Review

LACRIMAL GLAND DISEASE – CLINICIAN BEWARE!

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Summary

Lesions of the lacrimal gland can be benign or malignant, and a biopsy should be considered in any lesion that does not settle after a few week's conservative treatment. The imaging of choice remains high-resolution CT, *and not MRI*, with distinct differences noted between 'benign' and aggressive neoplastic disease. The optimal treatment for lesions which could be pleomorphic adenoma is intact excision, and the prognosis for malignant neoplastic disease remains guarded, despite debulking and high-dose regional radiotherapy, although local brachytherapy (for recurrence of disease) and adjunctive intra-arterial chemotherapy may play an important role in the future.

Key words: Lacrimal gland, pleomorphic adenoma, adenoid cystic carcinoma, malignant mixed tumour, primary adenocarcinoma, sarcoidosis, Wegener's granulomatosis, dacroadenitis, ductile actinomyces, reactive lymphoid hyperplasia

Introduction

The management of lacrimal gland disease – Keypoints for the clinician:

- Lacrimal gland disease may be benign or malignant, be solitary or part of systemic disease
- Acute dacroadenitis is painful, unilateral, and due to viral or bacterial infection
- Chronic lacrimal gland enlargement may be painless, bilateral, and associated with a systemic inflammatory disease such as sarcoidosis or Wegener's granulomatosis.
- Empirical steroid treatment can mask the presence of malignancy and delay diagnosis
- The management of benign neoplastic disease (pleomorphic adenoma) is intact excision
- Malignant epithelial disease carries a poor prognosis

Lacrimal gland disease, which may be benign or malignant, accounts for over a tenth of all orbital lesions [1] (Table 1). It can be of acute or gradual in onset, be benign in nature, or present a significant risk to both sight and life [2].

Typical symptoms of acute infective disease include conjunctival redness and oedema, a painful and often tender fullness in the lacrimal gland region, and an 'S-shaped' deformation of the upper lid.

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Table 1. Lacrimal gland: Benign and malignant disease

Benign dsease	Lacrimal ductule disease	Dacrocoele
		Lacrimal duct infection
	Inflammatory disease	Reactive lymphoid hyperplasia (RLH)
		Idiopathic vasculitis i.Sarcoidosis ii.Wegener's granulomatosis iii.IgG4 disease
	Infection	Acute dacroadenitis
		Lacrimal gland abscess
	Primary benign epithelial tumours	Pleomorphic adenoma
		Oncocytoma
		Myoepithelioma
	Solitary fibrous tumour	
	Plasmacytoma	
	Haemangioma	
	Myoepithelioma (arising from myoepithelial cells adjacent to epithelial cells)	
Malignant disease	Tumours of glandular epithelial origin	Adenoid cystic carcinoma
		Malignant mixed tumour (carcinoma ex-pleomorphic adenoma)
		Adenocarcinoma
		Squamous cell carcinoma
	Mucoepidermoid carcinoma	
	Lymphoma	
	Metastatic disease	

However, since dacryoadenitis is also a common presentation for rapidly-progressive malignancy, orbital imaging and tissue biopsy are required if medical treatment does not result in complete clinical resolution of disease within one to two months.

Benign lesions of the lacrimal gland

Infective disease

Keypoints:

Acute dacroadenitis presents with a puffy, red 'S' shaped upper lid

Mild to moderate cases are treated with non-steroidal medication.

Oral antibiosis should be added to more severe cases.

Inflammation of the lacrimal gland (dacroadenitis) can be due either to an acute infective process (typically viral), or to chronic lymphocytic infiltration. The clinical features of acute dacroadenitis include a prodromal ache and a puffy, painful red upper lid with a variable degree of ptosis (Figure 1), with initial therapy including oral non-steroidal anti-inflammatory medication. Antibiotics are reserved for more severe cases, but where an abscess is demonstrated (Figure 2), drainage should be performed if a rapid clinical improvement is not seen with antibiotic treatment. Finally, if after a few weeks there has not been complete clinical resolution, a biopsy should be performed to exclude a malignant process within the gland.

Chronic inflammatory disease

Keypoints:

Chronic dacroadenitis is usually painless

Biopsy is mandatory before initiating treatment with steroid

Systemic vasculitis should be excluded

In contrast to acute dacroadenitis, chronic lacrimal gland inflammation presents with an indolent painless fullness in one or both upper lids (Figure 3) [2] and imaging often identifies bilateral diffuse enlargement of the affected glands that mould around the surface of the globe (Figure 4).This differs to pleomorphic adenoma

of the lacrimal gland, in which the hardness of the lesion tends to indent the globe (Figure 10) [2].

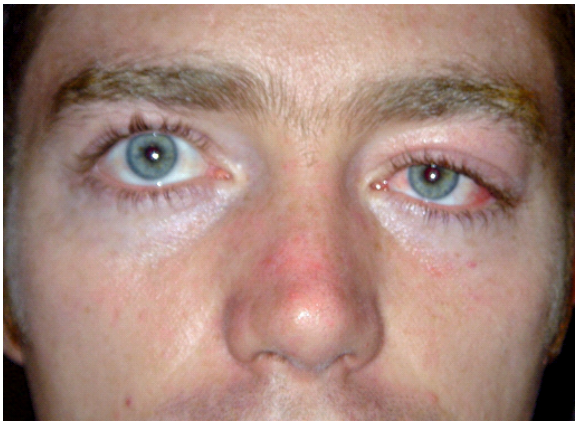

Figure 1. Acute dacroadenitis - sudden onset of puffy and red lid with complete ptosis

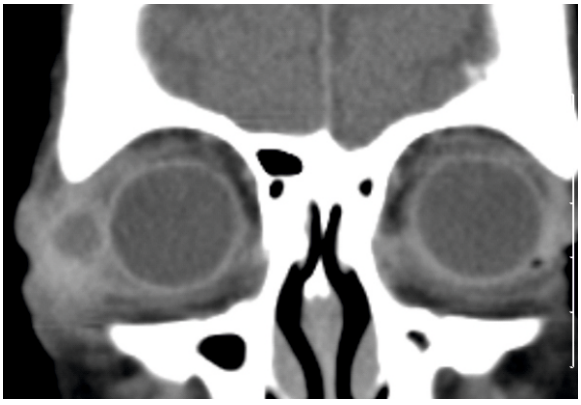

Figure 2. CT scan identifying an abscess within the lacrimal gland

Chronic lacrimal gland disease should be investigated with a chest X ray (Figure 5), and a vasculitic screen. These are performed to exclude certain idiopathic systemic inflammatory diseases such as Wegener's granulomatosis, sarcoidosis, and IgG4 disease [3]. In all cases, a tissue biopsy should be performed before beginning immunosupression which can mask the histological features of lymphoid malignancies and therefore delay diagnosis.

Once a suspected pleomorphic adenoma has been excluded on clinical and radiological grounds, an incisional biopsy of the gland can be achieved through a lateral upper lid skin crease incision. The skin and orbicularis fibres are opened and care is taken not to injure the levator muscle. With blunt dissection and exposure of the superolateral orbital rim using malleable retractors, the septum is opened immediately beneath the arcus marginalis, With inferior displacement of the orbital fat, which tends to prolapse through the opening in the septum, the orbital lobe of the lacrimal gland is mobilised from its fossa and a large incisional biopsy and haemostasis can readily be achieved (Figure 6). The orbital septum does not require suturing, and the skin is closed with a continuous 6/0 nylon suture which is removed after two weeks.

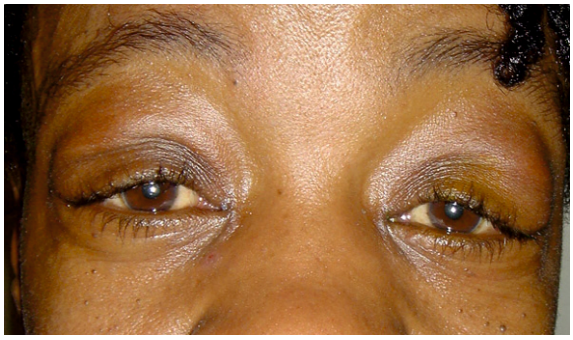

Figure 3. Bilateral chronic lacrimal gland inflammation due to sarcoidosis

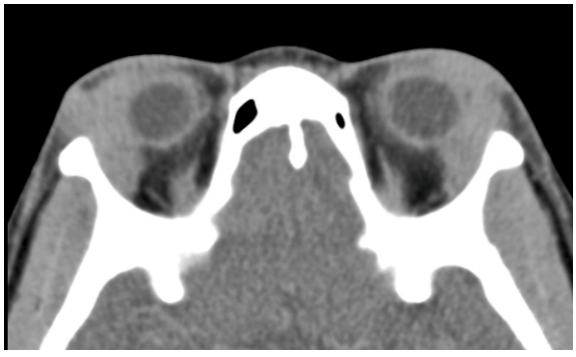

Figure 4. CT scan showing bilateral changes in sarcoidosis

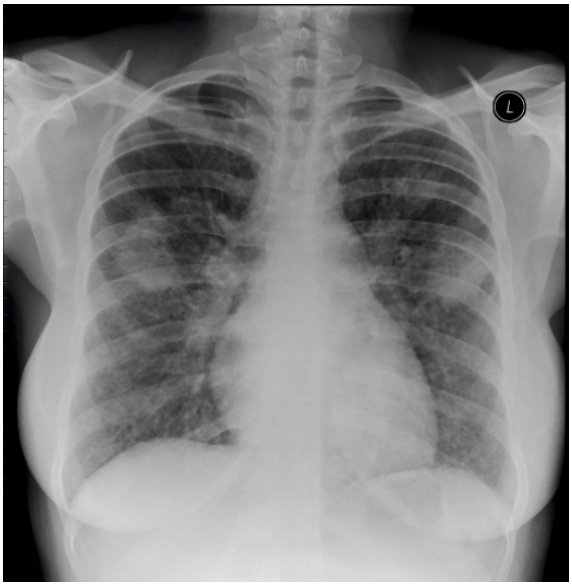

Figure 5. Sarcoidosis: Chest X ray demonstrating bilateral mediastinal adenopathy with enlargement of the hila

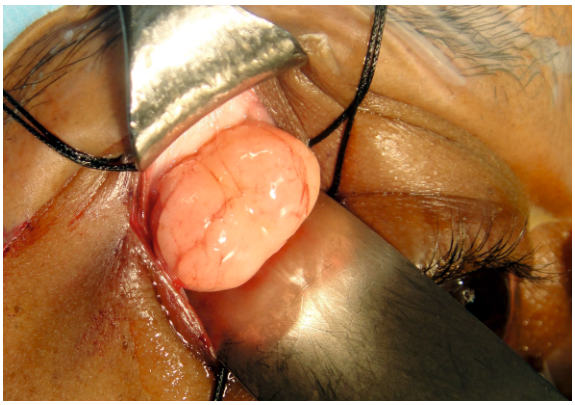

Figure 6. Peroperative view of biopsy of the lacrimal gland via a skin crease incision

Infection of the lacrimal ductules

Actinomyces may rarely lead to chronic infection of a lacrimal gland ductule, and typically presents with a foreign body sensation, temporal episcleritis, and chronic ocular discharge (Figure 7) [4]. The diagnosis is often delayed, with the patient being managed unsuccessfully with antimicrobial drops for presumed conjunctivitis. Treatment is complete excision of the involved ductile, and often a 'stone' is noted within its lumen, similar to those seen with canalicular involvement (Figure 8).

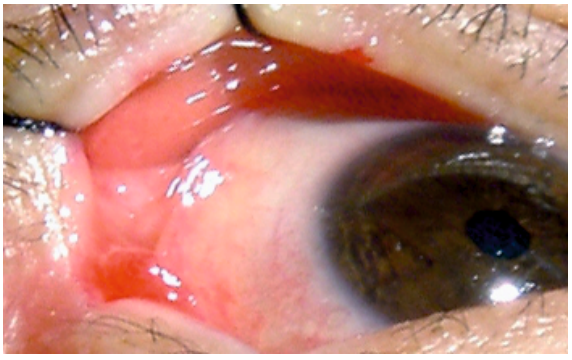

Figure 7. Actinomyces of a lacrimal ductile

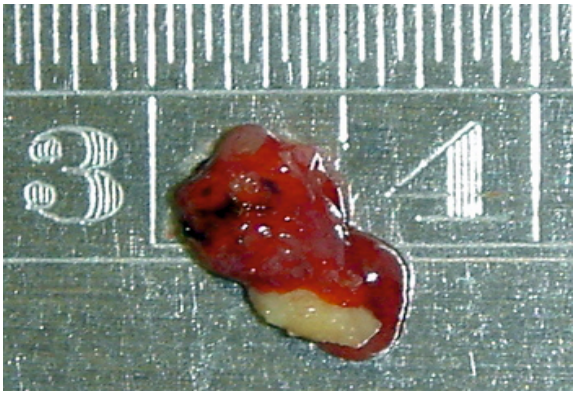

Figure 8. Lacrimal ductule actinomyces - excision specimen demonstrating calcific ductolith

Benign tumours of the lacrimal gland

Pleomorphic adenoma

Keypoints:

Pleomorphic adenoma has a very slow clinical course

Characteristic CT signs differentiate pleomorphic adenoma from malignant disease

Incomplete excision may lead to widespread orbital recurrence, or malignant transformation

Pleomorphic adenoma, a benign lacrimal epithelial tumour, accounts for a quarter of all lacrimal gland neoplasms and one half of the epithelial tumours. Although it may occur at any age after childhood [5, 6], typically disease becomes apparent in the fifth and sixth decades of life and old photographs frequently show subtle signs several decades earlier. The presenting clinical features include a slowly-progressive, painless fullness of the upper lid and hypoglobus, although proptosis is rare in view of the position of the lacrimal gland anterior to the equator of the globe (Figure 9). Pleomorphic adenoma is characteristically hard, and with its slow growth tends to cause indentation of the globe (Figure 10) and a buckling of the sclera, clinically detected as macular choroidal folds. These structural changes occur at the posterior pole, distant to the lesion, and often persist even after removal of the tumour with consequent

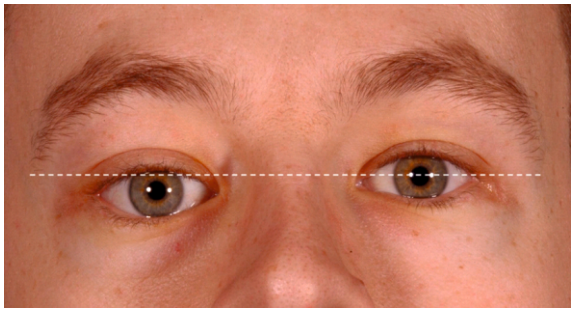

Figure 9. Hypoglobus of the right eye due to pleomorphic adenoma of the lacrimal gland (dotted line indicating the horizontal axis)

impairment of vision. CT imaging identifies a smooth expansion of the lacrimal gland fossa, preservation of cortical bone, and indentation of the globe, with calcification infrequently occurring [7]. Most adenomas arise within the orbital lobe of the lacrimal gland and remain unnoticed for decades due to expansion of the lacrimal fossa behind the tough orbital rim. These

Table 2. Distinguishing radiological features of benign and neoplastic epithelial disease of the lacrimal gland

	Pleomorphic adenoma	Malignant epithelial disease
Margins:	Well-defined	Indistinct
Location:	Centred in the lacrimal fossa	Posterior extension along the lateral wall of the orbit
Relationship to globe:	Indentation of the globe Inferomedial globe displacement (large lesions)	Lesion molds around the globe Lateral rectus displacement (with rapid tumour proliferation)
Effect on neighbouring bone:	Scalloping (thinning) of the lacrimal fossa	No scalloping. Pitting of the bone suggests local invasion
Density:	Typically homogenous; may be cystic	Diffuse calcification in a third of cases
Metastatic spread:	Rarely occurs *	Early spread to orbitaperiosteum, bone, temporalis fossa, superior orbital fissure, and middle cranial fossa

** The exception being in cases where there has been an incisional biopsy, or incomplete excision, or where there has been malignant transformation (to malignant mixed tumour), this also more likely following incomplete excision*

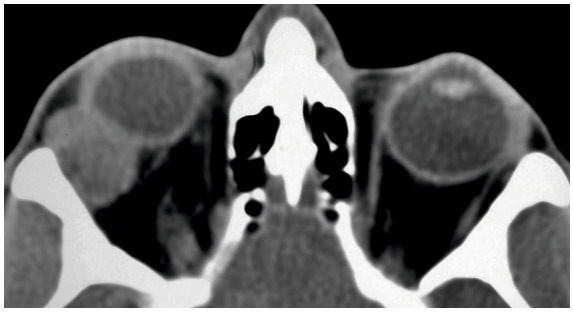

Figure 10. CT showing pleomorphic adenoma with indentation of the globe

features contrast markedly with those of primary lacrimal malignancies, in which more acute inflammatory symptoms and signs are seen, and which show markedly different radiological features (Table 2).

The diagnosis of pleomorphic adenoma is made on the basis of the history and CT imaging. Management is complete and intact excision (Figure 11), because inadvertent incisional biopsy carries a significant risk of aggressive recurrence or neoplastic transformation (Figure 12) [8]. Excision is achieved via an upper lid skin crease incision, which can be extended into the lateral skin rhytids if a lateral osteotomy is required for larger lesions.

Histological features of pleomorphic adenoma include sheets, cords or masses of epithelial cells of ductal origin, with the term 'pleomorphic' referring to adjacent myxoid and pseudocartilagi-nous areas. If the resection margin is inadequate, tumour recurrence can arise from microscopic extension into the "pseudocapsule" of compres-sed neighboring tissues. If an inadvertent biopsy is performed, this being more likely with an unusual history or atypical radiological signs, the biopsy tract and the tumour must be carefully excised to minimise

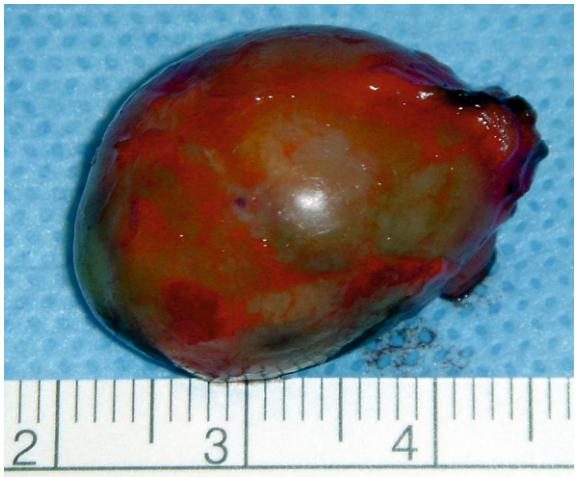

Figure 11. Macroscopic view of intact excision of pleomorphic adenoma

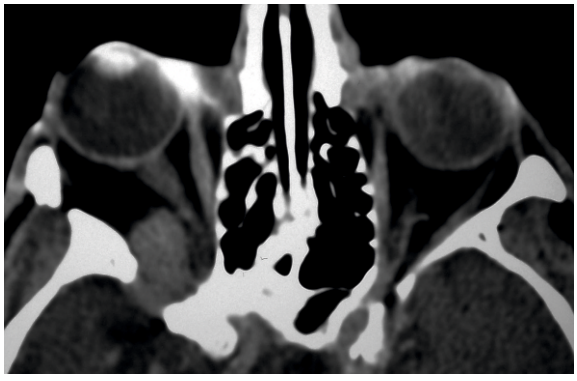

Figure 12. Malignant transformation of previously incompletely excised pleomorphic adenoma

the risks of pervasive recurrence and late malignant transformation.

Occasionally, a pleomorphic adenoma may arise anterior to the orbital rim (termed 'palpebral pleomorphic adenoma'; Figure 13), or from accessory lacrimal glands within the eyelids. These 'ectopic' adenomas behave in a similar way to adenomas of the orbital lobe of the lacrimal

gland, emphasising the importance of performing intact excision of any firm mass that might conceivably be a pleomorphic adenoma.

Within 20 years, one fifth of these benign lesions undergo malignant transformation, and the clinician should suspect such a change wherever a suspected pleomorphic adenoma has undergone an accelerated change in symptoms, especially when accompanied by pain.

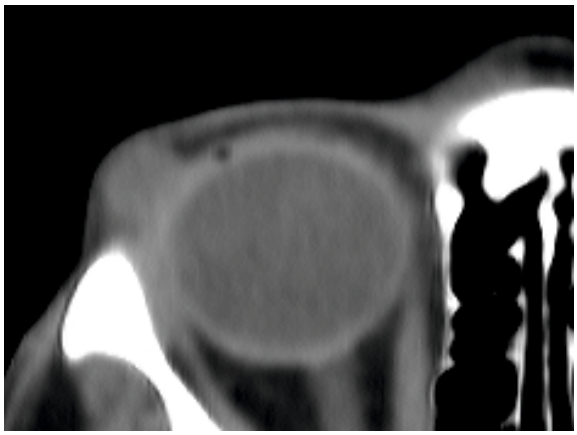

Figure 13. CT identifying palpebral pleomorphic adenoma

Malignant lesions of the lacrimal gland

Epithelial neoplasia

Keypoints:

Adenoid cystic carcinoma is the most common epithelial neoplasm

Presentation is relatively acute (days to weeks)

The mainstay of treatment is surgical debulking followed by high-dose external beam fractionated radiotherapy, to include the lateral orbital wall and cavernous sinus

The prognosis is poor - mean survival is 5 years

Intra-arterial cytoreductive chemotherapy (IACC) may improve survival

Epithelial neoplasia is the commonest primary lacrimal malignancy, of which the most frequently encountered is adenoid cystic carcinoma [9, 10]. Unlike the very gradual changes seen in pleomorphic adenoma, these primary malignant epithelial tumours can occur at any age, present with a shorter history (weeks to months), and are typically accompanied by pain, inflammation, and a mass effect (Figure 14). CT imaging identifies a diffuse mass centred in the lacrimal fossa, molding around the surface of the globe (Figure 15).

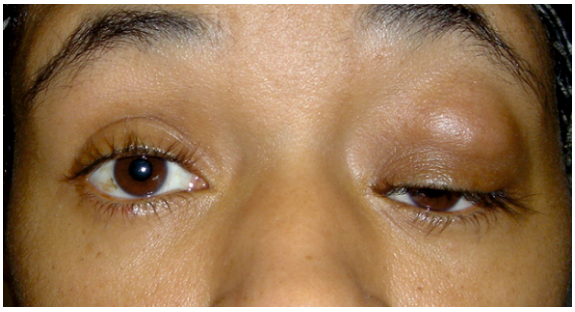

Figure 14. Adenoid cystic carcinoma: Presentation with mass effect

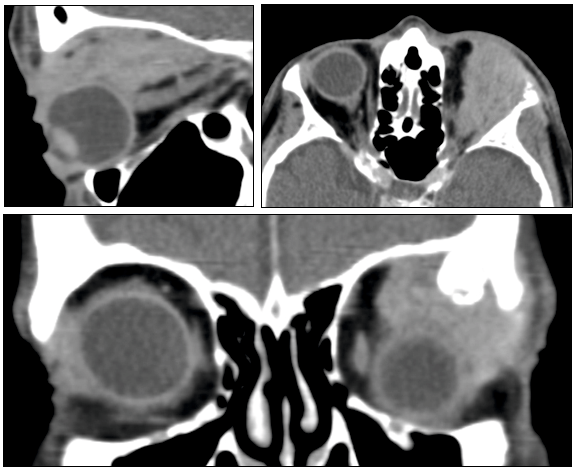

Figure 15. CT identifying biopsy proven epithelial

Adenoid cystic carcinoma

Adenoid cystic carcinoma, accounting for up to 10% of all orbital malignancies in one series, has a high associated mortality despite treatment [11, 12]. At surgery, the cut surface of the mass typically appears grey-white, and microscopy identifies small hyperchromatic, basophilic cells with a varying amount of stroma. Five microscopic patterns of tumour architecture have been described (Table 3), of which the basaloid form carries a significantly worse prognosis than cribriform (Figure 16).

Although in the past patients have been managed with extended orbital exenteration, there is no evidence that such a destructive approach improves survival. Current best practice is considered to be extensive tumour debulking and adjunctive fractionated high-dose radiotherapy, to a total of approximately ~ 55 Gray[1]. Adenoid cystic carcinoma has a high propensity for perineural spread, and although brachytherapy (proposed for recurrences following primary excision) delivers a high dose to the lacrimal gland fossa, such an approach spares the neighbouring orbital structures, and thus fails to treat the extraocular muscles,

[1]Because of the invasive nature of the tumour, the irradiated field should include the lacrimal fossa, superolateral soft tissues of the orbit, lateral orbital wall, orbital apex, and superior orbital fissure and anterior cavernous sinus.

Table 3. Adenoid cystic carcinoma: Histological differentiation

1.	Cribriform
2.	Tubular
3.	Basaloid (solid)
4.	Sclerosing
5.	Comedo - carcinomatous

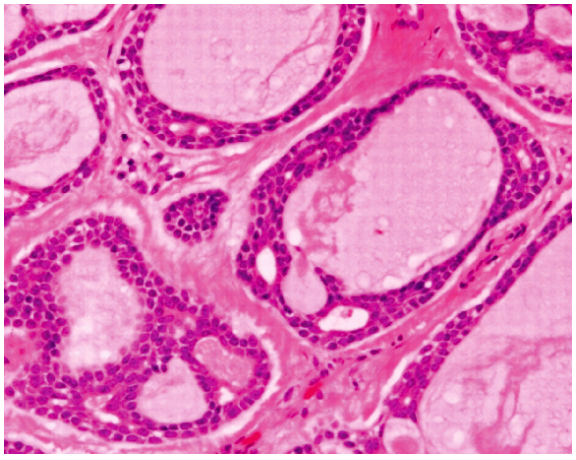

Figure 16. Histology of adenoid cystic carcinoma showing basaloid variant

superior orbital fissure and anterior cavernous sinus, all of which are a risk of tumour infiltration [13]. Finally although these tumours are not thought to respond to cytotoxic agents, promising results with adjunctive intra-arterial cytoreductive chemotherapy (IACC) have recently been described [14]. Tse et al in 2006 reported their experience in 9 patients with adenoid cystic carcinoma who underwent IACC followed by orbital exenteration and chemoradiotherapy. Compared to a similar series of patients undergoing conventional local therapy, this group was associated with a significantly lower mortality over 5 years (17% vs. 57%), in addition to a lower rate of recurrence within the same time period (24% vs. 71%). No study has yet reported the effect of IACC and radiation *without* orbital exenteration.

Malignant mixed tumour

Carcinoma arising within a pleomorphic adenoma is known as a "malignant mixed tumour", and imaging will sometimes show bony changes typical of the preceding benign tumour, with the malignant transformation often accompanied by an accelerated clinical history and pain. Following their intact excision, these lesions are best treated with high-dose fractionated radiotherapy, using the same fields and total irradiation used for adenoid cystic carcinoma. Since many of these tumours, which may have an outer core of benign adenoma, are excised intact, they seem to carry a better prognosis than primary adenoid cystic carcinoma or adenocarcinoma of the lacrimal gland.

Primary adenocarcinoma

The most common malignancy is adenoid cystic carcinoma, with primary adenocarcinoma of the lacrimal gland infrequently encountered. The latter can rapidly pervade the orbital soft tissues, temporalis fossa and cranial cavity (Figure 17), with current management being tumour debulking followed by radiotherapy. For large fungating lesions, exenteration and radiotherapy can be considered.

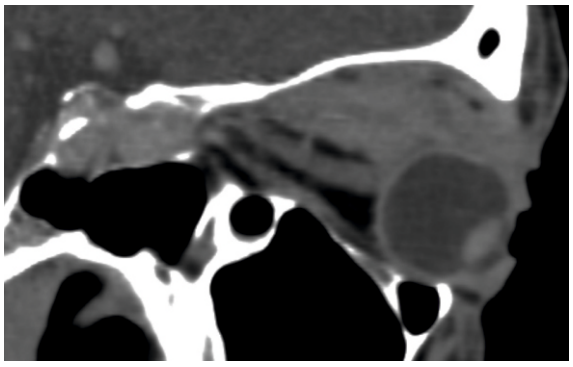

Figure 17. Sagittal CT image showing adenocarcinoma of the lacrimal gland with widespread pervasion of the orbit

Lymphoid proliferations

The lacrimal gland may be affected by the spectrum of lymphoid proliferations, this ranging from 'benign' reactive lymphoid hyperplasia to aggressive malignant B and T cell tumours[2].

Benign follicular lymphoid reactions ("reactive lymphoid hyperplasia"), can be differentiated from follicular lymphoma on immunohistochemical grounds [15, 16]. They are managed with a slowly-tapering course of oral corticosteroids or other immunomodulators [17], with low-dose orbital radiotherapy being reserved for refractive cases.

Lymphoma of the lacrimal gland may present over weeks to months, reflecting the severity of the underlying disease [18, 19, 20]. Pain and inflammatory features are uncommon, but, where

[2]Lymphoproliferative disease of the orbit ranges from benign or reactive lymphoid hyperplasia (RLH), through indeterminate or atypical lymphoid proliferations, to malignant lymphomas. The latter are almost exclusively of B cell origin, although T cell tumours are very rarely encountered.

present, are considered to carry a worse prognosis (Figures 18 - 20, showing diffuse large B cell lymphoma, DLBCL). The treatment and prognosis of lymphoma of the lacrimal gland depend on the histological type, clinical staging, and the extent of systemic disease. Patients require full assessment by an oncologist to exclude systemic lymphoma, and management may include local radiotherapy and chemotherapy. Where there is recrudescence of disease following treatment, further macroscopic debulking of tumour can be performed.

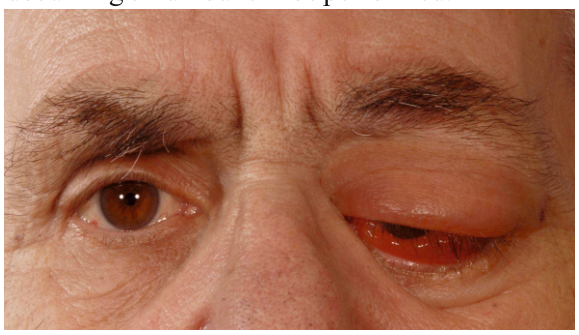

Figure 18. Presentation of diffuse large B cell lymphoma of the lacrimal gland, in this case with inflammatory signs, including painful proptosis and ptosis

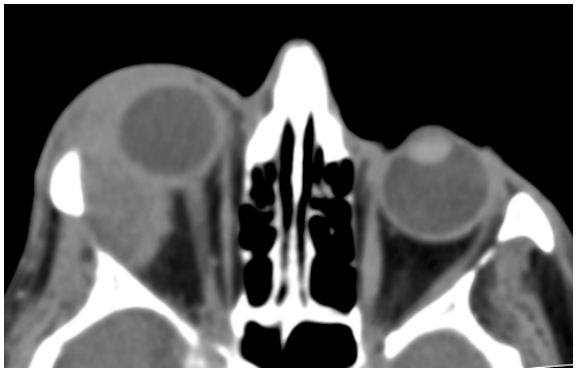

Figure 19. CT scan identifying biopsy proven diffuse large B cell lymphoma of the lacrimal gland

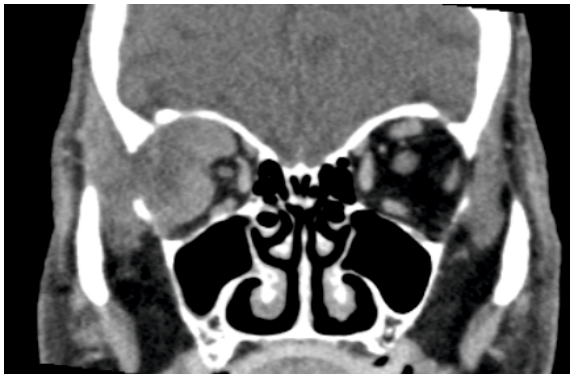

Figure 20. Regional recurrence of diffuse large B cell lymphoma following chemotherapy and radiotherapy, involving superior and lateral rectus muscles, and temporalis fossa

Metastatic disease

Secondary metastatic lesions are rarely seen in the lacrimal gland (Figure 21) and they usually carry a poor prognosis. Treatment of such deposits reflects that for the primary tumour, but generally consists of orbital irradiation, with or without chemotherapy. Finally, orbital exenteration can be useful as a palliation for fungating tumours of the lacrimal gland.

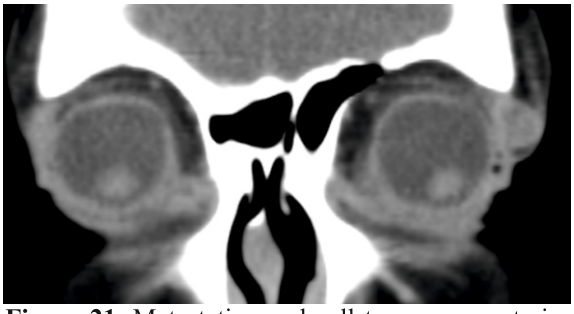

Figure 21. Metastatic renal cell tumour on anterior surface of lacrimal gland

Summary for the clinician

Keypoints for the clinician:

- The majority of lacrimal gland lesions are infective or neoplastic.
- Empirical treatment with corticosteroid is dangerous because it can mask malignancy, obscure the histological picture, and delay the diagnosis.
- A biopsy should always be performed before initiating steroid treatment
- Non-steroidal drugs and antibiotics are used to treat acute dacroadenitis, but malignancy should be suspected if there is little clinical response, or there is residual enlargement of the gland after a few weeks.

The presenting features of benign and malignant lacrimal gland disease can be similar, and for this reason a biopsy should be considered for any lesion that does not respond within a few weeks to medical therapy. The best imaging remains high-resolution CT, which usually allows the clinician to differentiate a 'benign' pleomorphic adenoma from malignant epithelial neoplasias. The correct approach to the former is intact excision without prior biopsy, this carrying a good prognosis. For diffuse lesions in which a biopsy has identified malignancy, management consists of debulking and fractionated high-dose radiotherapy, but despite treatment the prognosis remains poor. Adjunctive intra-arterial chemotherapy might play a role in future, and

brachytherapy, which treats a limited field, is not appropriate for a malignancy which tends to pervade the orbit and cavernous sinus.

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