

ISSN Print: 2708-2709
ISSN Online: 2708-2717

Journal of Diabetes, Metabolism and Endocrinology
https://jdmeonline.com/

Research Article

Histopathological Spectrum of Lacrimal Gland Lesions: A Retrospective Clinicopathological Study of 68 Cases from a Tertiary-Care Centre

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Article History
Received: 18.09.2026
Accepted: 05.10.2026
Published: 24.10.2026

doi: 10.61336/jdme.0704.16

Abstract: Background: Lacrimal gland lesions span a wide range of epithelial, lymphoproliferative, melanocytic and mesenchymal entities. Because their clinical and radiological features overlap considerably, histopathological examination is required for a definitive diagnosis. The reported distribution of these lesions differs between series, reflecting variation in referral patterns, geography and inclusion criteria. **Aim:** To describe the histopathological spectrum of lacrimal gland lesions and to correlate the histopathological findings with the available clinical, demographic and radiological features. **Materials and Methods:** This retrospective study reviewed lacrimal gland specimens received in the Department of Pathology & Laboratory Medicine, Nizam's Institute of Medical Sciences, Hyderabad, in collaboration with the Department of Ophthalmology, Neelima Institute of Medical Sciences, over a 42-month period (January 2021 to June 2024). Inflammatory lesions and lesions of the lacrimal sac or drainage system without lacrimal gland involvement, were excluded. Clinical, demographic, radiological and histopathological data were analyzed and lesions were grouped as benign epithelial, malignant epithelial, lymphoproliferative, or mesenchymal and melanocytic. **Results:** Sixty-eight cases were included. The mean age was 43.2±16.8 years and 40 patients (58.8%) were female. Benign epithelial tumors formed the largest category (32/68; 47.1%), followed by lymphoproliferative lesions (17/68; 25.0%), mesenchymal and melanocytic tumors (13/68; 19.1%) and malignant epithelial tumors (6/68; 8.8%). Pleomorphic adenoma was the most frequent single diagnosis (18/68; 26.5%), followed by papilloma (7/68; 10.3%) and oncocytoma (5/68; 7.4%). All lymphomas were of B-cell lineage: MALT lymphoma in 9 cases (13.2%) and B-cell non-Hodgkin lymphoma in 8 (11.8%). Soft-tissue tumors accounted for 11 cases (16.2%) and melanoma for 2 (2.9%). Adenoid cystic carcinoma was the commonest malignant epithelial tumor (4/68; 5.9%). Bone destruction on imaging was confined to malignant lesions ($p = 0.001$). **Conclusion:** Benign epithelial tumors, chiefly pleomorphic adenoma, were the dominant group in this series, while lymphoproliferative and mesenchymal lesions together made up a substantial share. Histopathology, supported by immunohistochemistry and radiological correlation, remains central to accurate diagnosis and management.

Keywords: Lacrimal Gland, Pleomorphic Adenoma, Lymphoma, Malt Lymphoma, Adenoid Cystic Carcinoma, Melanoma, Mesenchymal Tumor, Histopathology, Immunohistochemistry

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INTRODUCTION

The lacrimal gland is a specialized exocrine gland situated in the supertemporal orbit and divided by the lateral horn of the levator aponeurosis into orbital and palpebral lobes. It secretes the aqueous component of the tear film and is composed of acinar and ductal epithelial cells, myoepithelial cells, resident lymphoid cells and supporting stroma. This cellular heterogeneity explains the broad range of lesions that can arise within the gland [1,4].

Lacrimal gland pathology includes inflammatory, epithelial, lymphoproliferative, melanocytic and mesenchymal lesions and their relative frequency varies considerably between published series [5-10]. Epithelial tumors form a large proportion of neoplastic lesions, with pleomorphic adenoma being the most common benign entity and adenoid cystic carcinoma the most common malignant one [3,11,16,20]. Lymphoproliferative disorders constitute another important group, particularly in older patients and in those with autoimmune disease [12-15]. The proportions reported by any single center depend heavily on its referral pattern, geographic setting and on whether inflammatory lesions are counted [1,2].

Patients typically present with eyelid swelling, proptosis, ptosis, discomfort or a slowly enlarging supertemporal mass. Pain, rapid growth and bone erosion raise suspicion of malignancy, but none of these features is specific [16,17]. Imaging localizes the lesion and defines its extent, yet tissue diagnosis remains indispensable for definitive classification. Immunohistochemistry (IHC) is especially valuable in lymphoid lesions and in selected epithelial, melanocytic and mesenchymal tumors [12,14,18].

Data on the spectrum of lacrimal gland lesions from Indian tertiary-care centers remain limited [9,19]. The present study was therefore undertaken to describe the histopathological spectrum of lacrimal gland lesions in our setting and to examine their demographic, clinical and radiological characteristics.

Aim and Objectives

Aim: To study the histopathological spectrum of lacrimal gland lesions and to correlate the histopathological findings with the available clinical, demographic and radiological features.

Objectives

- To determine the frequency and distribution of lacrimal gland lesions
- To describe the age and sex distribution of the lesions
- To analyse the clinical presentation and laterality
- To classify the lesions as benign epithelial, malignant epithelial, lymphoproliferative, or mesenchymal and melanocytic
- To evaluate the contribution of special stains and immunohistochemistry were performed
- To correlate histopathological findings with clinical and radiological findings where available

MATERIALS AND METHODS

Study Design and Setting

This retrospective clinicopathological study was conducted on lacrimal gland specimens received in the Department of Pathology & Laboratory Medicine, Nizam's Institute of Medical Sciences, Hyderabad, in collaboration with the Department of Ophthalmology, Neelima Institute of Medical Sciences, over 42 months from January 2021 to June 2024. Sixty-eight cases met the study criteria.

Inclusion Criteria

Patients of any age and either sex with a lacrimal gland lesion who underwent biopsy or surgical excision, whose specimen was adequate for histopathological evaluation and whose clinical and demographic records were sufficient for analysis.

Exclusion Criteria

Inadequate or autolyzed specimens; inflammatory lesions; lesions of the lacrimal sac or drainage system without lacrimal gland involvement; recurrent lesions whose primary histopathology was performed elsewhere; and cases with insufficient clinical records.

Data Collection and Histopathology

Age, sex, laterality, presenting symptoms, duration of symptoms and radiological findings were retrieved from the medical records. Archived slides were reviewed for all cases. Hematoxylin and eosin (H&E) staining was performed on every specimen and special stains, namely periodic acid–Schiff (PAS), Ziehl–Neelsen (ZN) and Grocott Methenamine Silver (GMS), were applied where indicated.

Immunohistochemistry

IHC was performed according to diagnostic need. The core panel comprised pancytokeratin, EMA, CD117, CD20, CD3, CD138, kappa, lambda, IgG and IgG4. Additional markers, including CK7, CK20, p63, CD34, SMA, MSA, S100, Ki-67, Melan-A and HMB-45, were used in selected cases. Lesions were classified according to the WHO Classification of Tumors of the Eye and Orbit.

Statistical Analysis

Data were entered in Microsoft Excel and analyzed with SPSS version 22.0. Descriptive statistics (frequencies, percentages, means and standard deviations) were calculated. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate and a p-value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Profile

Sixty-eight lacrimal gland lesions were analyzed. The mean age at presentation was 43.2±16.8 years (range, 8–78 years). Forty patients (58.8%) were female and 28 (41.2%) were male, a male-to-female ratio of 1:1.4. The right gland was involved in 32 cases (47.1%), the left in 30 (44.1%) and both glands in 6 (8.8%).

Eyelid swelling was the commonest presenting symptom (34/68; 50.0%), followed by proptosis (28/68; 41.2%), pain or tenderness (21/68; 30.9%), ptosis (18/68; 26.5%) and diplopia (9/68; 13.2%) (Table 3). The mean duration of symptoms was 8.5±6.2 months. Pain or tenderness was significantly more frequent in malignant lesions ($p = 0.032$).

Histopathological Spectrum

The distribution of lesions is shown in Table 1. Benign epithelial tumors formed the largest category (32 cases; 47.1%). Pleomorphic adenoma was the most common single diagnosis (18 cases; 26.5%), followed by papilloma (7; 10.3%), oncocytoma (5; 7.4%) and cylindroma (2; 2.9%). Lymphoproliferative lesions accounted for 17 cases (25.0%); all were B-cell lymphomas, comprising 9 MALT lymphomas and 8 B-cell non-Hodgkin lymphomas. Mesenchymal and melanocytic tumors accounted for 13 cases (19.1%), including 11 soft-tissue tumors and 2 melanomas. Malignant epithelial tumors made up 6 cases (8.8%): 4 adenoid cystic carcinomas and 2 adenocarcinomas.

Age and Sex by Category

Lymphoproliferative lesions occurred at a higher mean age than benign epithelial lesions and showed the most marked female predominance. Malignant epithelial tumors were more frequent in males (Table 2).

Special Stains and Immunohistochemistry

IHC was performed in all 17 lymphomas and in selected epithelial, melanocytic and mesenchymal tumors. In the lymphomas, CD20, CD3, kappa and lambda confirmed B-cell lineage and light-chain restriction. Pancytokeratin, EMA, CD117, CK7, CK20 and p63 were applied to selected epithelial tumors and SMA, MSA, S100, CD34, Ki-67, Melan-A and HMB-45 to selected mesenchymal and melanocytic tumors. Special stains (PAS, ZN and GMS) were performed in 12 cases (17.6%) and no fungal or mycobacterial organisms were identified.

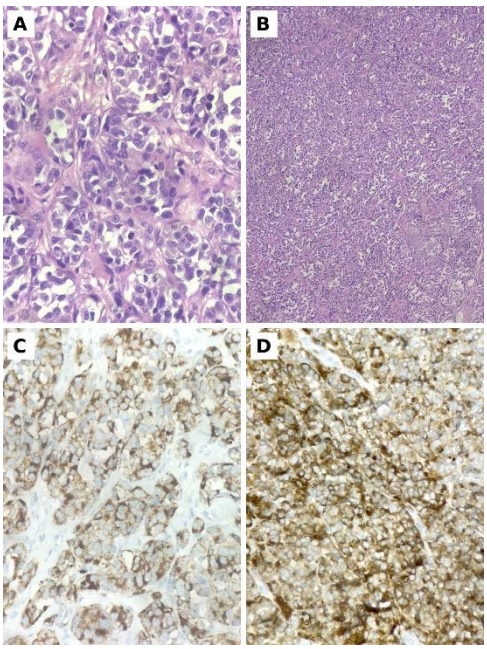


Figure 1: Melanoma of the Lacrimal Gland. (A) Large Polyhedral Tumor Cells with Pale to Eosinophilic Cytoplasm, Vesicular Nuclei and Prominent Nucleoli, Arranged in Pseudo-Alveolar Organoid Nests (H&E, 40×). (B) Low-Power View Showing a Diffusely Cellular Tumor Composed of Nests and Sheets (H&E, 10×). (C) Diffuse Cytoplasmic Immunopositivity for HMB-45 (IHC). (D) Diffuse Cytoplasmic Immunopositivity for Melan-A (IHC)

Table 1: Histopathological Classification of Lacrimal Gland Lesions (n = 68)

Category	Diagnosis	No. of cases	%
Benign epithelial	Pleomorphic adenoma	18	26.5
	Papilloma	7	10.3
	Oncocytoma	5	7.4
	Cylindroma	2	2.9
	Subtotal	32	47.1
Lymphoproliferative	MALT lymphoma	9	13.2
	B-cell non-Hodgkin lymphoma	8	11.8
	Subtotal	17	25.0
Mesenchymal and melanocytic	Soft-tissue tumors	11	16.2
	Melanoma	2	2.9
	Subtotal	13	19.1
Malignant epithelial	Adenoid cystic carcinoma	4	5.9
	Adenocarcinoma	2	2.9
	Subtotal	6	8.8
Total		68	100.0

Representative Morphology – Melanoma

Melanoma of the lacrimal gland showed large polyhedral tumor cells with pale to eosinophilic cytoplasm, large open (vesicular) nuclei and prominent nucleoli, arranged in pseudo-alveolar, organoid nests and clusters (Figure 1A, B). The tumor cells showed diffuse cytoplasmic positivity for HMB-45 and Melan-A, confirming melanocytic differentiation (Figure 1C, D).

Representative Morphology – Adenoid Cystic Carcinoma

Adenoid cystic carcinoma showed a predominantly cribriform architecture, with basaloid tumor cells surrounding pseudo cystic spaces filled with hyalinized, eosinophilic basement-membrane-like material (Figure 2A–D). On IHC, p63 highlighted the abluminal myoepithelial cell population, CD117 was expressed by the luminal ductal cells and Ki-67 showed scattered nuclear positivity (Figure 3A–C).

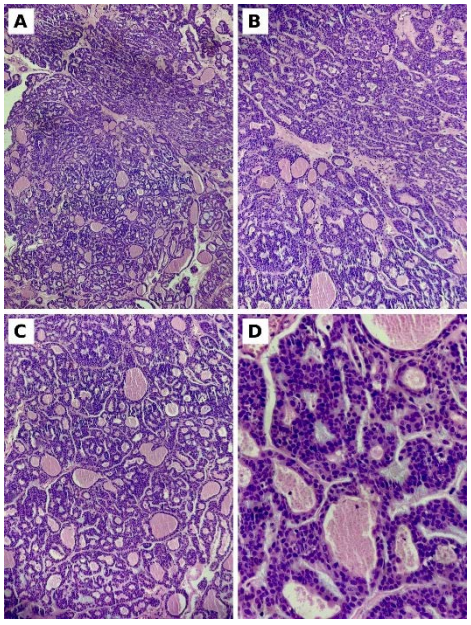


Figure 2: Adenoid Cystic Carcinoma of the Lacrimal Gland (H&E). (A) Cribriform Pattern with Hyalinized Globules (5×). (B, C) Cribriform Nests of Basaloid Cells with Numerous Punched-Out Pseudocysts Containing Eosinophilic Hyaline Material (10×). (D) Higher Magnification Showing Small, Uniform Basaloid Cells with Hyperchromatic Nuclei Around Hyaline-Filled Pseudocystic Spaces (40×)

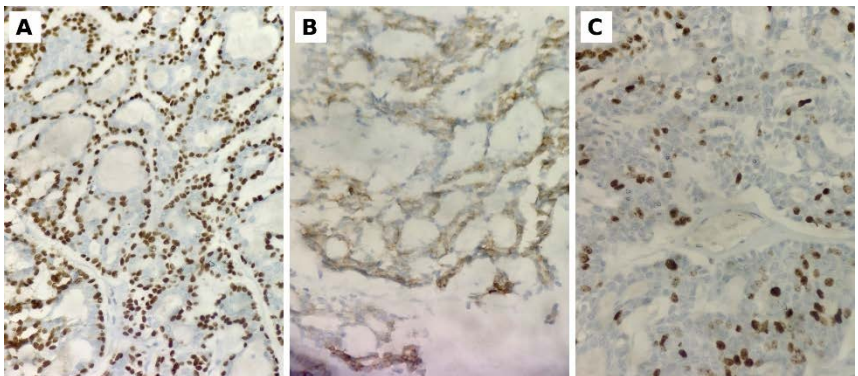


Figure 3: Immunohistochemistry in Adenoid Cystic Carcinoma. (A) p63 Showing Nuclear Staining of the Myoepithelial Cells Surrounding the Pseudocysts. (B) CD117 Showing Membranous and Cytoplasmic Staining of the Luminal Ductal Cells. (C) Ki-67 Showing Scattered Nuclear Positivity in Tumor Cells

Table 2: Age and Sex Distribution by Major Lesion Category

Lesion category	Mean age (years)	Male: Female	Female (%)
Benign epithelial (n = 32)	35.0±13.8	13: 19	59.4
Lymphoproliferative (n = 17)	52.3±14.6	5: 12	70.6
Mesenchymal and melanocytic (n = 13)	47.0±17.1	7: 6	46.2
Malignant epithelial (n = 6)	48.5±18.3	4: 2	33.3

Table 3: Clinical Presentation and Laterality (n = 68)

Parameter	No. of cases	%
Eyelid swelling	34	50.0
Proptosis	28	41.2
Pain/tenderness	21	30.9
Ptosis	18	26.5
Diplopia	9	13.2
Right-sided lesion	32	47.1
Left-sided lesion	30	44.1
Bilateral lesion	6	8.8

Table 4: Radiological Findings and Radiological–Histopathological Concordance (n = 52)

Radiological finding	No. of cases	%
Lacrimal gland enlargement	46	88.5
Orbital infiltration	12	23.1
Bone destruction	5	9.6
Concordance measure	Result	%
Overall concordance	34/52	65.4
Epithelial tumors	13/16	81.3
Mesenchymal/other evaluated lesions	8/17	47.1

Table 5: Associated Systemic Diseases (n = 68)

Systemic disease	No. of cases	% of total
Sjögren syndrome	6	8.8
Systemic lupus erythematosus	3	4.4
Rheumatoid arthritis	2	2.9
Total	11	16.2

Clinical Presentation

Clinical presentation and laterality are summarized in Table 3.

Radiological Correlation

Imaging was available in 52 cases (76.5%): CT in 45 and MRI in 18, with some patients undergoing both. Lacrimal gland enlargement was the commonest finding (46/52; 88.5%), followed by infiltration of adjacent orbital structures (12/52; 23.1%) and bone destruction (5/52; 9.6%). Bone destruction was seen only in malignant lesions ($p = 0.001$). Overall radiological–histopathological concordance was 65.4% (34/52); concordance was 81.3% (13/16) for epithelial tumors and 47.1% (8/17) for mesenchymal and other evaluated lesions (Table 4).

Associated Systemic Disease

Eleven patients (16.2%) had an associated systemic disease: Sjögren syndrome in 6, systemic lupus erythematosus in 3 and rheumatoid arthritis in 2 (Table 5).

DISCUSSION

This study describes 68 lacrimal gland lesions seen over 42 months at a tertiary-care center. Benign epithelial tumors were the largest group (47.1%), followed by lymphoproliferative lesions (25.0%), mesenchymal and melanocytic tumors (19.1%) and malignant epithelial tumors (8.8%). Because inflammatory lesions were excluded, these figures

describe the distribution among non-inflammatory lesions only and cannot be compared directly with series that include inflammatory disease in the denominator [1,2,4].

Pleomorphic adenoma was the commonest single lesion (18 cases; 26.5%), accounting for 56.3% of benign epithelial tumors. It characteristically presents as a slowly enlarging, painless mass and complete excision with an intact capsule is essential, since capsular breach or incomplete removal increases the risk of recurrence and, rarely, malignant transformation [14,20]. Cystic and morphologically unusual variants have also been described and may cause diagnostic difficulty [9,14].

Lymphoproliferative lesions made up one-quarter of the series. All were of B-cell lineage, with MALT lymphoma the most frequent subtype, consistent with the recognized predominance of extranodal marginal zone lymphoma among ocular adnexal and lacrimal gland lymphomas [12]. The occurrence of Sjögren syndrome and other autoimmune disorders in a subset of our patients is clinically relevant, as chronic autoimmune antigenic stimulation is associated with an increased risk of B-cell lymphoma [15]. IgG4-related disease is an important differential diagnosis of lymphoid-rich lacrimal gland enlargement, which is why IgG and IgG4 were included in our IHC panel [8,11].

Mesenchymal and melanocytic tumors accounted for 19.1% of cases. The two melanomas in this series showed classical epithelioid morphology, with nested, organoid growth of large cells with prominent nucleoli and were confirmed by diffuse HMB-45 and Melan-A positivity (Figure 1). Because melanoma, soft-tissue tumors and poorly differentiated carcinoma can overlap morphologically in the orbit, a targeted IHC panel is essential for correct classification. Primary melanoma of the lacrimal gland is exceptional, so clinical and ophthalmic evaluation to exclude metastasis or extension from a cutaneous, conjunctival or uveal primary is advisable in such cases.

Malignant epithelial tumors constituted 8.8% of the series, with adenoid cystic carcinoma (ACC) the most frequent, in keeping with its status as the commonest primary malignant epithelial tumor of the lacrimal gland [6,16]. Our cases showed the characteristic cribriform architecture with hyalinized, basement-membrane-like globules (Figure 2). The biphasic nature of the tumor was demonstrated by p63-positive abluminal myoepithelial cells and CD117-positive luminal ductal cells, while Ki-67 provided an estimate of proliferative activity (Figure 3). ACC is clinically important because of its infiltrative growth, propensity for perineural invasion and high risk of local recurrence and distant metastasis [13,17]. Molecular studies have shown frequent MYB rearrangement and a close morphological and genetic relationship with salivary gland ACC [5,10,18]. Careful histopathological assessment, supported by IHC and imaging, is therefore crucial for planning management.

Overall radiological–histopathological concordance was 65.4% and was higher for epithelial tumors than for the other categories evaluated. This underlines the complementary roles of imaging and histopathology: imaging localizes the lesion and defines its extent, whereas tissue examination establishes the diagnosis. The finding that bone destruction occurred only in malignant lesions supports its value as a radiological warning sign [16].

Overall, females predominated, most strikingly among lymphoproliferative lesions. These demographic patterns should be interpreted cautiously in view of the modest sample size and the referral characteristics of a tertiary-care institution.

Limitations

- The retrospective design may introduce selection and information bias
- The sample size was relatively small, particularly for malignant epithelial tumors, which limited subgroup statistical analysis
- The study was conducted at a single tertiary-care center, which limits generalizability
- Follow-up data were incomplete in some cases, precluding assessment of recurrence and survival
- Immunohistochemical panels were selected according to diagnostic need and were not uniform across cases
- Inflammatory lesions were excluded, which limits direct comparison with series that include inflammatory pathology
- Radiological investigations and reporting were not fully standardized

CONCLUSION

This retrospective study of 68 lacrimal gland lesions demonstrates a broad histopathological spectrum, in which benign epithelial tumors were the largest category, followed by lymphoproliferative and mesenchymal and melanocytic lesions. Pleomorphic adenoma was the most common individual diagnosis, MALT lymphoma the predominant lymphoproliferative subtype and adenoid cystic carcinoma the most frequent malignant epithelial tumor. Accurate diagnosis and appropriate management depend on integrating clinical assessment, imaging, histopathology and immunohistochemistry. Larger multicenter studies with standardized clinical, radiological and pathological data are needed to define the epidemiology and clinicopathological profile of lacrimal gland lesions in the Indian population more clearly.

Acknowledgement
The authors thank the Departments of Pathology & Laboratory Medicine and Ophthalmology at Nizam's Institute of Medical Sciences and Neelima Institute of Medical Sciences for their support and the technical staff of the histopathology laboratory and the medical records department for their assistance.

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