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Pleomorphic Adenoma of the Lacrimal Gland

Ophthalmic History: A 32 y.o. female presented with a 5 year history of a 3.0 cm right orbital superotemporal mass with proptosis, hypoglobus, and limited upgaze/elevation of the eye . There was no sign of optic neuropathy. Gross total excision of the mass was performed. Exam: VA 20/40 OD, 20/20 OS; IOP 7 OD, 10 OS; Hertel 22 OD, 17.5 OS; conj/sclera, cornea, AC, iris, lens, vitreous: unremarkable.

Discussion: 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 appear to display similar genetic aberration found in the salivary gland counterparts. On MRI, pleomorphic adenomas appear as isointense lesions with regular margins and angles.[4] 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].
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] 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 difficult and may infiltrate normal orbital structures and result in orbital exenteration. In rare instances recurrence in the frontoparietal areas of the brain have been reported [13].

Pathology: On gross examination, PAs typically have a capsule/pseudocapsule surrounding the mass lesion. Histologically, PAs demonstrate significant histologic heterogeneity with varying proportions of epithelial and mesenchymal components. 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].

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 appears to be 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]. 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 case was reported in which a patient developed adenocarcinoma with recurrent nodules of recognizable pleomorphic adenoma 32 years after the initial resection[18].

Molecular Genetics: The *PLAG1* gene translocation t(5;8)(p13;q12) has been found to be highly specific for PAs[20]. 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. Immunohistochemistry for *PLAG1* showed strong staining in approximately half of the PAs studied. *PLAG1* is frequently activated and overexpressed in PAs and is thought to be a key event in the development of both salivary and lacrimal gland PAs[19]. 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]. Alterations including amplification, gene fusion, and translocations, in 12q genes such as HMGIC, HMGA2, and MDM2 are thought to play a role in in malignant transformation[19,23].

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