

Epithelial tumors of the lacrimal gland: an update

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Purpose of review

The goal of this article is to offer an update on the treatment and prognosis of the most common epithelial tumors of the lacrimal gland, report on new pathological entities and offer a review of the classification of lacrimal gland tumors.

Recent findings

Improvements have been made in the understanding of lacrimal gland lesions with the knowledge that lacrimal gland tumors compare to the more common counterparts of the major salivary glands. Therefore, the WHO's classification of salivary gland tumors has been adapted to the lacrimal gland pathology. Until recently, primary adenocarcinomas of the lacrimal gland were not further subclassified, but they can now be divided into low-grade and high-grade malignancies. The adjunctive use of intra-arterial cytoreductive chemotherapy for the management of adenoid cystic carcinoma is one of the most important advancements on the management of these aggressive tumors. Another important step forward has been taken on carcinoma ex pleomorphic adenoma of the lacrimal gland, which is subclassified into noninvasive carcinoma, with an excellent prognosis after complete excision and invasive carcinoma for which the prognosis is still guarded despite adjunctive radiotherapy.

Summary

This article offers an update on diagnosis, classification and treatment of common and rare epithelial lacrimal gland tumors.

Keywords

adenoid cystic carcinoma, classification lacrimal gland neoplasm, lacrimal gland tumors, pleomorphic adenoma

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Introduction

According to a clinical series from the Wills Eye Hospital, lacrimal gland tumors represent almost 10% of the space-occupying orbital lesions, with epithelial lesions accounting for 20% of the total and inflammatory and lymphatic lesions for the remaining 80%. Among the epithelial lesions, 55% are benign and 45% are malignant [1]. Among benign lesions the most common are pleomorphic adenomas and dacryops, whereas among the malignant lesions adenoid cystic carcinoma is the most common (66%), followed by carcinoma ex pleomorphic adenoma (18%), primary adenocarcinoma (9%) and mucoepidermoid carcinoma (3%) [1].

Clinical features

In this section we will describe the clinical features of benign and malignant lacrimal gland lesions.

Benign lacrimal gland tumors

Benign tumors of the lacrimal fossa include pleomorphic adenoma and dacryops. Pleomorphic adenoma represents

the most common benign epithelial lesion of the lacrimal gland (12%) [2]. Patients affected by pleomorphic adenoma usually have a long history of painless proptosis. Unusual clinical presentations with abrupt orbital inflammation or as a painful subcutaneous nodule have also been reported [3•]. Orbital imaging shows a well defined, round or oval mass in the lacrimal fossa, without bone erosion. Unusual radiological presentations include lacrimal gland masses dominated by low-density areas resembling cysts [4•]. A complete surgical excision of the pleomorphic adenoma is recommended with an intact capsule, though incisional biopsy should be avoided given the potential risks of recurrences or even of malignant transformation of the lesion. Recently, Currie and Rose [5••] evaluated the long-term risk of recurrence after excision of pleomorphic adenomas of the lacrimal gland with a minimum follow-up of 5 years and they found no recurrences in patients that had an excision with an intact capsule, in those with a breach of the capsule during an attempt of intact excision and in those that underwent complete excision after previous incomplete excision. They reported a benign recurrence in one patient who underwent previous incisional biopsy,

showing that complete excision of pleomorphic adenoma should be considered curative, even though a long follow-up is warranted [5**]. Recently, Lai *et al.* [6**] raised the question ‘is there a role for biopsy in pleomorphic adenoma of the lacrimal gland?’ They reviewed the literature and found that the majority of previous studies against biopsy have included cases with incomplete excision or biopsy alone. On the basis of their results, they suggest that in a minority of patients with pleomorphic adenoma, biopsy may be considered for diagnosis and management. In addition, if surgical resection is required, they recommend complete excision including the biopsy tract to ensure complete removal [6**]. Although normally pleomorphic adenomas occur within the lacrimal gland, its occurrence in an accessory lacrimal gland of Wolfring has recently been reported [7].

Dacryops are a relatively common entity (6%) that usually affect the palpebral lobe of the lacrimal gland where they are visible upon eversion of the upper lid. Occasionally, they may affect the orbital lobe causing proptosis and ‘S’-shaped ptosis and in this case, it may be difficult to differentiate a dacryops from other entities. On imaging, they present as cystic lesions filled with clear fluid. Histopathology shows a cyst lined by lacrimal duct epithelium. Recently, primary squamous carcinomas presumably arising from a lacrimal duct cyst, benign mixed cell tumor combined with a lacrimal cyst and hemangiopericytoma associated with dacryops have been reported, whereas we observed a monoclonal lymphoid infiltrate in combination with dacryops in one case (unpublished data) [8–10]. Complete excision of the orbital dacryops is recommended and recurrences are rare. When dealing with a palpebral lobe dacryops, care should be taken not to damage the orifices of the gland, in order to avoid dry eye complications.

Recently a new entity, defined as benign fibrous histiocytoma, a relatively common mesenchymal tumor that commonly originates from ocular and adnexal tissues, has been reported to occur in the lacrimal gland [11*]. Finally, a primary bilateral cystadenoma of the lacrimal gland was surgically excised by Bajaj *et al.* [12].

Malignant lacrimal gland tumors

The clinical features of adenoid cystic carcinoma (ACC), the most common malignant lesion of the lacrimal gland, include globe dystopia, proptosis and ‘S’-shaped ptosis. Pain is considered a strong indicator of aggressive behavior, especially if associated with hypoesthesia in the frontotemporal region and it is secondary to invasion of the orbital nerves. The duration of symptoms is relatively shorter in comparison with benign tumors, usually within 6 months. Radiologically, bone erosion occurs early on

and the margins of the lesion may appear irregular; focal calcification within the lesion may occur. Adenoid cystic carcinomas may arise from the accessory lacrimal glands and ectopic lacrimal gland tissue [13**]. In an attempt to find a prognostic correlation with histologic subtype, many studies have been published. Gamel and Font [14] found that the presence of a ‘basaloid’ pattern affects the prognosis negatively. They found a 5-year survival rate of 21% for patients with basaloid pattern compared with 71% for patients with ‘nonbasaloid’. Lee *et al.* [15] found that a better prognosis was noted if the tumor had a cribriform ‘Swiss cheese’ appearance. In a group of salivary and lacrimal gland ACCs, Hamper *et al.* [16] found prognostic correlation with a glandular pattern on histology, with the tumor size and the different subtypes based on cytophotometry. In contrast with these findings, Friedrich and Bleckmann showed that only the stage of the tumor had an impact on prognosis whereas the localization or the histological subtypes did not show any impact on survival [17]. Strianese *et al.* [18*] studied the relationship among apoptosis related markers and prognosis in 21 malignant epithelial tumors of the lacrimal gland, including 11 adenoid cystic carcinomas. They found that increased Bcl-2 staining was significantly correlated with a poor survival.

The treatment of lacrimal gland adenoid cystic carcinoma is still controversial and different treatment modalities have been compared to evaluate their impact in long-term survival. According to Bartley and Harris, the question ‘is there a cure yet?’ remains unanswered [19]. A study by Wright *et al.* [20] compared the outcomes in a group of 38 patients affected by adenoid cystic carcinoma and were treated using three different methods: dacryoadenectomy alone, dacryoadenectomy with radiotherapy, radiotherapy alone and extended cranio-orbital resection. The authors found that, although patients tended to survive longer when treated with surgical resection with radiotherapy than radiotherapy alone, the rate of disease-free survival after treatment of ACC appeared to be unaltered by cranio-orbital resection. Esmaeli *et al.* [21] reported a series of seven patients with locally advanced ACC that underwent exenteration with superior and lateral orbitectomy followed by radiotherapy of the orbit and the skull base. They achieved a satisfactory local control of the disease, but despite this aggressive approach five patients developed distant metastasis and died [21]. More recently, a significant improvement for the prognosis of lacrimal gland ACC seems to be offered by the use of intra-arterial cytoreductive chemotherapy (IACC) as an adjunct to conventional surgery and radiation therapy, as reported by Tse *et al.* [22]. They treated a group of nine patients with IACC followed by orbital exenteration and radiotherapy and compared their outcome with a historical cohort of seven

patients treated with conventional therapies. They found a significant reduction of cause-specific death rate and recurrence rate in the study group compared with the control.

Another important chapter includes carcinoma ex pleomorphic adenoma (Ca ex PA), also called carcinoma in pleomorphic adenoma, malignant mixed tumor or pleomorphic carcinoma, which is a relatively common malignant tumor of the lacrimal gland with an incidence of 12% among malignant neoplasms of the lacrimal gland and a similar incidence among the salivary gland malignancies [23]. Typically it occurs in the 6th or 7th decade, one decade later than pleomorphic adenoma. To fit with the diagnosis, both benign and malignant components of the lesion need to be identified, whereas if the benign component does not appear the diagnosis is of pleomorphic carcinoma only. The main criteria for histopathological diagnosis are frank carcinomatous infiltrative areas, marked atypia, numerous atypical mitosis and necrosis [24]. Most commonly the malignant component is represented by a poorly differentiated adenocarcinoma or an undifferentiated carcinoma, but adenoid cystic carcinomas have also been described [25^{*}]. Ca ex PA should be sub-classified into noninvasive, also termed intracapsular or carcinoma *in situ*, minimally invasive (<1.5 mm from the capsule) and invasive carcinoma (>1.5 mm from the capsule). Noninvasive and minimally invasive carcinomas have an excellent prognosis with complete surgical excision without adjunctive radiotherapy. Our anecdotal experience with an intracapsular Ca ex PA underwent complete surgical excision with an

intact capsule and has been followed for over 1 year without adjunctive radiotherapy and is now alive and free of local recurrence. On the contrary, invasive Ca ex PAs are aggressive tumors with a poor prognosis. Another patient with CA ex PA and with invasion of the capsule was treated with local resection and radiotherapy. After 8 months of follow-up a recurrence was diagnosed. The patient was exenterated with additional radiotherapy, but died of extensive metastasis after 1 year. A recent article focused on the role of adjunctive radiotherapy on the local control in a group of 63 patients with invasive Ca ex PA of the parotid gland and found that the 5-year local control rate had significantly improved from 49 to 75% [26^{**}].

Since Katz *et al.* [27] presented the first case of primary ductal adenocarcinoma of the lacrimal gland and referred this rare tumor to the more common salivary gland tumor classification of the WHO, this has become the standard practice and now ophthalmologists and pathologists are revising the lacrimal gland classification according to the salivary gland tumor classification by WHO (Table 1) [24,27,28].

On the basis of the WHO's classification of salivary gland tumor, Devoto and Croxatto [29] reported a new entity affecting the lacrimal gland described as primary cystadenocarcinoma. This unique entity in the lacrimal gland follows the clinical course of the more common lesion in the salivary gland with an indolent behavior and no need for adjunctive radiotherapy [29]. The lesion was completely excised with an intact capsule and no

Table 1 Classification of lacrimal gland tumors

Epithelial neoplasms	Nonepithelial neoplasms	Tumor-like conditions
Benign epithelial tumors	Lymphoma	Lacrimal duct cysts
Pleomorphic adenoma	Plasmacytoma	Ectopic lacrimal gland
Oncocytoma	Hemangioma	Chronic dacryoadenitis
Warthin's tumor	Hemangiopericytoma	Inflammatory pseudotumors
Myoepithelioma	Fibrous histiocytoma	Benign lymphoepithelial lesion
Sialoblastoma	Solitary fibrous tumor	
Malignant epithelial tumors	Neurofibroma and schwannoma	
Adenoid cystic carcinoma ^a	Lipoma	
Carcinoma ex-pleomorphic adenoma ^a	Metastatic or secondary tumors	
Adenocarcinoma (NOS) ^a		
Mucoepidermoid carcinoma ^b		
Polymorphous low-grade carcinoma ^b		
Basal cell adenocarcinoma ^b		
Acinic cell carcinoma ^b		
Ductal adenocarcinoma ^a		
Squamous cell carcinoma ^a		
Clear cell carcinoma ^b		
Cystadenocarcinoma ^b		
Mucinous adenocarcinoma ^b		
Epithelial–myoepithelial carcinoma ^b		
Oncocytic carcinoma ^a		
Carcinosarcoma ^a		

NOS, not otherwise classified.

^a High-grade neoplasms.

^b Low-grade neoplasms.

Adapted from [24].

adjunctive radiotherapy was administered and the patient is alive and well 7 years postoperatively. Anecdotally, we are following another patient affected by primary cystadenocarcinoma of the lacrimal gland that underwent complete surgical excision of the original lesion, but the patient experienced an intraoperative capsule breach with leakage of fluid content and developed a local recurrence 1 year later. The patient underwent surgical excision of the recurrent tumor followed by radiotherapy and is now 3 years postoperatively alive and free of recurrence.

Basal cell adenocarcinoma has been reported to occur in the salivary glands and only recently in the lacrimal gland also; the differential diagnosis include especially the solid basaloid variant of adenoid cystic carcinoma that has a much worse prognosis [30].

Rare tumors of the lacrimal gland include solitary fibrous tumor of the lacrimal gland fossa, a primary extramedullary plasmacytoma of the lacrimal gland, and sialoblastoma, a rare congenital locally aggressive epithelial tumor [31].

Conclusion

The management of lacrimal gland tumors has been rapidly evolving in recent years due to the knowledge that they compare histologically and behave clinically similarly to the more common counterparts affecting the major salivary glands. Primary adenocarcinomas of the lacrimal gland can now be divided into low-grade and high-grade malignancies; the revised classification of lacrimal gland tumors allows a precise diagnosis and appropriate management of rare lacrimal gland lesions, as it has been in the case of primary cystadenocarcinoma or the intracapsular Ca ex PA. Important advances have been made on the treatment of adenoid cystic carcinomas, pleomorphic adenomas and dacryops.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 439–440).

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