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Orbital Pathology Update

Pleomorphic adenoma of the lacrimal gland: A review with updates on malignant transformation and molecular genetics

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Abstract

Pleomorphic adenoma (benign mixed tumor) is the most common epithelial neoplasm of the lacrimal gland. It is usually a slow growing, well-circumscribed, mass that is identical to its salivary gland counterpart. Patients generally have an excellent prognosis for vision and long-term survival after complete surgical excision. There is a tendency to reoccur, especially if there is an incomplete excision, and rarely, malignant transformation to carcinoma ex pleomorphic adenoma can occur, which has a much poorer prognosis. The molecular genetics of lacrimal gland pleomorphic adenomas have only recently been studies, but appear to display similar genetic aberration found in the salivary gland counterparts.

Keywords: Pleomorphic adenoma, Lacrimal gland, Malignant transformation, Molecular genetics

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Introduction

The lacrimal gland, an almond shaped, bi-lobed, eccrine secretory gland, approximately 2 cm long that lies in the lacrimal fossa in the supero-lateral part of each orbit, secretes a watery physiologic fluid which lubricates and provides nutrients for the eye and contains the bactericidal enzyme lysozyme.[1] Many different types of neoplasms, including metastases,[2] can arise within the lacrimal gland, which account for 5% to 25% of all orbital neoplasms.[3] Primary lacrimal gland neoplasms often arise in the orbital lobe where the gland attached to the orbital rim about the lacrimal fossa. The most common is the benign mixed tumor or pleomorphic adenoma (PA), a benign mixed tumor consisting of epithelial and mesenchymal components.[2] These neoplasms characteristically presents with slow, painless enlargement of the lateral portion of the upper eyelid in the 3rd and 4th decades of life, with no clear gender predominance.[4] Although benign, these epithelial tumors have a propensity to recur and undergo malignant transformation if incompletely excised, leading to increased morbidity in these patients.[5]

The purpose of this review is to summarize in a multifaceted manner the data available in the literature regarding the clinicopathologic features, radiographic findings, treatment, malignant transformation, and advances in molecular genetics in patients with lacrimal gland pleomorphic adenomas.

Clinical features

Pleomorphic adenomas (PA) are the most common epithelial tumor to arise within the lacrimal gland. They are usually slow growing and patients commonly present with slight fullness in the temporal upper lid, to those with frank proptosis, diplopia, visual impairment, and eyeball displacement.[6] Due to the location of the tumor, at or near

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the lacrimal fossa bone, the enlarging tumor characteristically displaces the eye downward and nasally. The duration of symptoms is a very important clinical indicator of a PA. The vast majority of patients with lacrimal gland PAs have had some degree of the aforementioned symptoms for over a year, which correlates with the usual slow growing nature of the tumor. The suspicion for malignancy increases when the symptoms have been less than 10 months.[6] Additionally, sensory loss and pain are not common symptoms of lacrimal gland PA and when present, should raise concern for a malignant neoplasm such as adenoid cystic carcinoma or mucoepidermoid carcinoma.[6,7] However, it should be noted that very rare atypical presentations have been reported in the literature and include patients with PAs having presenting symptoms mimicking inflammatory lesions such as orbital cellulitis or painful subcutaneous nodules.[7,8]

Radiographic imaging

Diagnostic imaging is critical for the clinical diagnosis of lacrimal gland neoplasms. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are ideal, with MRI as the preferred method for visualization of the surrounding bone and examination for intracranial infiltration.[6] On MRI, pleomorphic adenomas appear as isointense lesions with regular margins and angles.[4] For a PA, a well circumscribed mass identified within the lacrimal fossa is usually seen (See Fig. 1A and 1B).[6] Certain radiographic findings may illicit concern for a more aggressive malignancy and these include irregular shaped mass, bone invasion or erosion, molding of the mass to the globe or lateral orbital wall, and calcification.[6,7] If the radiographic findings and clinical findings are suggestive of PA, a diagnostic biopsy is not recommended as it may result in tumor recurrence later. A recurrence rate of up to 30% over five years has been reported when biopsy specimens had been taken.[6] Fortunately, in recent years, the rate of inadvertent biopsy of PAs has dramatically decreased as a result of improved radiologic evaluation.[7,9]

Treatment

Surgical intervention by lateral orbitotomy is the mainstay of treatment with complete resection of an intact capsule.[6,10,11] Incomplete capsule removal or defect in the capsule at the time of surgery can lead to significantly high rate of recurrence caused by the displacement of the myxoid component of PA into the orbital cavity.[2,12] Incisional or needle core biopsies are strictly contraindicated.[12] Radiation, while not commonly used, may be considered for rare pleomorphic adenomas that are inoperable or for recurrent/residual lesions. The prognosis is excellent when the lesion is completely excised with an intact capsule, with a less than 3% recurrence rate after 5 years. Recurrence is even more difficult to treat as they are often multiple and infiltrate normal orbital structures, leaving orbital exenteration as the only therapeutic option in some cases. In very rare instances recurrence in the frontoparietal areas of the brain have been reported in patients with incompletely resected PAs.[13]

Pathological findings

On gross examination, PAs typically have a pseudocapsule surrounding the mass lesion. It is imperative that the capsule

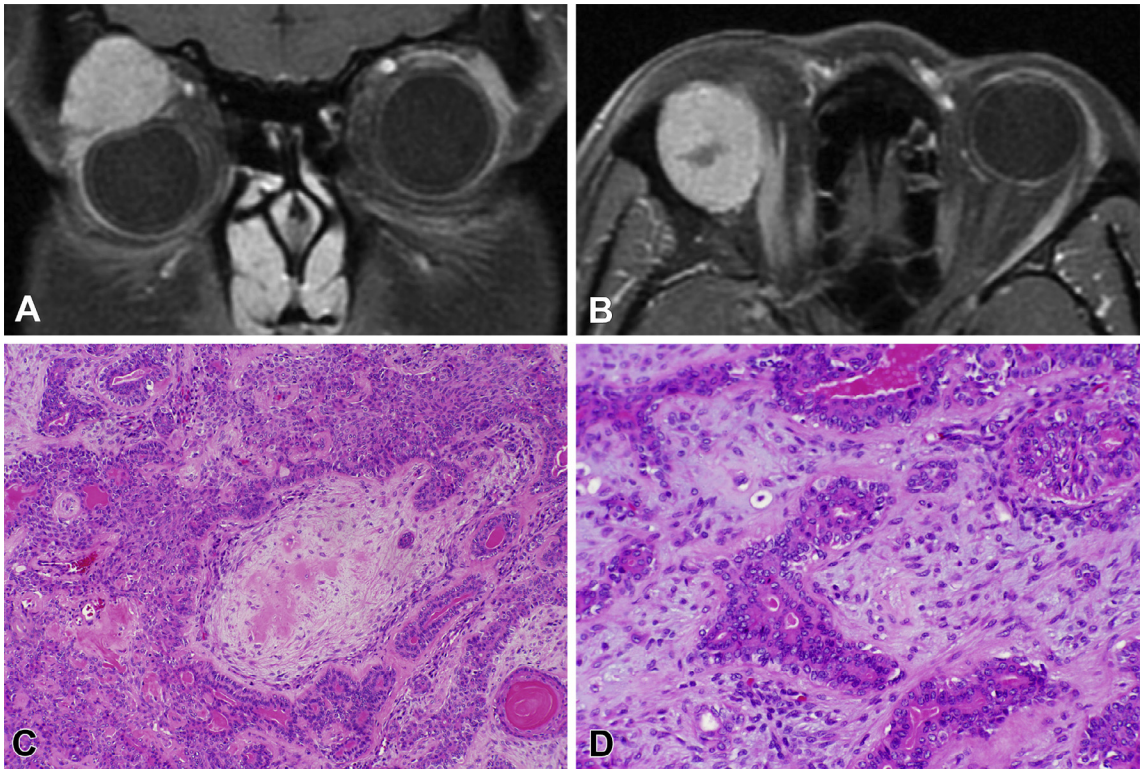

Fig. 1. Images A and B show T1-weighted MRI images demonstrating a well circumscribed superior orbital mass that has mass effect on the right eye. Images C and D are photomicrographs which highlight the biphasic nature of the neoplasm with an epithelial component forming cord and tubules and a chondromyxoid mesenchymal component.

be carefully examined for any evidence of disruption. Histologically, PAs demonstrate significant histologic heterogeneity with varying proportions of epithelial and mesenchymal components (See Fig. 1C and 1D). The epithelial cells form characteristic double-layer ductal structures, acini, irregular tubules, strands, and sheets with surrounding myoepithelial cells. The elements are typically dispersed within a background of loose myxoid tissue containing chondroid and rarely, foci of bone.[3,8,14,15] Islands of squamous metaplasia may also be present and in most cases there is no evidence of dysplasia or elevated mitotic activity.[8,15] No apparent difference in biological behavior has been reported between tumors composed largely of epithelial elements and those composed entirely of mesenchymal elements.[15]

Malignant transformation

A carcinoma arising in a pleomorphic adenoma is referred to as a carcinoma ex pleomorphic adenoma (Ca-ex-PA) or a malignant mixed tumor and conveys a poor prognosis.[3,5,12,15] The incidence of malignant transformation is increased with the duration of the tumor and accounts for approximately 10% of all malignant lacrimal gland tumors.[6,16] The longest interval reported in the literature for metastatic transformation of a PA is 60 years.[17] Seventy-five percent of the transformed carcinomatous component is to adenocarcinoma,[2] but can have a variety of morphologies including mucoepidermoid carcinoma, adenoid cystic carcinoma, salivary duct carcinoma, and adenocarcinoma not otherwise specified (NOS).[16] Older literature reports approximately up to 10% of pleomorphic adenomas undergo malignant change within 20 years after first treatment and 20% by the end of 30 years.[6] This number is significantly increased if the PA was not completely excised during initial resection.[2,12] With recent advances in therapy the prognosis appears to have improved. In a 2009 review of 118 lacrimal gland tumors, including 57 pleomorphic adenomas, it was shown that only 3 of the pleomorphic adenomas recurred and none underwent malignant transformation.[18] A case of malignant transformation of a lacrimal pleomorphic adenoma to squamous cell carcinoma 19 years after the initial surgical resection with metastases to the lungs has been reported.[19] Another interesting case was reported in which a patient developed adenocarcinoma with recurrent nodules of recognizable pleomorphic adenoma 32 years after the initial resection.[18] Unfortunately, no biomarkers currently exist to help predict the risk of malignant transformation of PA.

Molecular genetics

Molecular studies on salivary gland PAs revealed that the development of CA-ex-PA follows a multi-step model of carcinogenesis, with the progressive loss of heterozygosity at 8q, then 12q, and finally 17p.[16] Early alterations of chromosomal arm 8q often involve PLAG1 (8q12.1), an adenoma associated gene, and MYC (8q22.1-q24.1) a known oncogene, resulting in overexpression. The PLAG1 gene translocation t (5;8)(p13;q12) has been found to be highly specific for PAs[20], potentially making it a powerful diagnostic marker.

Alterations including amplification, gene fusion, and translocations, in 12q genes such as HMGIC, HMGA2, and MDM2 are thought to play a role in malignant transformation.[16,21] As aforementioned, 17p loss is common in Ca-ex-PAs, indicating the tumor suppressor gene, p53, is thereby commonly lost in the late carcinogenesis of CA-ex-PA.[16] Additionally, many genes that regulate tumor angiogenesis, growth factors, and cell-cell adhesion also play a role in the development and progression of Ca-ex-PA.

While the molecular genetics of salivary gland PAs have been more extensively studied, very little has been published on the genetic alterations in lacrimal gland PAs. High-resolution array-based comparative genomic hybridization has been used to study the genomic profiles of a series of lacrimal gland PAs and Ca-ex-PAs.[5] This analysis showed that lacrimal gland PAs have no or few copy number alterations and that losses involving 1p, 6q, 8q, and 13q and gains of 9p are recurrent alterations. The average number of genomic imbalances per tumor was 3.25 in primary and recurrent PAs compared with 7.7 in CA-ex-PAs. Overall, these findings support the notion that PAs are genetically stable tumors. The only recurrent copy number alteration identified in CA-ex-PAs was a gain of 22q12.3-qter. A detailed analysis of their array data identified 2 major candidate target genes, NFIB and PDGFB, which may be activated as a result of copy number gains involving 9p and 22q. It was also shown that the translocation target gene PLAG1 was frequently overexpressed in PAs and less frequently in Ca-ex-PAs and HMGA2 is overexpressed in a small subset of PAs. No genomic imbalances with break points in PLAG1 were found but this was thought to be due to balanced translocations which is a well-known genetic phenomenon in PAs. Immunohistochemistry for PLAG1 showed strong staining in approximately half of the PAs studied. These findings support previous studies showing that PLAG1 is frequently activated and overexpressed in PAs.[19] PLAG1 activation is thought to be a key event in the development of both salivary and lacrimal gland PAs. Overall, their findings showed that lacrimal gland PAs have similar genetic profiles to salivary PAs.

Conclusion

While lacrimal tumors are overall rare, pleomorphic adenoma is the most common epithelial tumor found to arise in this gland. Accurate clinical diagnosis followed by appropriate surgical excision leads to an excellent prognosis in the vast majority of cases. Local recurrence, which is often a result of incomplete excision and malignant transformation to carcinoma-ex pleomorphic adenoma, are associated with increased morbidity and mortality. The molecular genetics of pleomorphic adenoma and carcinoma-ex pleomorphic adenoma are beginning to be better understood and current studies suggest that they harbor similar aberrations seen in their salivary gland counterparts.

Conflict of interest

The authors declared that there are no conflicts of interest.

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