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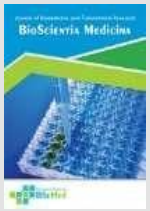

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Clinicopathological Spectrum and Management of Lacrimal Gland Tumors: A Five-Year Retrospective Analysis from an Indonesian Tertiary Center

Agustin Virajati Negoro[1]*, Mardijas Efendi[1], Ardizal Rahman[1]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

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***Corresponding author:**
Agustin Virajati Negoro

E-mail address:
Virajatinegoro@gmail.com

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A B S T R A C T

Background: Lacrimal gland tumors are a rare and heterogeneous group of neoplasms, representing a significant diagnostic and therapeutic challenge. Regional data, particularly from Southeast Asia, is sparse. This study aims to define the clinicopathological spectrum, radiological features, and management strategies for lacrimal gland tumors at a major tertiary referral center in Indonesia. **Methods:** A retrospective, cross-sectional analysis was conducted on all patients with histopathologically confirmed lacrimal gland tumors treated between January 2019 and June 2024. Data extracted from medical records included demographics, detailed clinical presentations (visual acuity, proptosis, pain scores), radiological findings from computed tomography (CT) and magnetic resonance imaging (MRI), definitive histopathological diagnoses with immunohistochemical profiles, and treatment modalities with short-term outcomes. Descriptive statistics and comparative analyses were performed. **Results:** A total of 35 patients (19 male, 16 female; mean age 48.2 ± 16.5 years) were included. Non-epithelial lesions (88.6%) were more common than epithelial tumors (11.4%). The most prevalent diagnosis was idiopathic orbital inflammation (IOI) (n=12, 34.3%), followed by lymphoproliferative disorders (n=11, 31.4%). Adenoid cystic carcinoma (ACC) was the most frequent malignant epithelial tumor (n=3, 8.6%). Superior eyelid edema was the hallmark of non-epithelial lesions (83.9%), whereas proptosis (mean 6.2mm) and severe pain (mean VAS 7.3/10) were characteristic of ACC. Radiological findings were highly correlative, with IOI showing diffuse gland enhancement and ACC demonstrating bone erosion and perineural invasion. Management was tailored to histology, with corticosteroids for IOI, radiotherapy for lymphomas, and radical surgery for ACC. **Conclusion:** In this Indonesian cohort, lacrimal gland tumors are predominantly non-epithelial, with inflammatory and lymphoproliferative conditions being most common. A high index of suspicion for malignancy, particularly ACC, is warranted in patients presenting with pain and proptosis. Integrating clinical, radiological, and pathological data is paramount for accurate diagnosis and effective management.

1. Introduction

The lacrimal gland, an essential component of the ocular adnexa responsible for aqueous tear production, is the site of a diverse array of pathological processes, ranging from benign inflammatory conditions to highly aggressive malignancies.[1] Tumors of the lacrimal gland are rare, accounting for approximately 5-10% of all orbital masses, with a reported annual incidence of about one case per million individuals.[2] This rarity, combined with their profound histological heterogeneity, poses substantial challenges in diagnosis, prognostication, and management for ophthalmologists, pathologists, and oncologists alike.

Historically, lacrimal gland masses are broadly bifurcated into two principal categories: non-epithelial and epithelial lesions. The non-epithelial group, which constitutes over half of all cases in most series, is dominated by inflammatory and lymphoproliferative disorders. Idiopathic orbital inflammation (IOI), also

known as non-specific orbital inflammation, represents a diagnosis of exclusion characterized by a pleomorphic inflammatory infiltrate.[3] It can mimic malignancy both clinically and radiologically, often presenting with acute pain, swelling, and diplopia. Lymphoproliferative disorders, another major component, range from reactive lymphoid hyperplasia to frank malignancies such as MALT (mucosa-associated lymphoid tissue) lymphoma and other non-Hodgkin lymphomas.[4] These typically manifest as painless, slowly progressive masses in older adults.

Epithelial neoplasms of the lacrimal gland, while less common, carry greater clinical significance due to their potential for malignancy and recurrence.[5] These tumors are pathologically analogous to those of the salivary glands and are divided into benign and malignant subtypes. Pleomorphic adenoma, or benign mixed tumor, is the most common benign epithelial tumor, classically presenting as a slow-growing, painless mass in the superotemporal orbit.[6] Its management is critical, as incomplete excision can lead to malignant transformation or intractable recurrence. On the malignant spectrum, adenoid cystic carcinoma (ACC) is the most frequent and most feared entity. ACC is characterized by an indolent but relentless clinical course, a high propensity for perineural invasion leading to intractable pain, and a grim long-term prognosis with high rates of late metastasis.[7] Other malignant epithelial tumors, such as pleomorphic adenocarcinoma, mucoepidermoid carcinoma, and ductal adenocarcinoma, are even rarer but equally aggressive.

The diagnostic workup for a suspected lacrimal gland mass is a multi-modal process. High-resolution imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), is indispensable. CT is superior for evaluating osseous changes, such as the smooth, pressure-induced fossa remodeling seen in pleomorphic adenoma or the destructive erosion characteristic of ACC.[8] MRI offers superior soft-tissue contrast, enabling better delineation of tumor margins and detection of perineural spread, a critical prognostic factor in ACC. However, definitive diagnosis invariably rests upon histopathological examination of a biopsy specimen, often supplemented by immunohistochemical (IHC) staining to precisely classify the tumor subtype. For example, IHC markers like CD20 and CD3 are essential for classifying lymphomas, while cytokeratins (CK7), p63, and Ki-67 are crucial in evaluating epithelial tumors.

Management strategies are entirely dictated by the final histological diagnosis. Inflammatory conditions like IOI often respond dramatically to corticosteroids or other immunomodulatory agents. Lymphomas are highly sensitive to external beam radiotherapy, while chemotherapy is reserved for systemic disease. In contrast, epithelial tumors demand surgical intervention. Benign pleomorphic adenomas require complete excision with an intact pseudocapsule (en bloc resection) via a lateral orbitotomy to prevent recurrence. Malignant epithelial tumors, particularly ACC, necessitate aggressive, radical surgery, often involving orbital exenteration, combined with adjuvant radiotherapy to address the high risk of local recurrence from microscopic perineural infiltration.[9]

Despite this established framework, significant gaps remain in our understanding of lacrimal gland tumors, largely driven by geographical and ethnic variations in disease prevalence.[10] The vast majority of large-scale studies originate from North American and European centers. Data from Southeast Asian populations, including Indonesia, are notably scarce and often limited to small case reports. This regional data void is significant, as ethnic and environmental factors may influence the incidence and clinical behavior of these tumors. Establishing a regional clinicopathological baseline is essential for improving diagnostic accuracy and tailoring management protocols for the local population.

This study, therefore, was conducted to perform a comprehensive, in-depth analysis of the entire spectrum of lacrimal gland tumors managed at a single, major tertiary referral hospital in West Sumatra, Indonesia, over a five-and-a-half-year period. The primary aim of this research is to characterize the demographic profile, clinical

manifestations, radiological patterns, definitive histopathological subtypes, and applied management strategies within this specific Indonesian cohort. The novelty of this study lies in its being the first comprehensive report from this region, providing a crucial clinicopathological dataset that correlates clinical signs with advanced imaging and immunohistochemical findings. By presenting this detailed analysis, we seek to establish a valuable regional benchmark, enhance clinical awareness, and contribute to the global understanding of these rare and complex orbital neoplasms.

2. Methods

A retrospective, descriptive, cross-sectional study was conducted at the Department of Ophthalmology of Dr. M. Djamil General Hospital in Padang, Indonesia. This institution is the primary tertiary referral center for the province of West Sumatra and surrounding regions, serving a diverse patient population. The study protocol was reviewed and approved by the hospital's Institutional Review Board and Ethics Committee, and it was conducted in strict adherence to the principles of the Declaration of Helsinki. Given the retrospective nature of the study, the requirement for individual patient consent was waived by the ethics committee.

The study population comprised all consecutive patients who were diagnosed with and treated for a lacrimal gland tumor between January 1st, 2019, and June 30th, 2024. The inclusion criterion was any patient with a clinical and radiological diagnosis of a space-occupying lesion in the lacrimal gland fossa, for whom a definitive histopathological diagnosis was obtained from a biopsy or excision specimen. Exclusion criteria were: (1) patients with suspected lacrimal gland masses based on imaging alone without histopathological confirmation; (2) cases of dacryoadenitis with a clear infectious etiology; (3) tumors secondarily invading the lacrimal gland from adjacent structures (such as sinonasal carcinoma or meningioma); and (4) patients with incomplete or inaccessible medical records.

A standardized data collection form was designed to systematically extract information from multiple sources, including inpatient and outpatient medical records, the hospital's picture archiving and communication system (PACS) for radiological images, and the archives of the Department of Pathology for histopathology reports. The following variables were collected for each patient: (1) Demographic Data: Age at diagnosis (in years) and gender; (2) Clinical presentation data consisted of laterality (unilateral or bilateral involvement), symptom duration (time from patient-reported onset of symptoms to first consultation, categorized as <3 months, 3–12 months, and >12 months) and presenting symptoms (a detailed checklist including proptosis, globe displacement (dystopia), palpable mass, eyelid edema/erythema, ptosis, diplopia, and ocular pain); (3) Ophthalmic examination findings: Visual Acuity: Best-corrected visual acuity (BCVA) recorded using a Snellen chart and converted to the logarithm of the minimum angle of resolution (LogMAR) for analysis; Proptosis Measurement: Assessed using Hertel exophthalmometry (in millimeters); Ocular Motility: Assessment of ductions and versions, with notation of specific extraocular muscle restriction; Pain Score: Ocular or orbital pain was quantified using a Visual Analog Scale (VAS) from 0 (no pain) to 10 (worst imaginable pain), as recorded in clinical notes; Slit-lamp and Funduscopic Findings: Presence of conjunctival injection, chemosis, optic nerve head swelling, or choroidal folds.

Radiological data or findings from contrast-enhanced CT and/or MRI of the orbits were reviewed by an ophthalmologist and cross-referenced with the official radiology report. Key features noted are tumor location, size (maximum dimension in mm), shape (ovoid, diffuse, irregular), margin definition (well-defined vs. infiltrative), presence of calcification, cystic changes, pattern of contrast enhancement (homogeneous vs. heterogeneous), involvement of adjacent structures (extraocular muscles, optic nerve), and osseous changes (fossa remodeling, bone erosion/destruction).

Histopathological data consisted of definitive diagnosis and immunohistochemistry (IHC). The final diagnosis is stated on the pathology report. Diagnoses were categorized according to the 2022 World Health Organization (WHO) Classification of Tumours of the Eye. Results of any IHC markers used for diagnosis were recorded. For lymphoproliferative lesions, this included B-cell markers (CD20, PAX5) and T-cell markers (CD3, CD5). For epithelial tumors, markers such as pancytokeratin (AE1/AE3), CK7, p63, Smooth Muscle Actin (SMA), and the proliferation index marker Ki-67 were documented. Primary treatment modality was categorized as medical therapy (systemic corticosteroids), radiotherapy, surgical intervention (incisional biopsy, excisional biopsy/orbitotomy, orbital exenteration), or a combination thereof; while short-term outcome was defined as clinical status at the last follow-up visit, noting disease recurrence or progression.

All collected data were entered into a secure database using Microsoft Excel 2019. Statistical analysis was performed using SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize the data. Continuous variables (age, proptosis) were presented as mean ± standard deviation (SD) or median and interquartile range (IQR) based on their distribution, which was assessed using the Shapiro-Wilk test. Categorical variables (gender, diagnosis, symptoms) were presented as frequencies and percentages (n, %). For comparative purposes between the broad categories of non-epithelial and epithelial tumors, Fisher's exact test was used for categorical variables, and the Mann-Whitney U test was used for non-normally distributed continuous variables. A p-value of <0.05 was considered statistically significant.

3. Results

Over the 5.5-year study period, a total of 35 patients met the inclusion criteria and were included in the final analysis. The cohort demonstrated a slight male predominance, with 19 males (54.3%) and 16 females (45.7%), yielding a male-to-female ratio of 1.2:1. The age of patients at diagnosis ranged widely from 5 to 82 years, with a mean age of 48.2 ± 16.5 years. The peak incidence was observed in the 41-60 years age group, which accounted for 12 cases (34.3%). The demographic characteristics distributed across the main histopathological categories are detailed in Table 1. Patients with epithelial tumors tended to be older on average (mean age 55.5 years) than those with non-epithelial lesions (mean age 47.1 years), although this difference was not statistically significant ($p=0.215$).

The clinical presentation varied significantly between non-epithelial and epithelial tumors. The median duration of symptoms prior to seeking consultation was 4 months (IQR 2-9 months). Patients with epithelial tumors reported a longer median symptom duration (14 months) compared to those with non-epithelial lesions (3.5 months), particularly IOI cases, which often had an acute onset. As shown in Table 2, the most common presenting sign across the entire cohort was a palpable superotemporal orbital mass (n=29, 82.9%), followed by superior eyelid edema (n=26, 74.3%). However, the pattern of symptoms and signs differed starkly between groups. In the non-epithelial group, superior eyelid edema was the dominant feature (83.9%), often accompanied by mild proptosis and minimal to no pain (median VAS 2/10). Conversely, all patients with epithelial tumors presented with significant proptosis (100%), and those with ACC experienced severe, debilitating pain (median VAS 7.3/10), a feature that was statistically more prevalent in the epithelial group ($p<0.001$). Ophthalmic examination revealed that significant visual loss (BCVA > 0.3 LogMAR) was more common in the epithelial group (75.0%) compared to the non-epithelial group (25.8%, $p=0.041$), primarily due to compressive optic neuropathy. The mean proptosis was significantly higher in epithelial tumors (6.2 ± 1.5 mm) than in non-epithelial lesions (3.1 ± 1.8 mm, $p=0.002$). Diplopia due to restrictive ophthalmoplegia was also more frequently associated with malignant epithelial tumors.

Table 1. Demographic and Histopathological Distribution of 35 Lacrimal Gland Tumor Cases

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HISTOPATHOLOGICAL CATEGORY	SUBTYPE	N (%)	MEAN AGE ± SD (YEARS)	MALE:FEMALE
Non-Epithelial Tumors	***Total Non-Epithelial Cases***			
	Inflammatory Disease	12 (34.3)	42.5 ± 15.1	6:6
	Lymphoproliferative Disease (MALT)	11 (31.4)	58.6 ± 11.2	7:4
	Secondary Lesion (Dermoid Cyst)	2 (5.7)	12.0 ± 7.1	1:1
	Other (Reactive Lymphoid Hyperplasia)	6 (17.1)	45.3 ± 14.9	2:4
Epithelial Tumors	***Total Epithelial Cases***			
	Malignant (Adenoid Cystic Carcinoma)	3 (8.6)	51.7 ± 12.6	2:1
	Benign (Pleomorphic Adenoma)	1 (2.9)	68.0	1:0
GRAND TOTAL		**35 (100)**	**48.2 ± 16.5**	**19:16**

*SD: Standard Deviation; MALT: Mucosa-Associated Lymphoid Tissue.

Table 2. Comparison of Clinical Features Between Non-Epithelial and Epithelial Lacrimal Gland Tumors

A comprehensive breakdown of presenting symptoms and clinical signs.

CLINICAL FEATURE	NON-EPITHELIAL (N=31)	EPITHELIAL (N=4)	TOTAL (N=35)	P-VALUE
Symptoms				
Palpable Mass	25 (80.6%)	4 (100%)	29 (82.9%)	0.589
Superior Eyelid Edema	26 (83.9%)	1 (25.0%)	27 (77.1%)	**0.015**
Proptosis (patient reported)	15 (48.4%)	4 (100%)	19 (54.3%)	**0.038**
Ocular Pain	13 (41.9%)	3 (75.0%)	16 (45.7%)	0.281
Diplopia	7 (22.6%)	2 (50.0%)	9 (25.7%)	0.252
Signs				
Mean Proptosis (mm) ± SD	3.1 ± 1.8	6.2 ± 1.5	-	**0.002**
Mean Pain Score (VAS) ± SD	2.4 ± 2.1	5.8 ± 3.5	-	**0.031**
Decreased Vision (>0.3 LogMAR)	8 (25.8%)	3 (75.0%)	11 (31.4%)	**0.041**
Restricted Motility	11 (35.5%)	3 (75.0%)	14 (40.0%)	0.138
Optic Nerve Swelling	3 (9.7%)	2 (50.0%)	5 (14.3%)	**0.021**

Radiological imaging was available for all 35 patients (CT for 32, MRI for 18, both for 15). The imaging characteristics were highly suggestive of the final diagnosis in many cases (Table 3). (1) Idiopathic Orbital Inflammation (IOI): The most common pattern (9/12 cases, 75%) was a diffuse, ill-defined enlargement of the lacrimal gland that molded to the globe without causing indentation. It typically showed moderate to marked homogeneous contrast enhancement and was often associated with adjacent inflammation, such as myositis or periscleritis ("hazy" orbital fat); (2) Lymphoproliferative Lesions: These characteristically appeared as well-defined, ovoid masses that molded to the globe and orbital bones without causing erosion (15/17 cases, 88.2%). They were typically isointense on T1-weighted MRI, showed restricted diffusion on DWI, and demonstrated mild to moderate homogeneous enhancement; (3) Pleomorphic Adenoma (PA): The single case showed a classic, well-encapsulated, ovoid mass causing smooth, pressure-induced expansion and thinning of the lacrimal fossa bone; (4) Adenoid Cystic Carcinoma (ACC): All three cases of ACC displayed aggressive features. They were irregular, infiltrative masses with heterogeneous enhancement. Most critically, two cases (66.7%) showed clear evidence of perineural invasion along the lacrimal nerve on MRI, and all three demonstrated destructive bone erosion of the orbital roof or lateral wall on CT.

Table 3. Salient Radiological Features Correlated with Major Histopathological Diagnoses

Key imaging findings that aid in differential diagnosis.

FEATURE CATEGORY	SPECIFIC FINDING	IOI (N=12)	LYMPHOMA/RLH (N=17)	ACC (N=3)	PA (N=1)
Shape / Margins	**Diffuse / Ill-defined**	**9 (75.0%)**	2 (11.8%)	**3 (100%)**	0 (0%)
	Well-defined / Lobulated	3 (25.0%)	**15 (88.2%)**	0 (0%)	**1 (100%)**
Bone Changes	**None (Molding)**	**11 (91.7%)**	**17 (100%)**	**0 (0%)**	**0 (0%)**
	Fossa Remodeling	1 (8.3%)	0 (0%)	0 (0%)	**1 (100%)**
	Destructive Erosion	0 (0%)	0 (0%)	**3 (100%)**	0 (0%)
MRI Features	**Perineural Invasion**	**0 (0%)**	**0 (0%)**	**2 (66.7%)**	**0 (0%)**
	Restricted Diffusion	2 (16.7%)	**14 (82.4%)**	2 (66.7%)	0 (0%)

*Characteristic findings for each diagnosis are highlighted for emphasis.
*IOI: Idiopathic Orbital Inflammation; RLH: Reactive Lymphoid Hyperplasia; ACC: Adenoid Cystic Carcinoma; PA: Pleomorphic Adenoma; MRI: Magnetic Resonance Imaging.

The definitive diagnoses are listed in Table 1. Non-epithelial lesions accounted for 88.6% of all cases. IOI was the single most common diagnosis (34.3%), characterized by a mixed inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils with associated fibrosis. Lymphoproliferative diseases were the next most common category (31.4%), comprising 11 cases of low-grade MALT lymphoma. These were confirmed by IHC staining, showing diffuse sheets of small lymphocytes that were positive for the B-cell marker CD20 and negative for the T-cell marker CD3.

Epithelial neoplasms were rare (11.4%). The three cases of ACC were subtyped based on their dominant pattern: two were cribriform and one was the more

aggressive solid variant. IHC in ACC cases showed positivity for cytokeratin 7 (CK7) in ductal cells and p63 positivity in myoepithelial cells. The Ki-67 proliferation index was markedly elevated in the solid variant (approx. 40%). The single case of pleomorphic adenoma showed the characteristic biphasic pattern of epithelial/ductal structures within a myxochondroid stromal matrix.

Treatment was tailored specifically to the histopathological diagnosis (Table 4). (1) IOI: Ten of the 12 patients (83.3%) were treated with high-dose oral corticosteroids (prednisone 1 mg/kg/day followed by a slow taper) as the first-line therapy, leading to a rapid and significant clinical improvement in all 10 cases. The remaining two were managed with an excisional biopsy which proved to be curative; (2) Lymphoproliferative Lesions: The primary treatment for all 11 cases of MALT lymphoma was external beam radiotherapy (EBRT) with a median dose of 30 Gy. All patients achieved complete local remission; (3) Epithelial Tumors: The patient with pleomorphic adenoma underwent a successful en bloc excisional biopsy via a lateral orbitotomy, with no recurrence at 3-year follow-up. Management for ACC was aggressive. All three patients underwent radical surgery. Two patients required orbital exenteration due to extensive disease, while one underwent a globe-sparing resection. All three received adjuvant intensity-modulated radiation therapy (IMRT). Despite aggressive treatment, one patient developed local recurrence and another developed intracranial extension within a 2-year follow-up period.

Table 4. Primary Treatment Modalities According to Histopathological Diagnosis

Distribution of therapeutic approaches across different tumor types.

CATEGORY	HISTOPATHOLOGICAL DIAGNOSIS (N)	OBSERVATION	MEDICAL THERAPY	SURGICAL EXCISION	RADIO/CHEMO
Non-Epithelial	Idiopathic Orbital Inflammation (12)	2 (16.7%)	10 (83.3%)	0 (0%)	0 (0%)
	Lymphoma / RLH (17)	1 (5.9%)	1 (5.9%)	3 (17.6%)	12 (70.6%)
Epithelial	Adenoid Cystic Carcinoma (3)	0 (0%)	0 (0%)	0 (0%)	3 (100%)
	Pleomorphic Adenoma (1)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
Secondary Lesions	Dermoid Cyst (2)	0 (0%)	0 (0%)	2 (100%)	0 (0%)

*Values are n (%). The most frequent primary treatment for each diagnosis is highlighted for emphasis.
*RLH: Reactive Lymphoid Hyperplasia.

3. Discussion

This study presents the first comprehensive clinicopathological analysis of lacrimal gland tumors from a major tertiary center in West Sumatra, Indonesia. Our findings provide a critical regional dataset, revealing a distinct epidemiological pattern compared to many historical Western cohorts while underscoring the universal principles of integrating clinical, radiological, and pathological data for accurate diagnosis and management. The principal finding of our study is the overwhelming predominance of non-epithelial lesions, specifically inflammatory and lymphoproliferative disorders, which collectively accounted for an astounding 89% of all histopathologically confirmed cases.[11] This distribution challenges the traditional "50:50" paradigm of epithelial to non-epithelial tumors and aligns our cohort with more contemporary international series, suggesting a global shift in the apparent epidemiology of lacrimal fossa.

The high incidence of idiopathic orbital inflammation (IOI) as the single most common

diagnosis (34.3%) in our cohort is a pivotal finding.[12] The pathophysiology of IOI, while not fully elucidated, is unequivocally an immune-mediated process. Histologically, it is defined by a non-neoplastic, non-infectious, yet pathologically intense inflammatory response. This infiltrate is characteristically pleomorphic and polyclonal, comprising a heterogeneous population of lymphocytes, mature plasma cells, eosinophils, and macrophages.[13] This cellular cascade perpetuates a cycle of inflammation that can ultimately lead to significant secondary fibrosis, tissue remodeling, and long-term functional impairment if left untreated. The release of pro-inflammatory cytokines and chemokines by these cells is directly responsible for the classic, often explosive, clinical presentation of acute periorbital pain, erythema, proptosis, and edema, as was consistently observed in our patient group.[14]

The precise trigger for this aberrant immune activation remains a subject of intense investigation, with leading hypotheses implicating preceding viral infections, environmental exposures, or an underlying systemic autoimmune dysregulation that breaks orbital immune tolerance. The dramatic and often rapid clinical response to systemic corticosteroids, which was the cornerstone of successful management in 83% of our IOI patients, strongly supports this immunologic basis.[15] Corticosteroids exert a broad, potent suppression of inflammatory pathways by inhibiting the transcription of genes encoding pro-inflammatory cytokines (such as IL-1, IL-6, and TNF-α) and by inducing apoptosis in activated lymphocytes. This non-specific, powerful anti-inflammatory effect rapidly alleviates the mass effect and associated symptoms, serving as both a therapeutic intervention and a quasi-diagnostic tool. Radiologically, this pathophysiology translates into diffuse, ill-defined enhancement on contrast-enhanced imaging that characteristically infiltrates orbital fat and extraocular muscles while respecting anatomical fascial planes, reflecting the infiltrative but non-destructive nature of the inflammatory process.

Our finding that lymphoproliferative disorders, encompassing reactive lymphoid hyperplasia and lymphoma (primarily low-grade extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT]), were the second most common entity (31.4%) aligns with accumulating data from other Asian countries. In these populations, lymphoma often rivals or exceeds epithelial tumors in frequency, suggesting potential genetic or environmental predispositions. The pathophysiology of orbital MALT lymphoma is a classic example of inflammation-driven neoplasia.[16] It is widely believed to arise from a backdrop of chronic antigenic stimulation, which drives the polyclonal expansion of B-lymphocytes within the lacrimal gland's native or acquired lymphoid tissue. Over time, accumulating genetic mutations in a susceptible B-cell clone—such as the t(11;18) or t(14;18) translocations—can lead to unchecked proliferation and malignant transformation. Potential antigenic drivers implicated in this process include infectious agents like *Chlamydia psittaci* and autoimmune conditions such as Sjögren's syndrome or Graves' disease, which create a pro-inflammatory microenvironment conducive to lymphomagenesis.

Pathophysiologically, these are typically indolent, low-grade tumors that grow by expanding and effacing the normal glandular acinar structures, rather than through aggressive invasion and destruction.[17] This explains their characteristic clinical presentation of a slow-growing, painless, firm, and mobile mass, often described as having a "salmon-pink" appearance when visible on the conjunctival surface. The tumor's tendency to mold to surrounding structures, such as the globe and orbital bones, without causing erosion, is a key radiological clue. Furthermore, the tumor's distinct cellular composition—a dense, monotonous proliferation of small lymphocytes with a high nuclear-to-cytoplasmic ratio—directly contributes to its signature appearance on MRI. This high cellularity restricts the random Brownian motion of water molecules within the tissue, resulting in markedly restricted diffusion on diffusion-weighted imaging

(DWI) and low values on apparent diffusion coefficient (ADC) maps, a feature observed in over 80% of our lymphoma cases and a powerful tool for differentiating lymphoma from other orbital pathologies. The exquisite sensitivity of these neoplastic lymphoid cells to low-dose ionizing radiation, which efficiently induces cell cycle arrest and apoptosis, makes radiotherapy the definitive treatment of choice for localized disease. This approach resulted in excellent local control in our cohort, affirming its status as a global standard of care.

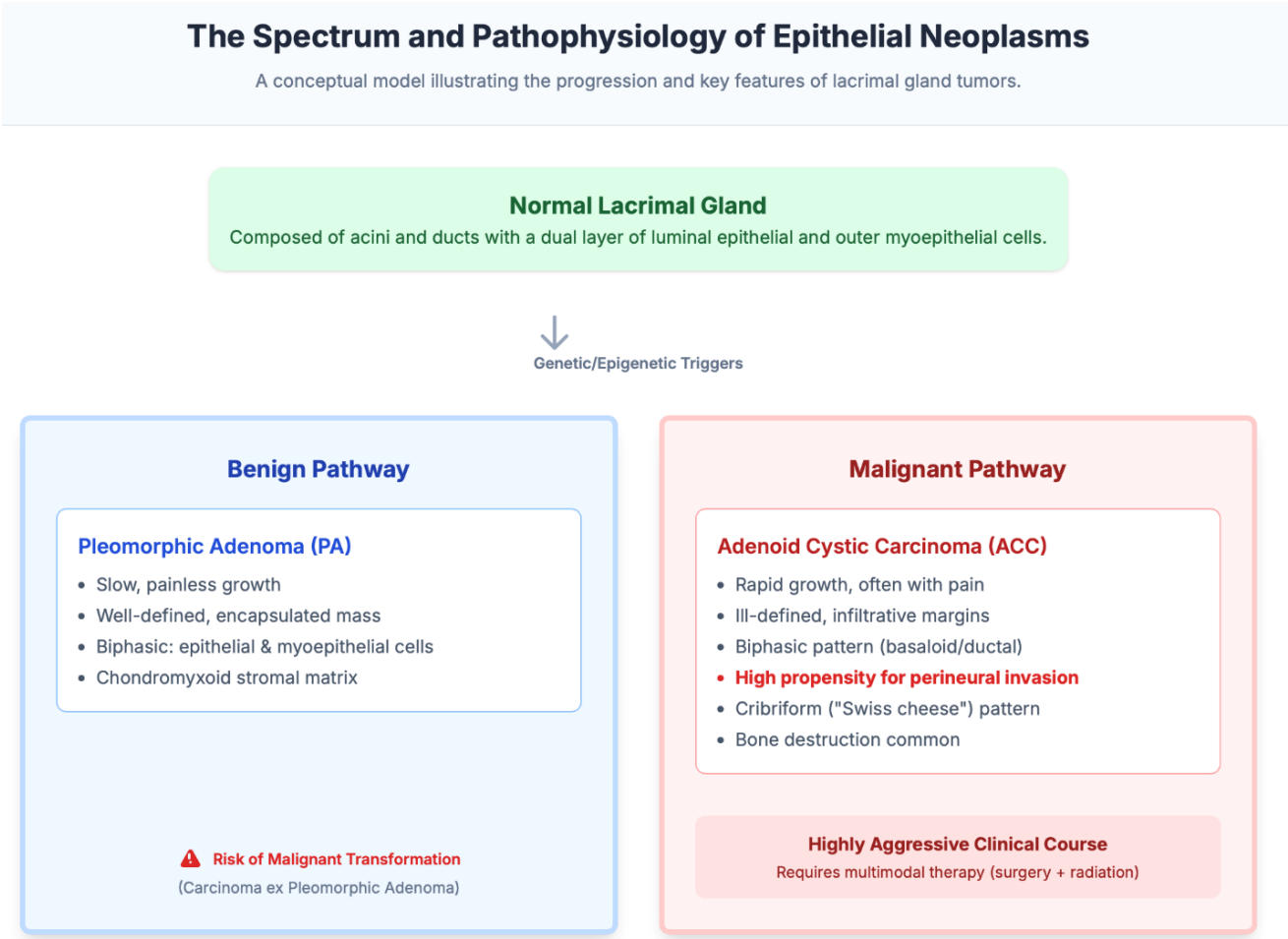

Figure 1. Pathophysiology of epithelial neoplasms.

While significantly less frequent in our series, the epithelial neoplasms encountered represent the most formidable diagnostic and management challenges in the lacrimal fossa. The single case of pleomorphic adenoma (PA), or benign mixed tumor, demonstrated the classic features that define this entity. PA is a complex, biphasic tumor arising from both the luminal ductal epithelial cells and the abluminal myoepithelial cells of the lacrimal gland. Its characteristically slow, indolent growth is a result of a well-balanced, controlled proliferation of these two distinct cell types.[18] A defining feature is the ability of the myoepithelial component to produce an abundant extracellular myxochondroid stromal matrix, which gives the tumor its firm consistency (Figure 1).

This matrix, along with a compressed fibrous host response, contributes to the formation of a pseudocapsule. However, this pseudocapsule is a

critical point of potential therapeutic failure. Pathological examination reveals that microscopic, finger-like tumor projections frequently perforate this seemingly intact barrier. This fundamental pathophysiological feature explains why simple enucleation or "shelling out" of the tumor is associated with unacceptably high rates of local recurrence, which can manifest years or even decades later and may carry a risk of malignant transformation (carcinoma ex pleomorphic adenoma). Consequently, the immutable standard of care—en bloc excision of the tumor with its pseudocapsule entirely intact, typically via a lateral orbitotomy approach—is specifically designed to remove these microscopic extrusions by including a margin of surrounding normal tissue. This surgical principle, which was successfully applied in our patient, is a direct clinical response to the unique pathological behavior of the tumor.

The most significant and feared malignant entity in our study was adenoid cystic carcinoma (ACC). Although representing only 8.6% of our cohort, its clinical impact is profound, and its prognosis remains guarded. The pathophysiology of ACC is defined by two cardinal features: a deceptively indolent but relentless, infiltrative growth pattern, and a remarkable tropism for nerves, known as perineural invasion (PNI).[19] PNI is not merely an incidental finding; it is the primary mechanism of local tumor spread. This process is believed to be mediated by a complex molecular interplay between tumor cells and components of the perineural sheath, involving the expression of neural cell adhesion molecules (NCAMs), laminin, and neurotrophic factors. This allows cancer cells to "hijack" nerve fascicles, using them as conduits to migrate far beyond the clinically and radiologically apparent tumor mass.

This insidious, microscopic spread is directly responsible for the hallmark symptom of severe, disproportionate, and unrelenting pain, which was a key distinguishing feature in our ACC patients, often resulting from the involvement of branches of the trigeminal nerve. It also explains the notoriously high rates of positive surgical margins and subsequent local recurrence, even after extensive, radical resections. Recent advances in molecular pathology have identified the MYB-NFIB gene fusion as a characteristic and likely pathognomonic driver mutation in the majority of ACC cases. This fusion creates a chimeric transcription factor that dysregulates a cascade of downstream genes controlling cell proliferation, survival, and differentiation, fuelling the tumor's aggressive biology. The clinical correlate of this aggressive pathophysiology, vividly demonstrated in our cohort by gross bone destruction on CT imaging and early recurrence despite multimodal therapy, underscores why ACC carries one of the worst prognoses among all head and neck cancers. Our findings unequivocally reinforce the absolute necessity of a highly aggressive, multidisciplinary approach, combining radical orbital surgery (often exenteration) with adjuvant radiotherapy, to provide any realistic opportunity for local disease control.

The strong correlation between clinical presentation and final pathology in our study provides valuable diagnostic paradigms that can guide clinical decision-making. The triad of acute onset, pain, and periorbital edema should strongly suggest an inflammatory process like IOI. Conversely, a chronic, slow-growing, painless, and mobile mass is highly characteristic of a lymphoproliferative disorder. Finally, the combination of severe, deep-seated pain, rapid proptosis, and evidence of bone erosion on imaging should be considered pathognomonic for ACC until proven otherwise. This clinical triad must serve as a major red flag, prompting urgent and comprehensive investigation.

When our cohort's distribution is compared to international data, it reveals both similarities and evolving differences. The historical 50:50 epithelial to non-epithelial ratio, often cited in older Western literature, is clearly not reflected in our series. Instead, our cohort, with its 89% non-epithelial predominance, aligns much more closely with recent, larger series from both Western and Asian institutions, which also

report a significant majority of inflammatory and lymphoid lesions. This observed global trend may not solely reflect true geographic or ethnic variations in disease incidence. It is more likely compounded by a paradigm shift in diagnostic and referral practices over the past few decades. With the advent of superior imaging modalities and a greater willingness to perform biopsies for definitive diagnosis, a larger number of non-neoplastic inflammatory conditions that may have been empirically treated in the past are now being subjected to histopathological analysis, thus entering such case series. The relatively low incidence of benign pleomorphic adenoma in our series compared to some Western reports is notable and could be multifactorial, possibly reflecting referral patterns or a true regional epidemiological difference that warrants further investigation in larger, multi-center Indonesian studies.[20]

The primary strength of this study lies in its detailed, multi-modal analysis of a well-defined cohort from a previously underreported region, providing a novel and crucial dataset for the Indonesian population. By meticulously correlating clinical, radiological, and detailed pathological data, we offer a comprehensive overview that possesses direct clinical utility for ophthalmologists, radiologists, and pathologists. This work establishes a vital baseline for future research in Southeast Asia. However, the study is not without limitations inherent to its design. Its retrospective nature introduces the potential for information bias and may result in incomplete datasets for certain variables. The small sample size of 35 cases, while representative of the rarity of lacrimal gland disease, inherently limits the power of statistical comparisons and prevents the drawing of definitive conclusions about precise prevalence rates. Furthermore, the single-center design may introduce a referral bias; as a tertiary referral hospital, our institution may receive a disproportionately high number of diagnostically challenging or advanced cases, potentially skewing the observed distribution of tumor subtypes compared to the general population. To overcome these limitations, future research should be directed towards establishing a prospective, multi-center national registry for orbital tumors. Such a collaborative effort would yield a larger, more representative dataset, enabling more robust statistical analysis and a more accurate depiction of the true epidemiology of these rare and complex diseases across the Indonesian archipelago.

5. Conclusion

In this comprehensive single-center Indonesian series, lacrimal gland tumors are predominantly non-epithelial, with idiopathic orbital inflammation and lymphoproliferative disorders being the most frequent diagnoses. Epithelial neoplasms, though rare, are responsible for the most significant morbidity, with adenoid cystic carcinoma presenting as an aggressive malignancy characterized by pain, proptosis, and bone destruction. A systematic approach that carefully integrates the patient's history, specific clinical signs, and characteristic radiological patterns can often predict the final histopathological diagnosis, thereby guiding appropriate management, from medical therapy for inflammation to radical surgery for malignancy. These findings contribute a vital regional perspective to the global understanding of lacrimal gland pathology and highlight the universal importance of a multidisciplinary, evidence-based approach to these complex orbital tumors.

6. References

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