients presenting as lacrimal gland prolapse (LGP).

● **METHODS:** This retrospective study included 89 patients presenting as LGP. Magnetic resonance imaging (MRI) scan was performed for all patients. Pathology and immunohistochemical staining of prolapsed tissue were performed during the surgery. The histopathological subtype was obtained, and the related clinical manifestations of different subtype were marked.

● **RESULTS:** Among the 89 patients involved, the histopathological subtype includes dacryoadenitis (43%; *n*=38), focal lymphocytes infiltration (20%; *n*=18), immunoglobulin G4 (IgG4)-related lacrimal gland inflammatory disease (15%; *n*=13), lacrimal gland (13%; *n*=12), and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (9%; *n*=8). As for manifestations of different subtypes, eyelid swelling was found the most frequent of lymphocytes infiltration (44%, *n*=8), and palpable lacrimal gland mass of dacryoadenitis (55%, *n*=21). All the IgG4-related lacrimal gland inflammatory disease (100%, *n*=13) and most dacryoadenitis (97%, *n*=37) presented as bilateral.

● **CONCLUSION:** LGP has the histopathological subtype most commonly as inflammation, followed by structural and lymphoproliferative changes. Most of patients present as eyelid swelling. Clinical manifestations can be significant to differentiate the diagnosis.

● **KEYWORDS:** lacrimal gland prolapse; clinicopathologic features; dacryoadenitis; IgG4-related lacrimal gland inflammatory disease; extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue

DOI:10.18240/ijo.2025.06.06

Citation: Qu YY, Dong L, Hu YG, Gao N, Li JM, Cheng QC, Gao S, Wei T, Ma JM, Zhang WH. Clinicopathologic features of 89 patients with lacrimal gland prolapse. *Int J Ophthalmol* 2025;18(6):1011-1015

INTRODUCTION

The lacrimal gland (LG) is an exocrine gland positioned in the anterior part of the upper outer aspect of the orbit. It has the function of secreting the aqueous part of the precorneal tear film, plays an important role in maintaining tear film stability, corneal transparency, and ocular surface health[1-2]. Chronic inflammation, hypertension, obesity and insufficient sleep can cause LG disfunction[3-4]. Lacrimal gland prolapse (LGP) is an LG dysfunctional condition that the orbital lobe of the LG prolapses inferiorly out of the fossa and present as a mass in the lateral upper eyelid, temporal ptosis, eyelid swelling, visual field deficit, *etc*[5]. It may occur unilaterally or bilaterally[6], congenital or acquired. Various acquired etiologies can be associated to LGP, examples including blepharochalasis syndrome, involutional changes, craniofacial deformities, thyroid ophthalmopathy, sarcoidosis, post-trauma, and infectious conditions, among which, aging is considered to be the main reason for LGP[6-7].

Of note, some LG diseases may present as bilateral LGP, such as extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-EMZL), immunoglobulin G4 (IgG4)-related lacrimal gland inflammatory disease (Mikulicz syndrome), LG tumors, dacryoadenitis[8-12]. Some of these diseases can be associated with systemic diseases, which require necessary systematic evaluation and treatment[11,13-14]. The prognosis differs when patients

Table 1 Demographics of 89 patients with lacrimal gland prolapse

Histopathological subtype	*n* (%)	Age		Sex, *n* (%)		Disease course (mo)	
		Mean	Range	Female	Male	Mean	Range
Total	89 (100)	42	13–75	72 (81)	17 (19)	29	1–240
Focal lymphocytes infiltration	18 (20)	32	16–59	16 (89)	2 (11)	31	1–240
Dacryoadenitis	38 (43)	42	17–67	35 (92)	3 (8)	27	1–240
IgG4-related lacrimal gland inflammatory disease	13 (15)	44	14–71	8 (62)	5 (39)	42	8–120
MALT-EMZL	8 (9)	60	44–75	4 (50)	4 (50)	25	11–60
Lacrimal gland	12 (13)	40	13–55	9 (75)	3 (25)	19	1–96

IgG4: Immunoglobulin G4; MALT-EMZL: Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

receive different treatments[15-16]. Thus, there is an urgency to differentiate the subtypes of LGP and other diseases with similar manifestations.

To date, there is a paucity of research available on these diseases that are easily confused with LGP. Previous studies have shown common subtypes of LGP and their distributions. However, their research mostly focused on the European populations[12,17], while differences may exist in difference races. Therefore, we herein reviewed the clinical features and histopathological types in 89 patients with probable LGP, all of which are Chinese.

PARTICIPANTS AND METHODS

Ethical Approval Our study was approved by the Ethics Committee of Beijing Tongren Hospital. Research procedures were performed in accordance with the tenets of the Declaration of Helsinki. All patients provided written informed consent.

We reviewed 89 patients referred to the Department of Ophthalmology at Beijing Tongren Hospital after being initially diagnosed with LGP from January 2017 to December 2022. Diagnosis of lacrimal gland disease was based on a combination of clinical manifestations, radiology, and histopathology. All data was collected retrospectively.

The study collected data including: patient demographics (age, gender), clinical manifestations (eyelid swelling, palpable lacrimal gland mass, proptosis, mechanical blepharoptosis, conjunctival injection, dry eye), magnetic resonance imaging (MRI) images and histopathological results.

A definite diagnosis was verified with histopathology. Mikulicz syndrome was diagnosed according to the criteria for IgG4-related ophthalmic disease defined by the Japanese Study Group in 2014. The histopathological features of Mikulicz syndrome presents as lymphoplasmacytic infiltration accompanied by follicular formation and marked fibrosis, while immunohistochemical staining showing many IgG4-positive cells[18-19]. The histopathologic features of MALT-EMZL include diffusely infiltrating cells associated with follicles that appear reactive. Besides, on immunophenotypic analysis, the cells are positive for B-cell markers CD19, CD20, and CD22 and negative for CD5, CD10, and CD23[20-21].

RESULTS

Demographics and Diagnoses Eighty-nine patients were included in this study. Most diagnoses were determined through clinical manifestations, radiology, and histopathology analysis. For patients who did not receive surgical histopathology, the classical clinical manifestations and the radiological characteristic of the respective conditions were evidence to diagnose. Among the population, the most prevalent histopathological subtype was dacryoadenitis (43%; n=38), followed by focal lymphocytes infiltration (20%; n=18), IgG4-related lacrimal gland inflammatory disease (15%; n=13), lacrimal gland tissue (13%; n=12), and MALT-EMZL (9%; n=8). Major population consists of women (n=72, accounting for 81%), and this gender predilection was noted for subgroups except for the MALT-EMZL group (50% male). The mean patient age was 42y (range: 13–75y). Of note, patients with MALT-EMZL were significantly older than patients in focal lymphocytes infiltration (P<0.001), dacryoadenitis (P<0.01) and LGP (P<0.01). And the average course of disease was 29mo (range: 1–240mo; Table 1). Besides, there was no distinction in the blood test of the patients, except those with IgG4-related lacrimal gland inflammatory disease.

Histopathological Features The histopathological feature of focal lymphocytes infiltration presented as mild hyperplasia of lacrimal gland tissue, atrophy of acinar, hyperplasia of duct in some area. Meanwhile hyperplasia with lymphocytes could also be found (Figure 1A). MALT-EMZL showed diffuse lymphocytes without lymphoid follicles, immunohistochemical staining of B-cell lymphoma CD21, CD23 and PAX-5 also showed positive results, which indicates MALT-EMZL (Figure 1B). Mikulicz syndrome showed a large number of lymphocytes infiltrating in the lacrimal gland tissue. Hyperplasia of lacrimal ducts and atrophy of lacrimal acini could also be found in the gland tissue (Figure 1C). Immunohistochemical staining of IgG4 was positive. Besides, mild hyperplasia of lacrimal gland tissue and mild lymphocyte infiltration in the interstitium could be observed in dacryoadenitis (Figure 1D). The different histopathological features of these subtypes, including cell composition, may

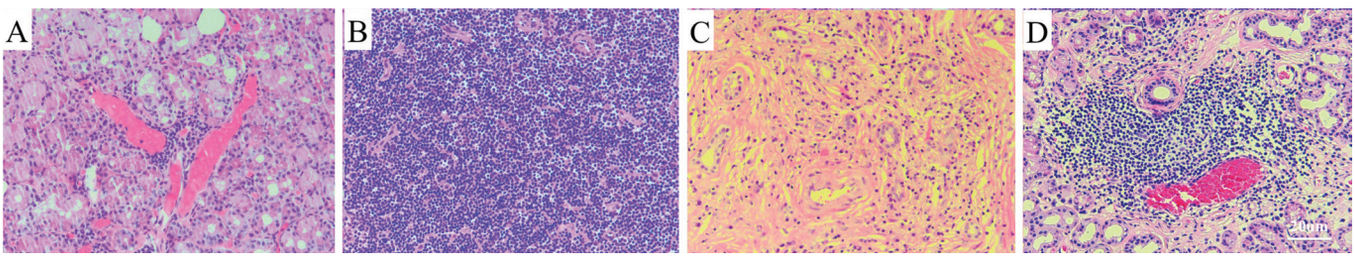

Figure 1 Histopathological features of different subtypes (200×) A: Focal lymphocytes infiltration, acinar atrophy and duct hyperplasia; B: MALT-EMZL, cell morphology of small round B cells without obvious cell atypia; C: Mikulicz syndrome, infiltration of a large number of lymphocytes and a small amount of plasma cells; D: Dacryoadenitis, mild hyperplasia of lacrimal gland tissue and mild infiltration of lymphocytes. MALT-EMZL: Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

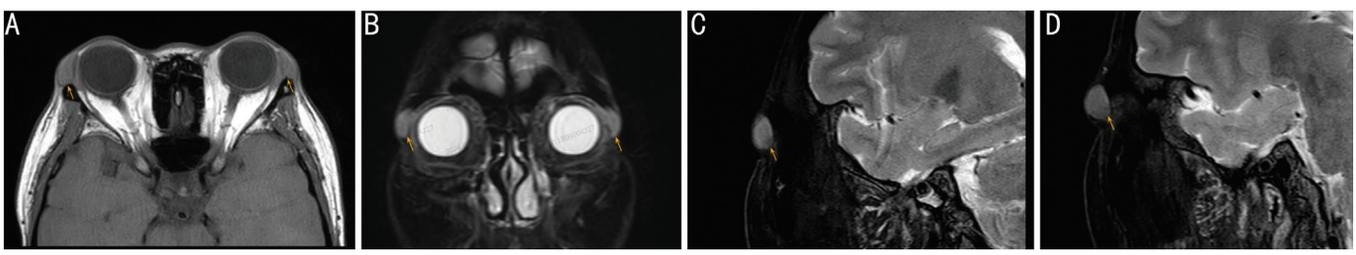

Figure 2 MRI images of lacrimal gland prolapse (arrowheads indicated the lacrimal gland) A: Axial position, T1 weighted; B: Coronal position, T2 weighted, fat suppressor sequence; C: Sagittal position, fat suppressor sequence, left side; D: Sagittal position, fat suppressor sequence, right side. MRI: Magnetic resonance imaging.

lead to various manifestations of LGP.

Among the population involved, the dacryoadenitis group (n=37, 97%) and Mikulicz syndrome group (n=13, 100%) was significantly more likely to present with bilateral disease, while the incidence of unilateral disease in patients with MALT-EMZL (n=8, 100%) was significantly higher than other groups (Table 2). These results indicated patients with similar manifestation but appears bilateral prefer to be caused by inflammation.

Clinical Features The signs and symptoms of clinical presentations of the involved 89 patients include palpable lacrimal gland mass (n=39; 44%), eyelid swelling (n=30, 34%), proptosis (n=9, 10%), mechanical blepharoptosis (n=6, 7%), conjunctival injection (n=4, 4%), and dry eye (n=3, 3%; Table 3).

Radiological Features The MRI images showed the LG were enlarged in the temporal orbit (Figure 2A, 2B), and the signal mildly improved in T2 weighted image (Figure 2B). Sagittal position with fat suppressor sequence also showed the enlarged and high signal lacrimal gland (Figure 2C, 2D).

Table 2 Symmetric analysis of different subtypes n (%)

Histopathological subtype	Unilateral	Bilateral
Focal lymphocytes infiltration (n=18)	5 (28)	13 (72)
Dacryoadenitis (n=38)	1 (3)	37 (97)
IgG4-related lacrimal gland inflammatory disease (n=13)	0	13 (100)
MALT-EMZL (n=8)	8 (100)	0
Lacrimal gland (n=12)	1 (8)	11 (92)

IgG4: Immunoglobulin G4; MALT-EMZL: Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

DISCUSSION

In our study, the patients were all referred to Beijing Tongren Hospital after a preliminary diagnosis of lacrimal prolapse in external hospital or outpatient department. Most patients received histopathological examination, which was the gold standard of diagnosis. For patients without histopathology results, clinical diagnosis was made based on classic clinical and radiographic manifestations of their respective symptoms. We found five histopathological subtypes, namely dacryoadenitis (43%), focal lymphocytes infiltration (20%), IgG4-related lacrimal gland inflammatory disease (15%), lacrimal gland tissue (13%), and MALT-EMZL (13%). According to clinical symptoms and orbital imaging studies, clinicians believed that focal lymphocytes infiltration and lacrimal gland should be diagnosed as LGP. Only about 1/3 (33%) of patients involved with probable LGP were ultimately diagnosed, showing that some LG diseases can be easily confused with LGP.

Characteristics and clinical manifestations were effective to differentiate the diagnosis. The results indicate that nearly half of LGP can be the result of inflammation, while elderly patients are more likely to have lymphoma rather than inflammation. Women are more likely to have LG diseases (81%), as was found in the current study[12,21-22]. Teo *et al*[23] in their Singapore research reported that patients with lymphoproliferative disease were more likely to be older, which proved our finding of

Table 3 The diagnoses and related clinical manifestations of different histopathological subtypes *n* (%)

Parameters	Eyelid swelling	Palpable lacrimal gland mass	Proptosis	Mechanical blepharoptosis	Conjunctival injection	Dry eye
Total (*n*=89)	30 (34)	39 (44)	9 (10)	6 (7)	4 (4)	3 (3)
Focal lymphocytes infiltration (*n*=18)	8 (44)	5 (28)	2 (11)	3 (17)	1 (6)	0 (0)
Dacryoadenitis (*n*=38)	8 (21)	21 (55)	3 (8)	3 (8)	2 (5)	1 (2)
IgG4-related lacrimal gland inflammatory disease (*n*=13)	8 (62)	4 (31)	1 (8)	0	0	1 (8)
MALT-EMZL (*n*=8)	2 (25)	5 (63)	1 (13)	0	0	0
Lacrimal gland (*n*=12)	4 (33)	4 (33)	2 (17)	0	1 (8)	1 (8)

IgG4: Immunoglobulin G4; MALT-EMZL: Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue.

MALT-EMZL more likely to occur in elderly patients without signs of active inflammation.

In this study, the distribution of different histopathological groups was in line with that of previous studies, which were conducted in other ethnic groups. Dacryoadenitis was the most common histopathological subtype in our series (43%), similar to what was found in a Korean study (52.6%)[24], a Singaporean study (46.4%)[23], an Australian study (50%)[25], and Western studies of Tang *et al*[22] (50%) and Huang *et al*[12] (60%). Researchers also found patients with dacryoadenitis were significantly younger[23], more likely to have pain, and need conjunctival injection[24].

When it comes to symmetric analyzing, we found that the incidence of bilateral disease was significantly higher in dacryoadenitis (97%) and IgG4-related lacrimal gland inflammatory disease (100%) patients. Ahn *et al*[24] found half (52.4%) of patients with IgG4-related dacryoadenitis had associated with systemic involvement, which indicates those happened bilateral might have more possibility associating with systemic abnormities. Previous studies showed IgG4-related disease (IgG4-RD), characterized by elevated serum IgG4 level, tissue swelling and invasion of IgG4-positive plasma cells, can involve multi-organ disturbance such as retroperitoneum, pancreas, salivary gland, and orbit[13,26-27]. Orbital structures were easily affected in IgG4-RD, while the LG is mostly involved[28-29]. All patients with IgG4-related lacrimal gland inflammatory disease in our study had bilateral involvement, while 85.7% was found in Korean populations[24]. Patients with IgG4-related dacryoadenitis were more likely to associate with systemic symptoms than patients with non-specific dacryoadenitis[24]. For treatment, previous studies showed patients with IgG4-RD can response to steroids[22]. However, dacryoadenitis recurred after initial treatment can be common, which usually need longer treatment than non-specific dacryoadenitis[27-29]. In addition, 10% of IgG4-related chronic dacryoadenitis can probably progress to orbital lymphoma. Chronic hyperplasia of lymphoid tissue may lead to morphologic changes and immunoglobulin gene rearrangement, resulting in B-cell proliferation and eventual malignant transformation[30], which further illustrates the importance of early diagnosis and treatment. However, earlier studies were lack of immunohistological work-up for IgG and IgG4, which might lead patients missing early diagnose. Nowadays, with higher awareness of IgG4-RD being given, Ahn *et al*[24] found IgG4-RD in 22.1% of lacrimal gland masses in Korean patients and 17.4% of bilateral lacrimal gland disease in Western populations[12], which may help patients get early treatment. Of note, we diagnosed IgG4-related lacrimal gland inflammatory disease in 15% of 89 Chinese patients proposed diagnosis with LGP, similar with the findings above.

LGP can easily confuse the diagnosis of LG diseases. The clinical findings of this study might help to discern these diseases with similar manifestations. In addition, clinicians are also recommended to be aware of systemic examinations for multi-organs, as patients who suffered systemic diseases often need long term of specific treatment and follow-up. We suggested that history and physical examination take precedence in initial diagnostic progress, with radiology serving as supplements. Particular attention should be paid to signs and symptoms of inflammation. Moreover, histopathology remains the gold standard for diagnosis.

ACKNOWLEDGEMENTS

Foundations: Supported by National Natural Science Foundation of China (No.82201214; No.82201221); Ophthalmic New Technology Incubation Fund Project of China Primary Health Care Foundation (No.2022 No.005); Shaanxi Key Research and Development Program (No.2021SF-156).

Conflicts of Interest: Qu YY, None; **Dong L,** None; **Hu YG,** None; **Gao N,** None; **Li JM,** None; **Cheng QC,** None; **Gao S,** None; **Wei T,** None; **Ma JM,** None; **Zhang WH**, None.

REFERENCES

1 Naing EE, Myint KT, Roddi R. Lacrimal gland prolapse: case report. *Surg Tech Dev* 2023;12(1):53-59.

2 Xiao B, Guo DL, Liu R, *et al*. Obstruction of the tear drainage altered lacrimal gland structure and function. *Invest Ophthalmol Vis Sci* 2023;64(10):13.

3 Mansukhani MP, Covassin N, Somers VK. Apneic sleep, insufficient sleep, and hypertension. *Hypertension* 2019;73(4):744-756.

4 Huang SZ, Si HL, Liu JM, *et al*. Sleep loss causes dysfunction in murine extraorbital lacrimal glands. *Invest Ophthalmol Vis Sci* 2022;63(6):19.

5 Eshraghi B, Ghadimi H. Lacrimal gland prolapse in upper blepharoplasty. *Orbit* 2020;39(3):165-170.

6 Eshraghi B, Najafi M, Babaei L, *et al*. Diagnosis and treatment of lacrimal gland prolapse: a narrative review. *Aesthetic Plast Surg* 2024;48(15):2786-2792.

7 Zhou JQ, Ding JW, Li DM. Blepharochalasis: clinical and epidemiological characteristics, surgical strategy and prognosis—a retrospective cohort study with 93 cases. *BMC Ophthalmol* 2021;21(1):313.

8 Ren TT, Liu R, Li J, *et al*. Primary Sjögren's syndrome misdiagnosed as Mikulicz's disease: a case report. *BMC Ophthalmol* 2023;23(1):336.

9 Luan FX, Liu R, Li J, *et al*. Evaluation of the efficacy of immune and inflammatory markers in the diagnosis of lacrimal-gland benign lymphoepithelial lesion. *Curr Issues Mol Biol* 2023;45(3):2013-2020.

10 Vest SD, Mikkelsen LH, Holm F, *et al*. Lymphoma of the lacrimal gland—an international multicenter retrospective study. *Am J Ophthalmol* 2020;219:107-120.

11 Chean CS, Sovani V, Boden A, *et al*. Lacrimal gland extranodal marginal zone B-cell lymphoma in the presence of amyloidosis. *Orbit* 2022;41(3):350-353.

12 Huang S, Juniat V, Satchi K, *et al*. Bilateral lacrimal gland disease: clinical features and outcomes. *Eye* (*Lond*) 2022;36(11):2163-2171.

13 Maritati F, Peyronel F, Vaglio A. IgG4-related disease: a clinical perspective. *Rheumatology* (*Oxford*) 2020;59(suppl 3):iii123-iii131.

14 Mancera N, Bajric J, Margo CE. IgG4-rich reactive lymphoid hyperplasia of the lacrimal gland. *Orbit* 2020;39(4):285-288.

15 Hintschich C. Eyelid surgery in Graves' orbitopathy. *Klin Monbl Augenheilkd* 2021;238(1):33-40.

16 Pupić-Bakrač A, Knežević J, Pupić-Bakrač J, *et al*. Aesthetic and functional outcomes of upper blepharoplasty combined with dacryoadenopexy in lacrimal gland prolapse. *Aesthetic Plast Surg* 2024;48(12):2246-2253.

17 Huang S, Juniat V, James C, *et al*. Histopathological characteristics of lacrimal gland prolapse. *Ophthalmic Plast Reconstr Surg* 2023;39(4):389-393.

18 Goto H, Takahira M, Azumi A, *et al*. Diagnostic criteria for IgG4-related ophthalmic disease. *Jpn J Ophthalmol* 2015;59(1):1-7.

19 Min HK, Lee YS, Yang SW, *et al*. Clinical outcomes and pathological characteristics of immunoglobulin G4-related ophthalmic disease versus orbital inflammatory pseudotumor. *Korean J Intern Med* 2019;34(1):220-226.

20 di Rocco A, Petrucci L, Assanto GM, *et al*. Extranodal marginal zone lymphoma: pathogenesis, diagnosis and treatment. *Cancers* (*Basel*) 2022;14(7):1742.

21 Swerdlow SH, Campo E, Pileri SA, *et al*. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;127(20):2375-2390.

22 Tang SX, Lim RP, Al-Dahmash S, *et al*. Bilateral lacrimal gland disease: clinical features of 97 cases. *Ophthalmology* 2014;121(10):2040-2046.

23 Teo L, Seah LL, Choo CT, *et al*. A survey of the histopathology of lacrimal gland lesions in a tertiary referral centre. *Orbit* 2013;32(1):1-7.

24 Ahn C, Kang S, Sa HS. Clinicopathologic features of biopsied lacrimal gland masses in 95 Korean patients. *Graefes Arch Clin Exp Ophthalmol* 2019;257(7):1527-1533.

25 Andrew NH, McNab AA, Selva D. Review of 268 lacrimal gland biopsies in an Australian cohort. *Clin Exp Ophthalmol* 2015;43(1):5-11.

26 Kamisawa T, Zen Y, Pillai S, *et al*. IgG4-related disease. *Lancet* 2015;385(9976):1460-1471.

27 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.

28 Sa HS, Lee JH, Woo KI, *et al*. IgG4-related disease in idiopathic sclerosing orbital inflammation. *Br J Ophthalmol* 2015;99(11):1493-1497.

29 McNab AA, McKelvie P. IgG4-related ophthalmic disease. part II: clinical aspects. *Ophthalmic Plast Reconstr Surg* 2015;31(3):167-178.

30 Cheuk W, Yuen HK, Chan AC, *et al*. Ocular adnexal lymphoma associated with IgG4+ chronic sclerosing dacryoadenitis: a previously undescribed complication of IgG4-related sclerosing disease. *Am J Surg Pathol* 2008;32(8):1159-1167.