



Clinical and Radiological Features of Diffuse Lacrimal Gland Enlargement: Comparisons among Various Etiologies in 91 Biopsy-Confirmed Patients

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Objective: To compare the clinical and radiological features of various etiologies of chronic diffuse lacrimal gland enlargement.

Materials and Methods: We retrospectively reviewed 91 consecutive patients who underwent surgical biopsy for chronic diffuse lacrimal gland enlargement and were diagnosed with non-specific dacryoadenitis (DA) (n = 42), immunoglobulin G4-related dacryoadenitis (IgG4-RD) (n = 33), and lymphoma (n = 16). Data on patient demographics, clinical presentation, and CT imaging findings (n = 73) and MRI (n = 43) were collected. The following radiologic features of lacrimal gland enlargement were evaluated: size, unilaterality, wedge sign, angle with the orbital wall, heterogeneity, signal intensity, degree of enhancement, patterns of dynamic contrast-enhanced, and apparent diffusion coefficient value. Radiological features outside the lacrimal glands, such as extra-lacrimal orbital involvement and extra-orbital head and neck involvement, were also evaluated. The clinical and radiological findings were compared among the three diseases.

Results: Compared to the DA and IgG4-RD groups, the lymphoma group was significantly older (mean 59.9 vs. 46.0 and 49.4 years, respectively; $p = 0.001$) and had a higher frequency of unilateral involvement (62.5% vs. 31.0% and 15.2%, respectively; $p = 0.004$). Compared to the IgG4-RD and lymphoma groups, the DA group had significantly smaller lacrimal glands (2.3 vs. 2.8 and 3.3 cm, respectively; $p < 0.001$) and a lower proportion of cases with a wedge sign (54.8% vs. 84.8% and 87.5%, respectively; $p = 0.005$). The IgG4-RD group showed more frequent involvement of the extra-orbital head and neck structures, including the infraorbital nerve (36.4%), paranasal sinus (72.7%), and salivary gland (58.6%) compared to the DA and lymphoma groups (4.8%–28.6%) (all $p < 0.005$).

Conclusion: Patient age, unilaterality, lacrimal gland size, wedge sign, and extra-orbital head and neck involvement differed significantly different between lymphoma, DA, and IgG4-RD. Our results will be useful for the differential diagnosis and proper management of chronic lacrimal gland enlargement.

Keywords: Lacrimal apparatus; Immunoglobulin G4-related disease; Lymphoma; Diagnostic imaging

INTRODUCTION

Despite its relatively small anatomical size, the lacrimal gland is the site of a highly diverse group of diseases,

ranging from inflammation to malignancies [1]. Lacrimal gland enlargement can be a localized condition but can also be the first manifestation of systemic diseases such as lymphoma, immunoglobulin G4 (IgG4)-related disease,

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and sarcoidosis, which require systemic evaluation and treatment. The heterogeneity of lacrimal gland diseases frequently poses a diagnostic dilemma for attending clinicians, as their management can vary depending on the diagnosis. However, the differential diagnosis of diffuse lacrimal gland enlargement may be difficult because patients with these disease entities commonly present with nonspecific clinical signs such as eyelid swelling or a palpable mass in the superolateral aspect of the orbit.

Chronic dacryoadenitis (46%–55% of cases) and lymphoma (21%–38%) are the two most common etiologies of chronic lacrimal gland enlargement [1-4]. While chronic dacryoadenitis may be idiopathic with an unknown cause, a significant proportion of cases have specific causes, such as IgG4-related disease, sarcoidosis, granulomatosis with polyangiitis, Sjogren's syndrome, and Churg-Strauss syndrome [1-4]. Idiopathic or nonspecific dacryoadenitis (DA) is a diagnosis of exclusion made after ruling out specific etiologies. Among 'specific' dacryoadenitis, IgG4-related dacryoadenitis (IgG4-RD) is the most common cause of chronic inflammation [2-4]. Differentiating between inflammation and lymphoma is essential for clinical treatment. In addition, although IgG4-RD corresponds to lacrimal gland inflammation, it has distinctive clinical outcomes such as a higher recurrence rate, more frequent systemic involvement, and association with malignancies [5-7]. The malignancies complicating IgG4-RD include lymphoma and non-lymphoid tumors of pancreatic, lung, and gastrointestinal cancers [8-10]. Therefore, it is important to differentiate IgG4-RD from DA.

CT and MRI have been used to evaluate various disorders of the orbital structures, including the lacrimal gland. Although the radiologic assessment of tumorous conditions involving the lacrimal gland has shown remarkable advances [11-16], it is difficult to differentiate diseases presenting as diffuse lacrimal gland enlargement, owing to their intrinsic similarities [17]. To our knowledge, no published studies have compared the clinical and radiological features among the common etiologies of diffuse lacrimal gland enlargement to assist in their differential diagnosis. Considering the high prevalence of DA, IgG4-RD, and lymphoma in patients with chronic lacrimal gland enlargement, a comparative study would provide valuable information for their differential diagnosis, as these conditions differ in prognosis and require different evaluation and treatment strategies. This study compared the clinical and radiological features of diffuse lacrimal gland enlargement among three common

etiologies: DA, IgG4-RD, and lymphoma.

MATERIALS AND METHODS

The protocols used in this study were approved by our Institutional Review Board (IRB No. 2020-1508), which waived the requirement for informed consent owing to the retrospective nature of the analyses and use of anonymized medical records. The methods and data reporting were performed according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18,19].

Study Population

The study population consisted of a historical cohort of consecutive patients who underwent incisional biopsy for lacrimal gland enlargement at our institution (a 2700-bed academic tertiary referral hospital in Seoul, Korea), which was performed by one author between January 2010 and January 2020. The indications for incisional biopsy of the lacrimal gland included chronic symptoms and signs lasting ≥ 3 months and diffuse lacrimal gland enlargement confirmed on orbital imaging examinations. Patients with typical signs of acute infectious inflammation were excluded from biopsy. Patients with lacrimal gland enlargement associated with thyroid eye disease were also excluded from biopsy because the clinical diagnosis was made at the discretion of the ophthalmologists. Patients without preoperative orbital imaging were also excluded from the study. Among 115 patients with lacrimal gland masses in our cohort who had preoperative images and a histopathologic diagnosis, those who underwent excisional biopsy for suspicious epithelial tumors (pleomorphic adenoma, $n = 15$; adenoid cystic carcinoma, $n = 4$) and those with dacryops ($n = 3$), solitary fibrous tumor ($n = 1$), and xanthogranulomatous inflammation ($n = 1$) were also excluded from the study population. Our cohort did not include any patients with sarcoidosis, granulomatosis with polyangiitis, Sjogren's syndrome, or Churg-Strauss syndrome. Finally, our study included 91 patients with histopathologic diagnoses of DA ($n = 42$), IgG4-RD ($n = 33$), and lymphoma ($n = 16$). IgG4-RD was diagnosed according to the criteria for IgG4-related ophthalmic disease defined by the Japanese Study Group in 2014 [20]. Data on patient demographics, laterality, symptom duration, orbital imaging findings, histopathological diagnosis, and associated systemic involvement were also collected.

Imaging Protocols for CT and MRI

Data from the preoperative orbital imaging examinations were retrospectively analyzed. Of the 91 included patients, 73 underwent CT scans, 43 underwent MRI scans, and 25 underwent both CT and MRI scans.

The CT scans were performed using various scanners (GE Medical Systems, GE Lightspeed VCT, GE Discovery CT750 HD, GE OPTIMA CT660, Siemens Somatom Sensation 16, Siemens Somatom Definition AS, Siemens Somatom Definition Edge, Siemens Somatom Definition Flash) with multidetector capabilities ranging from 16 to 128 channels. The techniques and parameters varied depending on the system used; however, most examinations were performed using a 128-channel CT scanner (Somatom Definition Flash; Siemens Medical Solutions). The detailed CT imaging protocols are described in the Supplement.

The MRI scans were performed using various 3T MRI scanners (Magnetom Skyra, Siemens; Achieva, Philips Medical Systems; Ingenia CX, Philips Medical Systems) with a 16- or 64-channel head and neck coil. However, most examinations were performed with a 3T MRI scanner (Magnetom Skyra, Siemens) with a 64-channel head and neck coil. The MRI protocol for head and neck tumors consisted of axial and coronal T1- and T2-weighted turbo spin-echo sequences with diffusion-weighted imaging and dynamic contrast-enhanced (DCE)-MRI. The detailed MRI protocols are described in the Supplement.

Imaging Analysis

Each CT or MRI scan was independently evaluated by two neuroradiologists, with 11 and 5 years of experience in head and neck imaging, respectively, and who were unaware of the patients' histopathologic diagnosis. We subsequently obtained consensus results by resolving any discrepancies in individual interpretations. Before the evaluations, the two neuroradiologists completed a training session using CT or MRI scans from 10 patients to help them achieve a standardized interpretation of the imaging findings.

The following radiologic features of lacrimal gland enlargement were evaluated: size, unilaterality, wedge sign, angle with the orbital wall, heterogeneity, signal intensity, degree of enhancement, DCE-MRI patterns, and apparent diffusion coefficient (ADC) value. Other radiologic features such as extra-lacrimal orbital involvement and extra-orbital head and neck involvement were also evaluated.

The size of the lacrimal gland was measured in axial scan mode using the image in which the lacrimal gland appeared

the largest [21]. A wedge sign was considered to be present when the lacrimal gland extended more posteriorly than the anterior edge of the trigone of the greater wing of the sphenoid between the lateral rectus muscle and lateral orbital wall [22]. The angle between the lateral orbital wall and lacrimal gland at the posterior end was evaluated and classified as either an acute or right/obtuse angle. Extra-lacrimal orbital involvement was defined as the involvement of orbital tissues other than the lacrimal gland such as fat, extraocular muscles, and the optic nerve in the orbital cavity. Extra-orbital head and neck involvement was defined as the involvement of the infraorbital nerve, paranasal sinus, salivary gland, nasopharynx, lymph nodes, and other systemic organs visible on orbital CT or MRI. Paranasal sinus involvement was defined as T2 iso-signal intensity mucosal thickening in patients who underwent MRI.

The lesion heterogeneity was determined by measuring the standard deviation (SD) of the Hounsfield units on contrast-enhanced CT, signal intensity on T2-weighted imaging, and contrast-enhanced T1-weighted imaging. Among all slices containing lacrimal glands, if more than 1/3 of the slices with an SD of 25% or more were identified, the lesion was defined as heterogeneous; otherwise, it was considered homogeneous. The signal intensity on conventional T2-weighted imaging of the lacrimal gland was categorized as high, iso, and low relative to that of the gray matter of the brain. The degree of enhancement on CT and MRI was categorized as high, intermediate, and low, relative to that of the adjacent muscle. The pattern of dynamic enhancement on DCE-MRI was categorized as washout, plateau, and prolonged [23]. The ADC values were measured on the ADC map images by placing the regions of interest over the lacrimal gland and tabulating the mean and SD values.

Statistical Analysis

The consensus interpretations between the two readers were used in the main analysis. To compare the clinical characteristics and radiologic features among the three disease groups, we performed analysis of variance and chi-square test for continuous and categorical variables, respectively, with post-hoc analysis using Bonferroni correction to further examine the between-group differences. Additionally, the inter-observer agreement between the two radiologists was calculated using Cohen's kappa statistic. Values < 0.20 were considered indicative of slight agreement, 0.21–0.40 indicative of fair agreement,

0.41–0.60 indicative of moderate agreement, 0.61–0.80 indicative of substantial agreement, and 0.81–1.00 indicative of near-perfect agreement. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp.).

RESULTS

Table 1 shows the baseline characteristics of the study population. The lymphoma group had a significantly older age (mean, 59.9 vs. 46.0 or 49.4 years, $p = 0.001$), a higher frequency of unilateral involvement (62.5% vs. 31.0% or 15.2%, $p = 0.004$), and a higher proportion of MRI scans

Table 1. Baseline Characteristics

	Nonspecific Dacryoadenitis (n = 42)	IgG4-RD (n = 33)	Lymphoma (n = 16)	<i>P</i>
Age, mean (range), years	46.0 (22–73)	49.4 (19–67)	59.9 (29–76)*	0.001
Sex				0.083
Male	13 (31.0)	12 (36.4)	10 (62.5)	
Female	29 (69.0)	21 (63.6)	6 (37.5)	
Unilateral involvement	13 (31.0)	5 (15.2)	10 (62.5)*	0.004
Symptom duration, median (range), months	4.5 (3–108)	7 (3–120)	6 (3–12)	0.380

Data are expressed as the number of cases with percentages in parentheses unless otherwise indicated. *Significantly different from nonspecific dacryoadenitis or IgG4-RD. IgG4-RD = immunoglobulin G4-related dacryoadenitis

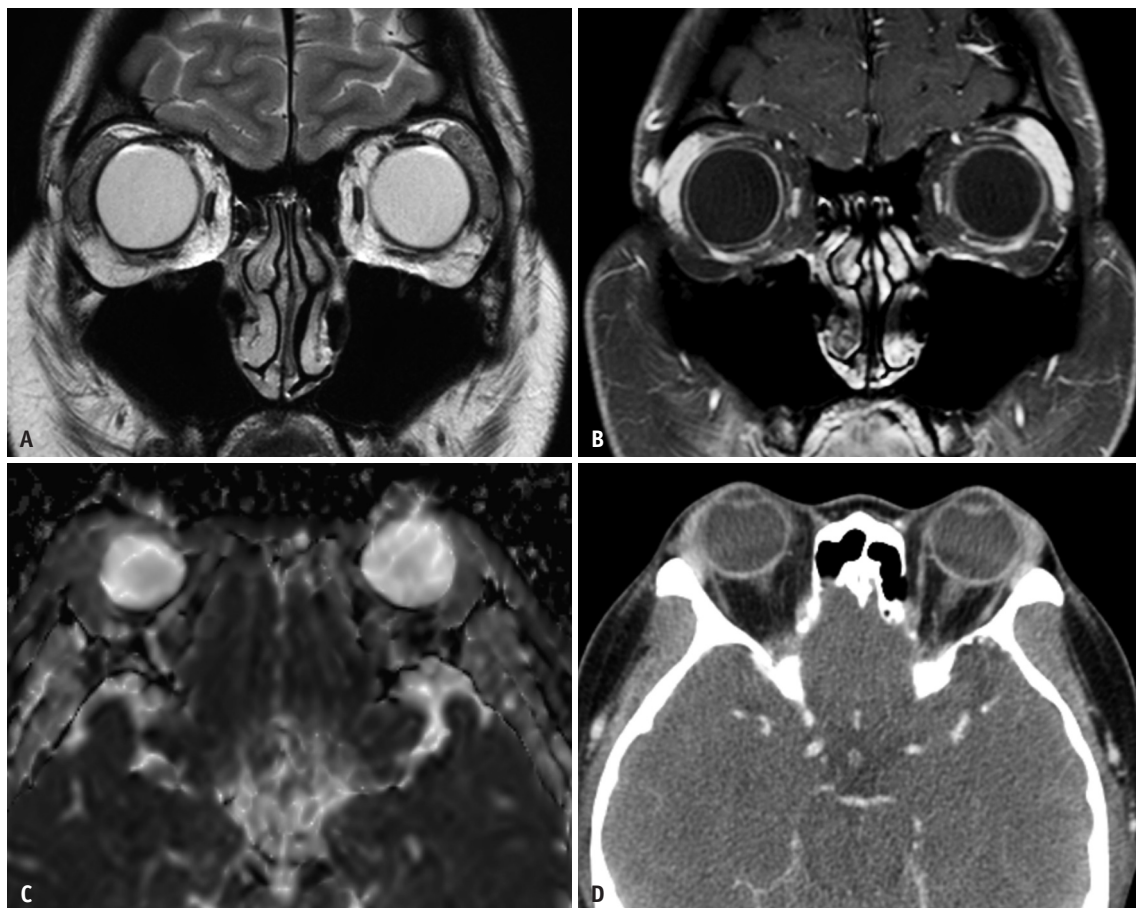


Fig. 1. Representative case of nonspecific dacryoadenitis in a 29-year-old female with a 36-month history of bilateral eyelid swelling. **A.** The coronal T2-weighted image shows homogeneous iso-signal intensity of the enlarged bilateral lacrimal glands. **B.** The lacrimal glands show homogeneous enhancement on the contrast-enhanced T1-weighted image. **C.** On the diffusion-weighted image, the mean apparent diffusion coefficient value of the mass was $1.290 \times 10^{-3} \text{ mm}^2/\text{s}$. **D.** The axial CT image shows homogeneous enhancement of the enlarged bilateral lacrimal glands without a wedge sign.

(75.0% vs. 47.6% or 33.3%, $p = 0.023$) compared to those in the DA and IgG4-RD group. We observed no significant differences in the other clinical characteristics including symptom duration and sex.

Representative cases of diffuse lacrimal gland enlargement associated with DA, IgG4-RD, or lymphoma are shown in Figures 1-3. Table 2 shows a comparison of the radiological features among the three disease groups. Regarding lacrimal gland enlargement, the DA group had a significantly smaller lacrimal gland size (mean maximal diameter, 2.3 vs. 2.8 or 3.3 cm, $p < 0.001$) and a lower proportion of cases with a wedge sign (54.8% vs. 84.8% or 87.5%, $p = 0.005$) compared to those in the IgG4-RD and lymphoma groups. The other radiologic features of the lacrimal gland did not differ significantly among the three groups (all $p > 0.05$).

We observed significant differences among the three groups in the proportions of cases showing extra-orbital head and neck involvement. The IgG4-RD group showed more frequent involvement of the extra-orbital head and neck structures, including the infraorbital nerve (36.4% vs.

4.8% or 6.3%, $p = 0.001$), paranasal sinus (72.7% vs. 25% or 0%, $p < 0.001$), and salivary glands (58.6% vs. 20.7% or 20.0%, $p = 0.004$) compared to the DA and lymphoma groups. Notably, infraorbital nerve involvement was a peculiar finding in the IgG4-RD group (sensitivity: 36.4%, specificity: 94.8%), and 80% (12/15) of the patients with infraorbital nerve involvement were diagnosed with IgG4-RD. Bilateral involvement of the infraorbital nerve was even more specific for IgG4-RD. Among the 12 patients with IgG4-related infraorbital nerve involvement, 83.3% (10/12) showed bilateral enlargement. In contrast, the other three cases with infraorbital nerve involvement (DA, $n = 2$; lymphoma, $n = 1$) showed unilateral involvement. We observed no differences in extra-lacrimal orbital involvement ($p = 0.411$). Extraocular muscle ($n = 3$) and orbital fat involvement ($n = 1$) were observed in the lymphoma group, while extraocular muscle ($n = 2$), intraorbital nerve ($n = 1$), and orbital fat ($n = 1$) involvement were observed in the IgG4-RD group, and extraocular muscle ($n = 4$) and orbital fat involvement ($n = 1$) were observed in the DA group.

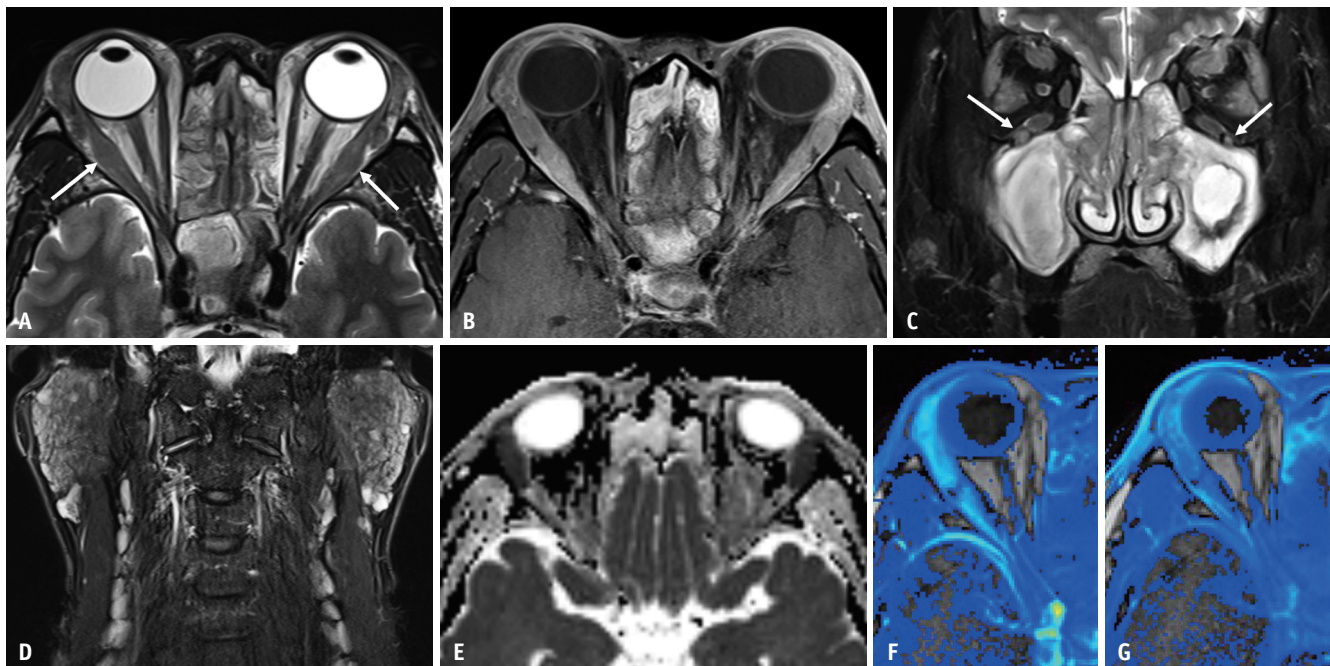


Fig. 2. Representative case of immunoglobulin G4-related dacryoadenitis in a 44-year-old male with a 12-month history of bilateral eyelid swelling.

A. The T2WI shows a mass with homogeneous iso-signal intensity without a wedge sign and bilateral thickening of the lateral rectus muscle (arrows). **B.** The mass shows homogeneous enhancement on the CE-T1WI. **C.** The coronal T2WI image shows bilateral thickening of the lateral and superior rectus muscles with bilateral involvement of the infraorbital nerves (arrows) and diffuse mucosal thickening of the nasal cavity and paranasal sinuses with T2 iso-signal-intensity infiltration. **D.** Multiple enlarged lymph nodes in the neck and heterogeneous signal intensity of the parotid glands are also visible bilaterally. **E.** On the diffusion-weighted image, the mean apparent diffusion coefficient value of the mass was $0.615 \times 10^{-3} \text{ mm}^2/\text{s}$. **F, G.** The dynamic CE MR image (**F**, color map of the initial 90-seconds time-signal intensity area under the curve; **G**, color map of the final 90-seconds time-signal intensity area under the curve [34]) shows enhancement in the early phase and washout in the delayed phase. CE = contrast-enhanced, WI = weighted image

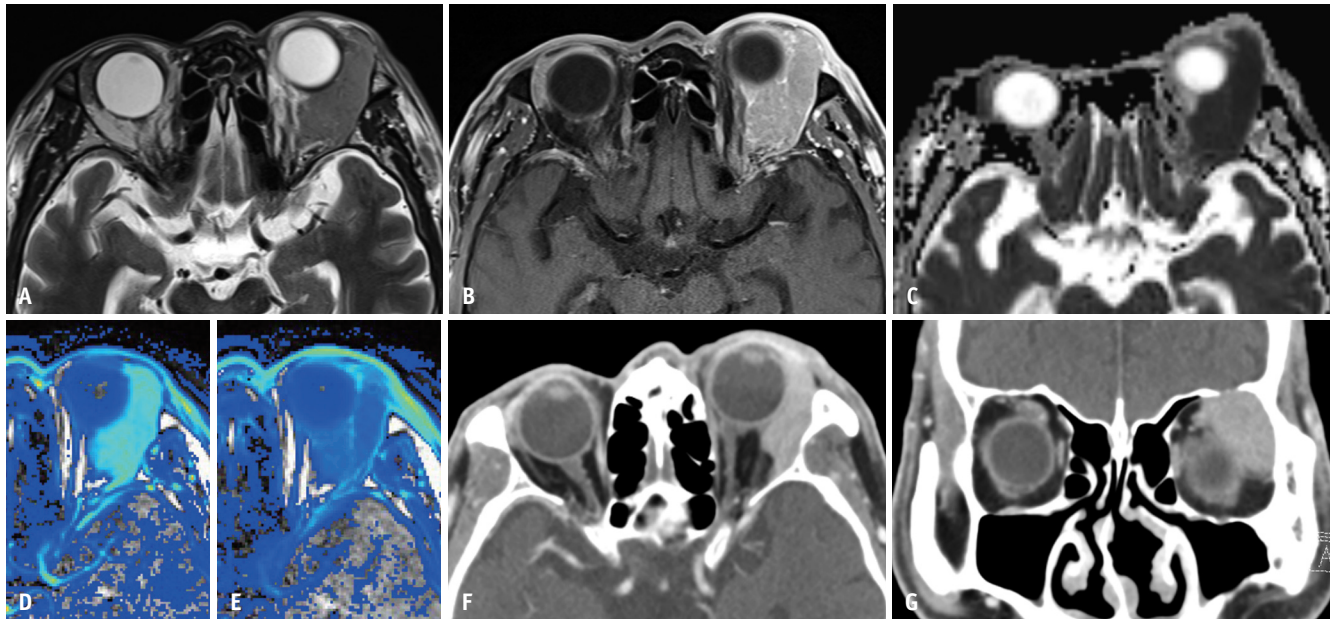


Fig. 3. Representative case of lymphoma involvement of the lacrimal gland in a 76-year-old male with a 9-month history of left eyelid swelling.

A. The T2WI shows a mass with homogeneous iso-signal intensity with a wedge sign and forming an obtuse angle with the lateral orbital wall in the left lacrimal fossa. **B.** The mass shows homogeneous enhancement on contrast-enhanced T1WI. **C.** On diffusion-weighted imaging, the mean apparent diffusion coefficient value of the mass was $0.615 \times 10^{-3} \text{ mm}^2/\text{s}$. **D-G.** The dynamic contrast-enhanced MR image shows enhancement in the early phase (**D**) and washout in the delayed phase (**E**). The axial and coronal reconstructed CT images show homogeneous enhancement of the mass involving the left lacrimal gland with bone erosion in the orbital roof. No enlarged infraorbital nerve or inflammation in the paranasal sinuses is evident (**F, G**). WI = weighted image

The result of the analysis of inter-observer agreement regarding radiologic features is summarized in Table 3. Between readers 1 and 2, the strength of agreement ranged from moderate to near-perfect agreement (Kappa, 0.554–0.944).

DISCUSSION

The results of our study revealed that the most common causes of chronic diffuse lacrimal gland enlargement included DA, IgG4-RD, and lymphoma and that each etiology had different clinical and radiological features. Lymphoma was associated with older age (60 vs. 46–49 years) and unilateral involvement (63% vs. 15%–31%, respectively). DA was associated with a smaller lacrimal gland (2.3 vs. 2.8–3.3 cm) and a more frequent absence of a wedge sign (45% vs. 12%–15%). IgG4-RD was more frequently involved in extra-orbital head and neck structures (36%–73% vs. 5%–29%) and infraorbital nerve involvement was highly specific for IgG4-RD (95%).

Previous studies have described the differentiation between inflammatory diseases and lymphoma in the orbit [1,2,13,15,24]. These studies reported that patients

with orbital lymphoma were significantly older and more commonly show unilateral involvement compared to patients with inflammatory disease [1,2,13,15,24]. Similarly, we also reported associations between lymphoma and older age (60 vs. 46–49 years) and more frequent unilateral involvement (63% vs. 15%–31%) compared to DA or IgG4-RD. Inflammatory disease of the lacrimal gland commonly shows bilateral involvement because it may often be accompanied by autoimmune or systemic diseases [25]. In patients with suspected chronic idiopathic dacryoadenitis, corticosteroids can be empirically administered before surgical biopsy [26]. However, a corticosteroid trial can also initially reduce the size of the lymphoma and delay its definitive diagnosis [27]. Our results highlight the importance of surgical biopsy for chronic diffuse lacrimal gland enlargement, particularly in patients aged > 60 years with unilateral disease involvement.

IgG4-related disease is characterized by the infiltration of IgG4-positive plasma cells into the tissues of isolated or multiple organs, with the lacrimal gland among the most frequently affected organs [28]. Similar to previous studies [5,6,28,29], we observed that the IgG4-RD group showed

Table 2. Comparative Analysis of Radiologic Features among Nonspecific Dacryoadenitis, IgG4-RD, and Lymphoma

	Nonspecific Dacryoadenitis	IgG4-RD	Lymphoma	P
Lacrimal gland				
Maximal diameter, mean (range), cm	2.3 (1.4–4.6)*	2.8 (1.8–4.3)	3.3 (1.7–5.6)	< 0.001
Wedge sign	23/42 (54.8)*	28/33 (84.8)	14/16 (87.5)	0.005
Angle with the orbital wall				0.311
Acute angle	10/42 (23.8)	5/33 (15.2)	1/16 (6.3)	
Right to obtuse angle	32/42 (76.2)	28/33 (84.8)	15/16 (93.8)	
Heterogeneity of lesions				
CT	7/33 (21.2)	4/28 (14.3)	1/12 (8.3)	0.647
T2WI	5/20 (25)	4/11 (36.4)	4/12 (33.3)	0.760
CE-T1WI	2/19 (10.5)	2/11 (18.2)	3/11 (27.3)	0.505
Enhancement degree on CT				0.183
High	32/33 (97)	27/28 (96.4)	10/12 (83.3)	
Intermediate	1/33 (3)	1/28 (3.6)	2/12 (16.7)	
Enhancement degree on MR				0.552
High	18/19 (94.7)	11/11 (100)	11/11 (100)	
Intermediate	1/19 (5.3)	0/11 (0)	0/11 (0)	
T2 signal intensity				0.300
Hypo	3/20 (15)	5/11 (45.5)	3/12 (25)	
Iso	17/20 (85)	6/11 (54.5)	9/12 (75)	
DCE pattern				0.923
Washout	5/7 (71.4)	4/5 (80)	2/4 (50)	
Plateau	1/7 (14.3)	0/5 (0)	1/4 (25)	
Prolonged	1/7 (14.3)	1/5 (20)	1/4 (25)	
ADC value, $\times 10^{-3}$ mm ² /s				
Mean (range)*	1.132 (0.556–2.111)	0.883 (0.615–1.238)	0.797 (0.613–1.042)	0.151
Other findings				
Extra-orbital involvement				
Infraorbital nerve	2/42 (4.8)	12/33 (36.4) [†]	1/16 (6.3)	0.001
Paranasal sinus	5/20 (25)	8/11 (72.7) [†]	0/12 (0)	< 0.001
Salivary gland	6/29 (20.7)	17/29 (58.6) [†]	3/15 (20.0)	0.004
Nasopharynx	4/42 (9.5)	7/33 (21.2)	1/16 (6.3)	0.301
Lymphadenopathy	6/16 (37.5)	12/22 (54.5)	1/8 (12.5)	0.129
Extra-lacrimal orbital involvement	5/42 (11.9)	4/33 (12.1)	4/16 (25.0)	0.411

Data are expressed as the number of cases with percentages in parentheses unless otherwise indicated. Includes 42 nonspecific dacryoadenitis, 33 IgG4-RD, and 16 lymphoma patients. *Significantly different from IgG4-RD or lymphoma, [†]Significantly different from nonspecific dacryoadenitis or lymphoma. ADC = apparent diffusion coefficient, CE = contrast-enhanced, DCE = dynamic contrast-enhanced, IgG4-RD = immunoglobulin G4-related dacryoadenitis, WI = weighted image

more frequent involvement of extra-orbital head and neck structures, including the infraorbital nerve (36%), paranasal sinus (73%), and salivary gland (59%), compared to the other two groups (5%–29%). A recently published article that reviewed the manifestations of IgG4-related disease in the head and neck region reported that most cases showed iso-to-low T2 signal intensity with diffuse homogeneous enhancement of the involved structures [29]. In our study, the T2 signal intensity of the lacrimal gland was mainly isointense in all three groups, with no significant

differences. However, T2 isointense mucosal thickening of the paranasal sinus distinguished IgG4-RD from other nonspecific rhinosinusitis, showing T2 high signal intensity. Another distinct feature in patients with IgG4-RD is infraorbital nerve involvement, which showed low sensitivity but high specificity for the diagnosis of IgG4-RD, with a positive predictive value of 80%. Furthermore, none of the patients with lymphoma or DA presented with bilateral involvement of the infraorbital nerve. These results are consistent with those of previous studies [30–32].

Table 3. Interobserver Agreement in Interpreting Radiologic Features

	Reader 1*	Reader 2*	Kappa	95% CI of Kappa
Lacrimal gland				
Wedge sign	65 (71.4)	65 (71.4)	0.785	0.643–0.926
Angle with the orbital wall			0.550	0.315–0.785
Acute angle	13 (14.3)	16 (17.6)		
Right to obtuse angle	78 (85.7)	75 (82.4)		
Heterogeneity of lesions				
CT	14 (19.2)	12 (16.4)	0.813	0.637–0.989
T2WI	12 (27.9)	13 (30.2)	0.606	0.343–0.868
CE-T1WI	3 (7.3)	7 (17.1)	0.554	0.183–0.926
T2 signal intensity			0.734	0.523–0.945
Hypo	16 (37.2)	11 (25.6)		
Iso	27 (62.8)	32 (74.4)		
DCE pattern			0.843	0.551–1.000
Washout	10 (62.5)	11 (68.7)		
Plateau	2 (12.5)	2 (12.5)		
Prolonged	4 (25.0)	3 (18.8)		
Other findings				
Extra-orbital involvement				
Infraorbital nerve	7 (7.8)	15 (16.7)	0.593	0.347–0.839
Paranasal sinus	12 (27.9)	13 (30.2)	0.944	0.835–1.000
Salivary gland	18 (24.7)	26 (35.6)	0.743	0.581–0.906
Lymphadenopathy	13 (28.3)	19 (41.3)	0.718	0.516–0.920
Extra-lacrimal orbital involvement	6 (6.6)	13 (14.3)	0.595	0.332–0.859

*Data are expressed as number of cases with percentage in parentheses. CE = contrast-enhanced, CI = confidence interval, DCE = dynamic contrast-enhanced, WI = weighted image

In our study, none of the advanced MRI features reliably differentiated DA, IgG4-RD, and lymphoma. Several studies have investigated the role of MRI in the differential diagnosis of orbital lymphoma and benign lymphoproliferative disorder [11,12,14-16,33]. Most studies reported a significantly lower mean ADC value for lymphoma compared to the value for benign lesions. In our study, although the mean ADC value of the DA group (1.13) was higher than those of the other groups (0.80–0.88), the difference was not statistically significant. Lymphoma has a lower ADC value due to restricted diffusion from hypercellularity; likewise, IgG4-RD may also show restricted diffusion due to dense lymphoplasmacytic infiltration. Thus, given the overlap of ADC values, their role is limited in the differentiation of DA, IgG4-RD, and lymphoma.

This study has several limitations. Among these limitations were the retrospective study design and recruitment of patients from a single tertiary referral center, which might have introduced a selection bias. A higher proportion of patients in the lymphoma group underwent MRI compared to the proportions in the other groups.

Because patients with lymphoma present with a relatively large mass in the lacrimal fossa at an old age, MRI is frequently performed to assess malignancy. Further large-scale, prospective, and multicenter studies are required to validate our results. In addition, our data may be flawed as some patients received treatments such as nonsteroidal anti-inflammatory drugs and steroids before referral. However, to exclude patients lacking reliable clinical data, we included only patients who underwent surgery and histopathological examination at our institution.

In conclusion, the clinical and radiological features differed among various etiologies (DA, IgG4-RD, and lymphoma) of chronic diffuse lacrimal gland enlargement, including patient age, unilaterality, lacrimal gland size, wedge sign, and extra-orbital head and neck involvement. Our findings suggest the need for biopsy in patients aged > 60 years with unilateral disease and wedge signs on radiologic images, considering the possibility of lacrimal gland lymphoma. In addition, patients with extraorbital head and neck involvement, particularly infraorbital nerve involvement, may have IgG4-RD and should undergo biopsy,

serum IgG4 level measurement, and systemic evaluation. Physicians should be aware of these features for the differential diagnosis and proper management of diffuse lacrimal gland enlargement.

Supplement

The Supplement is available with this article at <https://doi.org/10.3348/kjr.2022.0233>.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

Chong Hyun Suh, Jung Hwan Baek, and Jeong Hyun Lee who is on the editorial board of the *Korean Journal of Radiology* was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

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