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Bilateral lacrimal gland disease: clinical features and outcomes

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BACKGROUND: Patients with bilateral lacrimal gland disease are a unique subset of patients where there is a paucity of literature. This presentation often represents systemic disease or malignancy and can cause diagnostic difficulties. We aim to describe the diagnoses and features of bilateral lacrimal gland disease.

METHOD: Retrospective multi-centre case series involving 115 patients with bilateral lacrimal gland disease from 1995 to 2020.

RESULTS: 115 patients were included. Their ages ranged from 9 to 85 (mean 47.3 years) with a female predominance (73, 63.5%). The most common category of diagnosis was inflammatory (69, 60%) followed by lymphoproliferative (23, 20%), structural (17, 14.8%) and other conditions (6, 5.2%). The five most common specific diagnoses were IgG4 related disease (20, 17.4%) and idiopathic orbital inflammatory disease (20, 17.4%), lymphoma (16, 13.9%), lacrimal gland prolapse (13, 11.3%), and sarcoidosis (11, 9.6%). Corticosteroid treatment was used most commonly (29, 25.2%) followed by observation (25, 21.7%). At last follow up, the majority of patients had complete resolution, significant improvement with mild residual disease or stable disease without further progression (104, 90.4%).

CONCLUSION: Bilateral lacrimal disease may be due to a range of aetiologies, most of which are systemic. The most common are inflammatory and lymphoproliferative conditions. Due to the wide range of aetiologies of bilateral lacrimal gland disease, it is extremely difficult to accurately determine a cause based on clinical findings alone, highlighting the vital role of lacrimal gland biopsy in patients presenting with bilateral lacrimal gland disease.

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INTRODUCTION

Bilateral lacrimal gland disease is less common than unilateral disease [1]. It may represent a localized orbital disease, or be an indicator of systemic disease. Diagnostic considerations in unilateral cases include a focus on the spectrum of epithelial malignancies that would be extremely unlikely to present simultaneously in bilateral glands [2]. Bilateral disease would be expected to involve systemic associations as the two glands, while unified in physiology, are separated in space. There is however, a paucity of research available on the local diagnoses and systemic associations of bilateral lacrimal gland enlargement. We report the clinical features, investigative findings and outcomes for patients with bilateral lacrimal disease.

METHODS

Patients presenting with bilateral lacrimal gland disease to one of three academic orbital practices (Adelaide, Melbourne, and Los Angeles) between January 1995 and January 2020 were screened for study entry. Diagnosis of lacrimal gland disease was made utilizing a combination of clinical findings, laboratory investigations, radiologic studies, and biopsy. All patients were required to have either a serological test or biopsy performed to be included in the study.

Data collected included: patient demographics; clinical presentation; the presence of any systemic symptoms; serological, radiological and/or histopathological findings, final diagnosis, treatments and outcomes. All research was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Royal Adelaide Hospital Human Research Ethics Committee with a waiver of consent granted.

Statistical analyses

Continuous variables are reported as mean ± standard deviation. Categorical data are reported as frequency and percentage of the study population unless otherwise specified. A Fisher exact test or Chi-squared test were used when comparing categorical variables. The independent *t* test was used for continuous variables. The two-tailed significance threshold was set at $P < 0.05$.

For the following analyses, only category diagnoses of inflammatory and lymphoproliferative conditions were included. Univariate binary logistic regressions were performed to investigate the association between category diagnosis and various predictors. Those predictors with a p value < 0.5 were included in an initial multivariable binary logistic model. Backwards elimination was performed until all variables had a p value < 0.05. Odds ratios, 95% confidence intervals and global p values are presented.

Statistical analyses were conducted using Stata SE version 15.0 (Stata Corp. LP, College Station, TX), and IBM SPSS version 26.0 (IBM Corp. Armonk, N.Y, USA).

RESULTS

One hundred and fifteen patients were included in this study.

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Table 1. Demographic data by diagnosis.

Diagnosis	No. (%)	Age		Sex		Race			
		Mean	Range	Female No. (%)	Male No. (%)	Caucasian No. (%)	Asian No. (%)	Middle-Eastern No. (%)	Hispanic No. (%)
TOTAL	115	47.3	9-85	73 (63.5)	42 (36.5)	85 (73.9)	20 (17.4)	2 (1.7)	8 (7.0)
Inflammatory	69 (60.0)	40.7*	9-75	35 (50.7)	34 (49.3)	47 (68.1)	14 (20.3)	2 (2.9)	6 (8.7)
IOID	20 (17.4)	33.9	9-56	13 (65)	7 (35)	13 (65)	3 (15)	1 (5)	3 (15)
IgG4-RD	20 (17.4)	49.5	18-72	8 (40)	12 (60)	14 (70)	5 (25)	–	1 (5)
Sarcoidosis	11 (9.6)	36.9	29-53	6 (54.5)	5 (45.5)	6 (54.5)	4 (36.4)	1 (9.1)	
Xanthogranulomatous disease	8 (7.0)	40.4	29-59	3 (37.5)	5 (62.5)	7 (87.5)	1 (12.5)	–	
EBV dacryoadenitis	2 (1.7)	23.5*	19-28	1 (50)	1 (50)	2 (100)	–	–	
GPA	2 (1.7)	57.5	55-60	1 (50)	1 (50)	2 (100)	–	–	
Sjogren's	2 (1.7)	48.5	46-51	1 (50)	1 (50)	2 (100)	–	–	
Viral dacryoadenitis	2 (1.7)	23*	13-33	2 (100)	–	1 (50)	1 (50)	–	
Eosinophilic asthma	1 (0.87)	32	32	–	1 (100)	–	–	–	1 (100)
Unspecified vasculitis	1 (0.87)	75	75	–	1 (100)	–	–	–	1 (100)
Lymphoproliferative	23 (20.0)	56.5	28-85	18 (78.3)	5 (21.7)	16 (69.6)	5 (21.1)	–	2 (8.7)
Lymphoma	16 (13.9)	60.6*	28-85	12 (75)	4 (25)	12 (75)	4 (25)	–	
Reactive lymphoid hyperplasia	7 (6.1)	47.3	30-71	6 (85.7)	1 (14.3)	4 (57.1)	1 (14.3)	–	2 (28.6)
Structural	17 (14.8)	58.1*	31-76	16 (94.1)	1 (5.9)	16 (94.1)	1 (5.9)	–	–
Lacrimal gland prolapse	13 (11.3)	60.2	31-76	13 (100)	–	12 (92.3)	1 (7.7)	–	
Dacryops	4 (3.5)	51.3	36-68	3 (75)	1 (25)	4 (100)	–	–	
Other entities	6 (5.2)	54.1	28-78	4 (66.7)	2 (33.3)	6 (100)	–	–	–
Amyloidosis	2 (1.7)	50.5	44-57	1 (50)	1 (50)	2 (100)	–	–	
Lymphoma in Sjogren's with orbital lobe cysts	2 (1.7)	54	41-67	2 (100)	–	2 (100)	–	–	
Lymphoma in RA with orbital lobe cysts	1 (0.87)	78	78	1 (100)	–	1 (100)	–	–	
Unknown diagnosis	1 (0.87)	64	64	–	1 (100)	1 (100)	–	–	–

% for gender and race reported as proportion of the total number of patients with that diagnosis or within that category.
EBV Epstein-Barr virus, *GPA* Granulomatosis with polyangiitis, *IOID* Idiopathic orbital inflammatory disease, *IgG4-RD* IgG4-related disease, *RA* Rheumatoid arthritis.
* $= p < 0.05$ on Independent *t* test.

Demographics and diagnoses

Patient demographics and diagnoses are reported in Table 1. Most patients were women (73, 63.5%). The mean patient age was 47.3 ±16.8 years (range: 9–85 years). The most common ethnicity in our series was Caucasian (85, 73.9%), followed by Asian (20, 17.4%), Hispanic or Latino (8, 7.0%) and Middle-Eastern (2, 1.7%).

Inflammatory conditions accounted for 60.0% (69 patients) of the study population, followed by lymphoproliferative (23, 20.0%), structural (17, 14.8%) and other conditions (6, 5.2%). The five most common specific diagnoses were IgG4 related disease (20, 17.4%), idiopathic orbital inflammatory disease (IOID) (20, 17.4%), lymphoma (16, 13.9%), lacrimal gland prolapse (13, 11.3%), and sarcoidosis (11, 9.6%). Specific types of lymphoma reported include: follicular lymphoma (6, 37.5% of lymphoma diagnoses), extranodal marginal zone lymphoma (6, 37.5%), mantle cell lymphoma (2, 12.5%), T-cell lymphoma (1, 6.3%), and unknown type of lymphoma (1, 6.3%).

As a group, patients with an inflammatory condition were significantly younger than patients in other disease categories (40.7 ± 14.7 vs. 57.3 ± 15.0, $p < 0.0001$). The difference in mean was 16.7 years (95% confidence interval [CI]: 11.1, 22.2). As a group, patients with structural conditions were the oldest (58.1 ± 13.1 vs. 45.5 ± 16.8, $p = 0.004$). The difference in mean was 12.6 years (95% CI: 4.1, 21.1). When looking at specific conditions, patients with lymphoma had the oldest mean age when compared to patients with other conditions (60.6 ± 16.4 vs. 44.7 ± 15.7, $p = 0.0001$).

Patients with Epstein-Barr virus (EBV) and other forms of viral dacryoadenitis had the youngest mean age (23.3 ± 9.0 vs. 48.2 ± 16.4, $p = 0.003$). A significant association was noted between category of diagnosis (lymphoproliferative vs. inflammatory conditions) and age ($p = 0.008$) when adjusting for all other covariates in the multivariable model. For every one year increase in age, the odds of having a lymphoproliferative condition compared to an inflammatory condition are increased by 5.5% (Odds ratio [OR] = 1.055, 96% CI = 1.01, 1.10).

A female sex predilection was noted for most conditions except for IgG4 related disease (IgG4-RD) (12 of 20 [60%] male) and xanthogranulomatous disease (5 of 8 [62.5%] male).

Clinical presentation

The mean duration of symptoms prior to presentation, was 14.9 ± 24.0 months (range: 3 days–180 months). In all but one case,

Table 2. Clinical presentation by diagnosis.

Diagnosis	Palpable mass	Pain	Mechanical blepharoptosis	Periorbital oedema	Conjunctival injection	Globe dystopia	Change in visual acuity	Lacrimation	Decreased EOM	Dry eye	Lid swelling
Total $n = 115$	83 (72.2)	16 (13.9)	47 (40.9)	36 (31.3)	22 (19.1)	25 (21.7)	8 (7.0)	10 (8.7)	9 (7.8)	31 (27.0)	13 (11.3)
Inflammatory $n = 69$	50 (72.5)	14 (20.3)*	31 (44.9)	28 (40.6)*	20 (29.0)*	10 (14.5)	3 (4.3)	8 (11.6)	3 (4.4)	18 (26.1)	7 (10.1)
IOID $n = 20$	12 (60)	6 (30)	6 (30)	9 (45)	3 (15)	1 (5)10	–	3 (15)	1 (5)	4 (20)	1 (5)
IgG4-RD $n = 20$	15 (75)	3 (15)	6 (30)	7 (35)	3 (15)	7 (35)	1 (5)	1 (5)	1 (5)	6 (30)	3 (15)
Sarcoidosis $n = 11$	10 (90.9)	1 (9.1)	6 (54.5)	3 (27.3)	2 (18.2)	1 (9.1)	1 (9.1)	1 (9.1)	–	2 (18.2)	2 (18.2)
Xanthogranulomatous disease $n = 8$	8 (100)	–	8 (100)	5 (62.5)	7 (87.5)	–	–	–	–	3 (37.5)	–
EBV dacryoadenitis $n = 2$	2 (100)	1 (50)	2 (100)	2 (100)	2 (100)	–	–	1 (50)	–	–	–
GPA $n = 2$	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	1 (50)	–
Sjogren's $n = 2$	1 (50)	–	–	–	–	–	–	–	–	2 (100)	1 (50)
Viral dacryoadenitis $n = 2$	1 (50)	1 (50)	2 (100)	1 (50)	1 (50)	–	–	1 (50)	–	–	–
Eosinophilic asthma $n = 1$	–	–	–	–	–	–	–	–	–	–	–
Unspecified vasculitis $n = 1$	–	1 (100)	–	–	1 (100)	–	–	–	–	–	–
Lymphoproliferative $n = 23$	17 (73.9)	1 (4.3)	11 (47.8)	8 (34.8)	1 (4.3)	12 (52.2)*	5 (21.7)*	2 (8.7)	4 (17.4)	8 (34.8)	2 (8.7)
Lymphoma $n = 16$	13 (81.3)	1 (6.3)	9 (56.3)	6 (37.5)	1 (6.3)	10 (62.5)	5 (31.3)	2 (12.5)	4 (25)	4 (25)	–
Reactive lymphoid hyperplasia $n = 7$	4 (57.1)	–	2 (28.6)	2 (28.6)	–	2 (28.6)	–	–	–	4 (57.1)	2 (28.6)
Structural $n = 17$	12 (70.6)	1 (5.9)	1 (5.9)	–	–	–	–	–	–	–	2 (11.8)
Lacrimal gland prolapse $n = 13$	11 (84.6)	1 (7.7)	1 (7.7)	–	–	–	–	–	–	–	1 (7.7)
Dacryops $n = 4$	1 (25)	–	–	–	–	–	–	–	–	–	1 (25)
Other entities $n = 6$	4 (66.7)	–	4 (66.7)	–	1 (16.7)	3 (50)	–	–	2 (33.3)	5 (83.3)	2 (33.3)
Amyloidosis $n = 2$	1 (50)	–	1 (50)	–	–	–	–	–	–	2 (100)	1 (50)
Lymphoma in Sjogren's with orbital lobe cysts $n = 2$	2 (100)	–	1 (50)	–	–	2 (100)	–	–	1 (50)	2 (100)	–
Lymphoma in RA with orbital lobe cysts $n = 1$	1 (100)	–	1 (100)	–	1 (100)	1 (100)	–	–	1 (100)	1 (100)	–
Unknown diagnosis $n = 1$	–	–	1 (100)	–	–	–	–	–	–	–	1 (100)

Results expressed as No. (%). % reported as proportion of the total number of patients with that diagnosis or within that category.
EBV Epstein-Barr virus, *GPA* granulomatosis with polyangiitis, *IOID* idiopathic orbital inflammatory disease, *IgG4-RD* IgG4-related disease, *RA* rheumatoid arthritis, *EOM* extraocular movement.
* $= p < 0.05$ on Chi squared or Fisher exact test.

Table 3. Systemic symptoms and their diagnosis of patients with bilateral lacrimal gland disease.

Diagnosis	Total number of patients with condition	Number of patients with systemic symptoms	Dry mouth	Lymphadenopathy	Respiratory symptoms	Swollen salivary glands	Arthritis	Pancreatitis	Sinusitis	Rash
IgG4-RD	20	12 (55)	2 (10)	5 (25)	–	3 (15)	–	2 (10)	6 (30)	–
IOID	20	6 (30)	1 (5)	–	1 (5)	–	–	–	3 (15)	1 (5)
Sarcoidosis	11	7 (63.6)	–	2 (18.2)	3 (27.3)	2 (18.2)	–	–	–	–
Xanthogranulomatous disease	8	4 (50)	–	–	3 (37.5)	–	–	–	1 (12.5)	1 (12.5)
EBV dacryoadenitis	2	2 (100)	–	2 (100)	–	–	–	–	–	–
Sjogren's	2	1 (50)	1 (50)	–	–	1 (50)	–	–	–	–
Viral dacryoadenitis	2	2 (100)	–	–	2 (100)	–	–	–	–	–
Eosinophilic asthma	1	1 (100)	–	–	–	–	–	–	1 (100)	–
Lymphoma	16	3 (18.8)	–	2 (12.5)	–	1 (6.3)	–	–	–	–
RLH	7	3 (42.9)	–	1 (14.3)	–	1 (14.3)	–	–	1 (14.3)	–
Lymphoma in Sjogren's with orbital lobe cysts	2	2 (100)	2 (100)	–	–	1 (50)	–	–	–	–
Lymphoma in RA with orbital lobe cysts	1	1 (100)	–	–	–	–	1 (100)	–	–	–
Total	115	44 (38.3)	6	12	9	9	1	2	12	2

All results expressed as: *n* (% of patients with that specific diagnosis).
EBV Epstein-Barr virus, *IOID* Idiopathic orbital inflammatory disease, *IgG4-RD* IgG4-related disease, *RA* Rheumatoid arthritis, *RLH* reactive lymphoid hyperplasia.

patients presented for the first time with bilateral lacrimal gland disease. The single recurrence was in a patient with reactive lymphoid hyperplasia (RLH), which recurred seven years after initial treatment of unilateral disease.

Diagnoses and associated clinical presentations are reported in Table 2. The most common presenting clinical symptoms and signs were: palpable mass in the lacrimal fossa (83, 72.2%); mechanical blepharoptosis (47, 40.9%); periorbital oedema (36, 31.3%); dry eye (31, 27.0%); globe dystopia (25, 21.7%); and conjunctival injection (22, 19.1%). Symptoms noted to be specific to a condition include dermatochalasis, which was seen in seven of thirteen (53.8%) patients with lacrimal gland prolapse, and yellow discolouration of the eyelids, which was seen in all eight patients with xanthogranulomatous disease.

Patients presenting with periorbital oedema ($p = 0.009$), conjunctival injection ($p = 0.001$), and pain ($p = 0.001$) were more likely to have an inflammatory condition. Lymphoproliferative conditions were associated with globe dystopia ($p < 0.0001$) and change in visual acuity ($p = 0.002$). Dry eye and mechanical blepharoptosis were more frequently noted in lymphoproliferative conditions, however, this was not significant ($p = 0.34$, $p = 0.45$ respectively).

Forty-four patients (38.3%) presented with additional systemic symptoms. Systemic symptoms were much more commonly seen in inflammatory conditions ($p < 0.0001$). Specific symptoms and their conditions are summarised in Table 3.

In A multivariate analysis with category diagnosis (inflammatory vs. lymphoproliferative) as the dependent variable, the coefficients for globe dystopia ($p = 0.009$), conjunctival injection ($p = 0.047$), and the presence of systemic symptoms ($p = 0.016$) were significant. Patients without globe dystopia were 6.75 times more likely to have an inflammatory rather than lymphoproliferative condition (OR = 6.75, 95% CI: 1.62, 28.11). Conjunctival injection (OR = 10.56, 95% CI: 1.04, 107.9) and systemic symptoms (OR = 5.66, 95% CI: 1.38, 23.26) were additionally predictive of inflammatory disease.

Laboratory investigations

At least one laboratory investigation was performed in 88 (76.5%) patients.

Of the 35 patients who had serum IgG testing, 15 (42.9% of those tested) had elevated levels of IgG4 with a further five also having raised IgG2 levels. All but three patients with raised IgG4 were diagnosed with IgG4-RD.

ANA titres were elevated in 14 patients (12.2%). The majority of these patients (11, 78.6%) had an inflammatory condition. Of the eight patients (7.0%) with raised ACE, six (75%) had sarcoidosis, one (12.5%) had RLH and one (12.5%) had Sjogren's syndrome.

Eighty-nine patients (77.4%) underwent biopsy of the lacrimal gland. Patients who did not undergo biopsy included those who were diagnosed clinically and after serological testing, or those who were diagnosed with a systemic condition prior to presentation (i.e. known stage IV lymphoma or IgG4-RD previously diagnosed on salivary gland biopsy).

Radiological investigations

A total of 97 patients (84.3%) had imaging of the orbit, of which 55 patients (47.8%) underwent a computed tomography (CT) scan, 29 patients (25.2%) underwent magnetic resonance imaging (MRI), and 13 patients (11.3%) had both performed. Of the 18 patients (15.7%) who did not undergo imaging 15 patients (13.0%) were diagnosed clinically (EBV dacryoadenitis, viral dacryoadenitis, dacryops, and lacrimal gland prolapse). The other three patients (2.6%) had a diagnosis of either sarcoid or lymphoma with associated systemic imaging utilized for diagnosis.

Bilateral gland enlargement was seen on imaging in 83 patients (72.2%). Involvement of other orbital structures (extraocular muscles, infraorbital nerve, frontal nerve), preseptal swelling or orbital extension was noted in 21 patients (18.3%). Patients in

Table 4. Inflammatory conditions: treatment modalities and outcomes.

Condition	Treatment modality									
	Observation	Chemotherapy	Corticosteroids	Steroids and immunosuppression	Steroids and chemotherapy	NSAID	Steroids, immunosuppresion, radiotherapy	Steroids and surgery	Surgery	Unknown
IgG4-RD $n = 20$	1 (5)	–	7 (35)	6 (30)	3 (15)	1 (5)	1 (5)	–	1 (5)	–
IOID $n = 20$	9 (45)	–	8 (40)	1 (5)	1 (5)	–	–	–	1 (5)	–
Sarcoidosis $n = 11$	1 (9.1)	–	7 (63.6)	–	2 (18.2)	–	–	–	–	1 (9.1)
Xanthogranulomatous disease $n = 8$	–	2 (25)	–	2 (25)	3 (37.5)	–	–	1 (12.5)	–	–
EBV dacryoadenitis $n = 2$	1 (50)	–	1 (50)	–	–	–	–	–	–	–
Viral dacryoadenitis $n = 2$	2 (100)	–	–	–	–	–	–	–	–	–
GPA $n = 2$	–	–	–	2 (100)	–	–	–	–	–	–
Sjogren's $n = 2$	–	–	–	–	–	–	–	–	1 (50)	1 (50)
Unspecified vasculitis $n = 1$	–	–	1 (100)	–	–	–	–	–	–	–
Eosinophilic asthma $n = 1$	–	–	–	1 (100)	–	–	–	–	–	–
Total $n = 69$	14 (20.3)	2 (2.9)	24 (34.8)	12 (17.4)	9 (13.0)	1 (1.4)	1 (1.4)	1 (1.4)	3 (4.3)	2 (2.9)

All results expressed as: *n* (% of patients with that specific diagnosis).
EBV Epstein-Barr virus, *GPA* Granulomatosis with polyangiitis, *IOID* Idiopathic orbital inflammatory disease, *IgG4-RD* IgG4-related disease.

which inflammation extended beyond the lacrimal gland were affected by a range of diagnoses including IgG4-RD ($n = 9$), xanthogranulomatous disease ($n = 8$), amyloidosis ($n = 1$), sarcoidosis ($n = 1$), granulomatosis with polyangiitis (GPA, $n = 1$), and lymphoma ($n = 1$). Seven patients (6.1%) demonstrated sinus involvement and this was typically associated with IgG4-RD ($n = 6$) and sarcoidosis in a single case.

Additional radiological investigations were performed in a total of 37 patients (32.2%). Twelve (10.4%) chest X-rays were performed, of which eight patients were diagnosed with sarcoidosis. Six patients (5.2%) had a CT chest performed. These patients were diagnosed with sarcoidosis ($n = 4$), adult onset asthma and periocular xanthogranuloma ($n = 1$) and IOID ($n = 1$), respectively. Either a PET scan or a CT scan involving at least the chest, abdomen and pelvis was performed in 22 cases (19.1%). These patients were diagnosed with lymphoma ($n = 15$), IgG4-RD ($n = 4$), xanthogranulomatous disease ($n = 1$), and reactive lymphoid hyperplasia ($n = 1$).

Treatment, response and outcomes

Treatment outcome data were available for 106 patients (92.2%) with 9 patients (7.8%) lost to follow up. The mean length of follow up was 40.5 ± 58.4 months (range: 1–348 months). Medical treatment (68, 59.1%) was the main modality utilised, particularly corticosteroids (29, 25.2%). This was followed by observation in 21.7% of the Study population. Table 4 outlines the various treatment modalities used for inflammatory conditions.

Combination therapy with chemotherapy and radiotherapy was utilized in 15 patients (13.0%). Steroids combined with chemotherapy or immunosuppression was utilized in 23 cases (20.0%). Nine of the 20 patients (45.0%) with IgG4-RD required additional medication to steroids. Agents used include methotrexate, mycophenolate and azathioprine. Combination of debulking surgery and either medical or chemotherapy/radiotherapy treatment was applied in 6 (5.2%) cases.

Table 5 outlines treatment and outcomes listed by diagnosis. Two (1.7%) patients died during the follow-up period. One patient was diagnosed with follicular lymphoma, the other was originally diagnosed with IgG4-RD and later developed disseminated diffuse large B-cell lymphoma. Complete resolution was noted in 41 patients (35.7%), 47 cases (40.9%) had stable disease without further progression and 16 (13.9%) had significant improvement with mild residual disease.

DISCUSSION

Bilateral lacrimal gland enlargement can be due to a localised condition or associated with systemic disease. In our case series, we found inflammatory conditions to be the most common categorial diagnosis. IgG4-RD, idiopathic orbital inflammatory disease and lymphoma were the most common specific diagnoses. We found that although our results demonstrate some demographic and clinical characteristics that are more commonly associated with particular conditions, given the wide range of possible aetiologies, it remains difficult to predict the cause of bilateral lacrimal gland disease from presentation alone.

Bilateral lacrimal gland disease has also been described previously. In a case series by Tang et al., IOID was reported as the most common condition out of 97 patients (29, 29.9%). This was then followed by sarcoidosis (19, 19.6%), lacrimal gland prolapse (15, 15.5%), and lymphoma (11, 11.3%) [1]. Ahn et al. reported a total of 95 patients with lacrimal gland masses that underwent biopsy [3]. Of those, 33 (34.7%) had bilateral disease. Although they did not report individual diagnoses for this subset of patients, they found patients with chronic dacryoadenitis and in particular those with IgG4-related disease, were significantly more likely to have bilateral gland involvement [3]. Other literature on bilateral lacrimal gland disease is primarily limited to case reports

Table 5. Treatment and outcomes at last follow up of patients with bilateral lacrimal gland disease by diagnosis.

	Treatment					Outcomes					Mean follow up duration (months)
Diagnosis	Medical	Surgical	Combined medical and surgical treatment	Observation	Unknown	Complete resolution	Stable disease without further progression	Significant improvement with mild residual disease	Disease progression	Unknown	
TOTAL $n = 115$	68 (59.1)	13 (11.3)	6 (5.2)	25 (21.7)	3 (2.6)	41 (35.7)	47 (40.9)	16 (13.9)	2 (1.7)	9 (7.8)	40.5
Inflammatory $n = 69$	49 (71.0)	3 (4.3)	1 (1.4)	14 (20.3)	2 (2.9)	22 (31.9)	28 (40.6)	15 (21.7)	1 (1.4)	3 (4.3)	45.0
IOI $n = 20$	10 (50)	1 (5)	–	9 (45)	–	8 (40)	8 (40)	2 (10)	–	2 (10)	22.5
IgG4-RD $n = 20$	18 (90)	1 (5)	–	1 (5)	–	3 (15)	9 (45)	7 (35)	1 (5)	–	65.9
Sarcoidosis $n = 11$	9 (81.9)	–	–	1 (9.1)	1 (9.1)	1 (9.1)	6 (54.5)	3 (27.3)	–	1 (9.1)	24.7
Xanthogranulomatous disease $n = 8$	7 (87.5)	–	1 (12.5)	–	–	6 (75)	2 (25)	–	–	–	109.9
EBV dacryoadenitis $n = 2$	1 (50)	–	–	1 (50)	–	2 (100)	–	–	–	–	1
GPA $n = 2$	2 (100)	–	–	–	–	–	1 (50)	1 (50)	–	–	12
Sjogren's $n = 2$	–	1 (50)	–	–	1 (50)	–	2 (100)	–	–	–	5
Viral dacryoadenitis $n = 2$	–	–	–	2 (100)	–	2 (100)	–	–	–	–	3
Eosinophilic asthma $n = 1$	1 (100)	–	–	–	–	–	–	1 (100)	–	–	12
Unspecified vasculitis $n = 1$	1 (100)	–	–	–	–	–	–	1 (100)	–	–	30
Lymphoproliferative $n = 23$	18 (78.3)	–	–	4 (17.4)	1 (4.3)	7 (30.4)	8 (34.8)	1 (4.3)	1 (4.3)	6 (26.1)	41.6
Lymphoma $n = 16$	15 (93.8)	–	–	1 (6.3)	–	4 (25)	5 (31.3)	1 (6.3)	1 (6.3)	5 (31.3)	34.8
Reactive lymphoid hyperplasia $n = 7$	3 (42.9)	–	–	3 (42.9)	1 (14.3)	3 (42.9)	3 (42.9)	–	–	1 (14.3)	56.2
Structural $n = 17$	–	10 (58.8)	–	7 (41.2)	–	9 (52.9)	8 (47.1)	–	–	–	14.8
Lacrimal gland prolapse $n = 13$	–	10 (76.9)	–	3 (23.1)	–	9 (69.2)	4 (30.8)	–	–	–	19.5
Dacryops $n = 4$	–	–	–	4 (100)	–	–	4 (100)	–	–	–	1
Other entities $n = 6$	2 (33.3)	–	4 (66.7)	–	–	3 (50)	3 (50)	–	–	–	60.6
Amyloidosis $n = 2$	1 (50)	–	1 (50)	–	–	–	2 (100)	–	–	–	96
Lymphoma in Sjogren's with orbital lobe cysts $n = 2$	–	–	2 (100)	–	–	2 (100)	–	–	–	–	92.5
Lymphoma in RA with orbital lobe cysts $n = 1$	–	–	1 (100)	–	–	–	1 (100)	–	–	–	20
Unknown diagnosis $n = 1$	1 (100)	–	–	–	–	1 (100)	–	–	–	–	2

All results expressed as: *n* (%).
EBV Epstein-Barr virus, *GPA* granulomatosis with polyangiitis, *IOID* idiopathic orbital inflammatory disease, *RA* rheumatoid arthritis.

or series. These reports describe a range of diagnoses including: Kimura's disease [4, 5]; dacryops [6]; extramedullary hematopoiesis [7]; amyloidosis [8]; Rosai-Dorfman disease [1, 9]; tuberculosis [10]; following isoretinoin treatment [11]; sickle cell disease [12]; as an adverse effect of sodium valproate [13] and interferon alpha [14]; acute lymphocytic leukaemia; [15] Still's disease; [16] and bilateral lacrimal gland lymphoma in a patient with known Sjogren's syndrome [17]. Our series overlaps in many ways with these reports, although not surprisingly some of the more rare manifestations were absent from our population.

In our series, IOID was also one of the most common diagnoses with 20 (17.4%) reported cases. This is a similar proportion to the series by Tang et al., although slightly lower. The difference may be explained by the larger number of cases in our series classified as IgG4-RD (20, 17.4%). Some of these cases may have been previously classified as IOID, possibly inflating the proportion in Tang et al.'s study [1]. This is likely due to the different classifications used between the two case series. It is possible that not all their IOID patients were fully investigated for IgG4-RD given this was not considered a separate clinical entity in that study. However, given that IgG4-RD has its own specific histopathology, constellation of distinct clinical findings, and comprehensive diagnostic criteria, we believe it is better classified as its own entity, a notion that has been supported by other papers [18–20].

In our series, sarcoidosis was the fifth most common cause (11, 9.6%) of bilateral lacrimal gland disease, compared to the second most common cause (19, 19.6%) in Tang et al.'s case series. It is possible that the prevalence of sarcoidosis was lower in our case series as it is seen more commonly in African-American patients [21]. Our case series did not identify cases of that ethnicity in the data available, whereas they made up nearly half of the study population (48, 49.5%) in Tang et al.'s case series [1].

Clinical presentation

The finding of a palpable mass was noted commonly amongst all conditions (83, 72.2%) and is a non-specific finding that tends to unify the population rather than provide diagnostic clues. However, a number of clinical characteristics may assist in differentiating between various diagnoses. Age of presentation may be a useful indicator. Inflammatory conditions, in particular viral dacryoadenitis, were seen in younger patients as opposed to those with structural and lymphoproliferative conditions, where the patients were much more likely to be older. Pain, conjunctival injection, and periorbital oedema were more commonly seen in those with an inflammatory condition which is not surprising given the classic symptomatology. Globe dystopia and reduced visual acuity were more commonly seen in those with lymphoma, likely due to their mass effect. Tang et al. reported similar findings [1].

Dermatochalasis and yellow discolouration of the eyelids were two signs seen exclusively in lacrimal gland prolapse and xanthogranulomatous disease respectively. However, given that dermatochalasis is a very common finding in the aging population, it is a non-specific sign. Yellow discolouration conversely was rarely noted in other populations and is more specific for xanthogranuloma. Utilising factors such as age, globe dystopia, and eyelid changes may assist in selecting laboratory tests and imaging for further workup of the patient.

Systemic symptoms were also significantly more common in patients with inflammatory conditions. Lymphadenopathy, swollen salivary glands and respiratory symptoms were the three most common findings. Many inflammatory conditions seen in this series are well known to affect multiple organ symptoms. In particular, 12 of 20 patients with IgG4-RD had systemic involvement. Systemic symptoms are often associated with known inflammatory conditions and investigation for common processes such as IgG4-RD, sarcoidosis, Sjogren's syndrome, or xanthogranulomatous disease is appropriate in such cases.

Investigations

Radiological investigations play an important role in patients with bilateral lacrimal gland disease, particularly as it can assist in identifying the involvement of extra-lacrimal structures. This is particularly useful in IgG4-RD where sensory nerves and extra-ocular muscle enlargement can often be noted, as nine of the 17 patients with involvement of structures other than the lacrimal gland in our series were affected by IgG4-RD [22]. The other eight patients were found to carry a diagnosis of xanthogranulomatous disease. This is expected based on the clinical profile of such patients, and underscores the importance of systemic survey in patients affected by bilateral lacrimal gland disease with extensive orbital involvement [23].

Although biopsy currently remains the gold standard for histopathologic diagnosis, there may be a small subset of patients where biopsy may not be necessary. These include patients with bilateral lacrimal gland prolapse, or younger patients presenting with acute symptoms around the time of a recent viral illness. In our series, those diagnosed with viral or EBV dacryoadenitis (4, 3.5%) had an average age of 23.3 years with a mean duration of eleven days of symptoms prior to presentation and complete resolution of all symptoms within three months. Only one patient required a course of oral steroids tapered over two weeks and the rest were observed. Specific viral testing may help to identify an underlying pathogen such as EBV which was performed and positive in all of our cases. If rapid resolution is not noted with initial management strategies, a low threshold for biopsy is prudent. This is similar for our patients with lacrimal gland prolapse and dacryops. All patients presented with a painless, palpable mass with no other symptoms. In addition to clinical signs, these patients can have their diagnosis further supported with negative serological tests and/or unremarkable histological findings, as was the case in our series. All these patients had complete resolution of their condition following surgical intervention with dacryopexy or showed stable disease with observation.

Management and outcomes

Overall, stable disease or improvement in symptoms was seen in the majority of our patients with only two patients (1.7%) demonstrating progression. The proportion of patients with completely resolved disease was higher in our series than in previous reports (28% vs 35.7%) [1]. This may be related to underdiagnosis of IgG4-RD in the Tang et al series. The treatment of IgG4-RD may require the additional usage of immunosuppressants, or monoclonal antibodies in addition to corticosteroids [22], whereas IOID can typically be managed well with steroids alone [24]. This discrepancy in diagnosis may have led to less aggressive therapy in the Tang et al. study and a lower complete resolution rate as a result. Conditions requiring multiple management strategies were typically complex diagnoses such as amyloidosis where initial medical treatment with oral steroids and intralesional triamcinolone provided minimal improvement of symptoms, and where multiple conditions were involved such as lymphoma in patients with either Sjogren's syndrome or rheumatoid arthritis.

Our case series demonstrates the wide variety of aetiologies that may be found in a patient presenting with bilateral lacrimal gland disease and some diagnostic clues for assessment. Lymphoproliferative conditions are associated with increasing age, a painless palpable mass, reduced visual acuity and the presence of globe dystopia. Biopsy should be strongly considered in these patients, particularly as a lymphoproliferative condition was seen in nearly one in five patients in our series.

Given IgG4-RD was one the most common causes for bilateral lacrimal gland disease in our series, it appears prudent to suggest that patients presenting with bilateral lacrimal gland disease obtain serum IgG4 studies [20]. However, it should be noted there are a substantial subset of patients with biopsy proven IgG4-RD

who do not have an elevated serum IgG4 [25]. For this reason, biopsy with IgG4 staining is important for all patients even if serological levels are normal. Serum ACE was also noted to be useful in the diagnostic algorithm as sarcoidosis is another common cause [1]. Although ACE only has modest sensitivity and specificity, its elevation increases the support for the diagnosis of sarcoidosis, or even another granulomatous condition, and can prompt further investigation with either a chest x-ray or CT chest [26].

There are a few limitations to consider. Due to the retrospective nature of the study, there was no defined set of clinical symptoms, imaging, laboratory tests or outcomes that were universally assessed for each patient's presentation. Many causes of bilateral lacrimal gland disease remain extremely rare and thus were found in only a few cases within our series. This limits our ability to identify trends in clinical features for rareR conditions. Additionally, there is now emerging data on using MRI imaging and apparent diffusion coefficient values, particularly in assisting to differentiate between inflammatory and malignant lesions which was not considered in this study. These parameters should be considered when determining the aetiology of bilateral lacrimal gland disease if the information is available.

In conclusion, bilateral lacrimal gland disease represents a wide range of aetiologies, most of which are systemic diseases. In our series, we found inflammatory conditions to be the most common causes of bilateral lacrimal gland disease with IgG4-RD and IOID representing the two largest groups of patients in our study. We found several demographic and clinical features associated with particular conditions which may assist in formulating a list of primary differential diagnoses. However, due to the wide range of aetiologies of bilateral lacrimal gland disease, it is extremely difficult to accurately determine a cause based on clinical findings alone. This series also demonstrates that the majority of pathologies involved in bilateral lacrimal gland disease are systemic inflammatory conditions or malignancies and may be the first presentation of a multi-organ disease. Given these findings, it is important to identify the exact underlying aetiology, highlighting the vital role of lacrimal gland biopsy in patients presenting with bilateral lacrimal gland disease.

Summary table

What was known before

- Bilateral lacrimal gland disease is a rare and unique disease process of which there is a paucity of data. Bilateral lacrimal disease may be due to a wide range of aetiologies, most of which are systemic.

What this study adds

- The most common category of diagnosis was inflammatory followed by lymphoproliferative, structural and other conditions. The most common specific diagnoses were IgG4 related disease and idiopathic orbital inflammatory disease. Lymphoproliferative conditions are particularly associated with increasing age and globe dystopia. Conjunctival injection and systemic symptoms are predictors of inflammatory disease.

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AUTHOR CONTRIBUTIONS

SH was responsible for study design, ethics approval, data collection, analysis of data, constructing the tables, and drafting and revising the manuscript. VJ was responsible for study design, ethics approval, and drafting and revising the manuscript. AM, KS, and LC were responsible for the study design, collection of data and drafting and revising the manuscript. GD, DR, DS were responsible for the study design and drafting and revising the manuscript. All authors approve the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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