Lacrimal Gland Lesions (10% orbital lesions)

- Epithelial tumors (20%)
  - Benign (55%)
    - Ductal epithelial cyst (dacryops) – 17% of lacrimal gland lesions and 2% of orbital lesions
    - Pleomorphic adenoma (10-12% of lacrimal gland tumors)
  - Malignant (45%)
    - Adenoid cystic carcinoma (60% of malignant tumors)
    - Malignant mixed tumors (20%), adenocarcinoma NOS (10%), mucoepidermoid carcinoma (5%)
- Non-epithelial lesions (80%)
  - Inflammatory lesions
  - Infectious lesions
  - Lymphomas / leukemias
  - Other

Lacrimal Gland Tumors

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PRESENTATION TITLE

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Dr. Nora Laver declares she has no conflict of interest to disclose.

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PRESENTATION TITLE

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PRESENTATION TITLE
Orbital / Lacrimal Gland Lesions
Useful diagnostic Information

<table>
<thead>
<tr>
<th>MOST LIKELY BENIGN</th>
<th>MOST LIKELY MALIGNANT</th>
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<tbody>
<tr>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Present for years</td>
<td>Present less than 1 year</td>
</tr>
<tr>
<td>Painless</td>
<td>Painful or Anesthetic</td>
</tr>
<tr>
<td>Bilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Soft, rubbery, mobile</td>
<td>Hard, fixed</td>
</tr>
<tr>
<td>No bony changes or simply bone molding</td>
<td>Bone Destruction</td>
</tr>
</tbody>
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Clinical Presentation Case 1

A 43-year-old woman noted swelling and pain around her right eye for two weeks. She denied trauma, visual change or diplopia.

Following ophthalmic examination, she was placed on prednisolone acetate and gatifloxacin eye drops every two hours to the right eye.

The following day she noted worsening swelling and pain and was started on prednisone 40 mg daily by mouth and amoxicillin/clavulanate three times daily for a potential diagnosis of pseudotumor.

Ophthalmologic Examination Case 1

• Visual acuity was 20/30 in the right eye
• Her pupils were round, equal, briskly reactive, and without a relative afferent pupillary defect.
• Extraocular motility and confrontational visual fields were full in both eyes.
• Intraocular pressures were 21 mmHg OD and 13 mmHg OS.
• External examination of the right eye revealed a pink, temporal mass in the fornical conjunctiva, measuring 2.5 x 2.5 x 2.0 cm.
• There was no proptosis.
• CT scan of the orbits revealed a small extraconal mass in the lacrimal gland fossa of the right orbit.

Histopathology

Cyst lined flattened epithelial lining

Dacryops

• Cyst of the lacrimal gland duct that presents typically in young adults and middle-aged patients with female preponderance.
• Usually arises from the palpebral lobe of the lacrimal gland as a mass in the subpalpebral conjunctival fornix, developing spontaneously, following an episode of dacryoadenitis, or more rarely following conjunctival inflammatory or scarring conditions.
• Painless mass that can become inflamed and tender.
• Due to slowly progressive mass effect of the enlarging cyst, the globe can be displaced and motility can be restricted.
• Unclear etiology. Inflammation around the tear ducts or trauma to the tear ducts might cause hypersecretion of tears, destroy the contractility of the duct, weaken the walls, constrict the fornical opening, and lead to passive dilation of the duct with cyst formation.
Management

- Treatment for symptomatic dacryops often involves local resection through a superotemporal conjunctival fornical approach.
- Some dacryops will resolve with topical antibiotic/steroid ointment. Simple puncture and aspiration of the cyst can be performed to fistulize the cyst onto the conjunctival surface but closure and recurrence is a problem.

Clinical Presentation Case 2

- A 39-year old African male sought treatment for progressive proptosis of his left eye, decreased vision, and binocular vertical diplopia worsening over two years.
- At presentation his best corrected visual acuity was 20/25 OS, intraocular pressure of 37 mmHg and no afferent pupillary defect. A month later his visual acuity decreased to 20/60 in the left eye.
- There was no obvious exophthalmus present at that time. He was lost to follow up.

Ophthalmologic Examination Case 2

- He returned to the clinic 8 months later now with a visual acuity of 20/200, pinhole 20/40 OS, with a positive afferent pupillary defect and IOP of 25 mmHg OS.
- He had 7 mm of exophthalmos on the left, as well as choroidal folds and blurred left disc margins.
- Humphrey visual field revealed a left inferonasal defect consistent with the left supero-temporal orbital mass.
- He had limited extraocular muscle motility but showed no pain.

Clinical Presentation Case 2

Left eye proptosis, 7 mm exophthalmus
Magnetic resonance imaging of the orbit revealed a well-defined, heterogeneous mass measuring 21mm x 23 mm, likely arising from the left lacrimal gland.

**Surgical treatment**

The mass was excised completely via a lateral orbitotomy.

The lesion appeared circumscribed and entirely excised.

**Clinical Management**

- The patient’s best corrected visual acuity was 20/50 on postoperative day 1.
- On day 2, his BCVA was 20/30 with no afferent pupillary defect, IOP of 15 mmHg and color vision 11/11.

**Post Surgical day 2**

**Histopathology**

The tumor showed anastomosing trabeculae of epithelial cells with well-formed ductal structures closely associated with a myxochondroid stromal component.
Growth patterns and cells

- Squamous Differentiation
- Tubular growth pattern

Cellular patterns

- Basaloid
- Plasmacytoid

Atypical Cytomorphology

- Hypercellularity, cellular pleomorphism, nuclear hyperchromasia, nuclear enlargement and mitotic figures

Atypical cells with capsular involvement

- Cells in cycle – Ki67 immunostain
**Diagnosis**

- **PA vs Pleomorphic adenoma with atypia vs Intracapsular carcinoma**
  - The changes were focal, therefore a diagnosis of atypical pleomorphic adenoma was rendered. However, it was discussed with the surgeon the higher probability of local recurrence and the fact that the lesion bordered on an intracapsular carcinoma.
  - Close follow-up with images has not shown local recurrence, 3 years and a half post surgery.

**WHO Classification of Carcinoma Ex PA**

- Non-invasive CXPA – intracapsular
- Minimally invasive CXPA (< 1.5 mm invasion)
- Widely invasive CXPA (>1.5 mm) with Her-2 overexpression
  - Di Palma proposes two prognostically relevant categories:
    - Early CXPA
    - Widely invasive CXPA (> 6 mm invasion)

**Diagnosis**

- Pleomorphic adenoma typically presents as a well-defined mass showing cytologically benign tumor cells of epithelial derivation demonstrating both epithelial, myoepithelial and mesenchymal differentiation.
- The reported proliferation rate is low measured by Ki67 immunostaining (1-5%).
- Although uncommon, pleomorphic adenomas with atypia or features of frank malignancy have been described.

**Discussion**

- Tumor extension through a fibrous capsule causes concern for malignant transformation, especially if there is parenchymal invasion of individual tumor cells.
- However, capsular involvement in the absence of abnormal cytomorphologic changes is an acceptable feature of benign mixed tumors.
- Hypercellularity is acceptable if abnormal cytomorphologic features are absent (including high mitotic rate).
- Morphologic atypia, such as enlarged, pleomorphic or hyperchromatic nuclei and frequent or abnormal mitoses, is more indicative of carcinomatous transformation.

**Discussion**

- Tumors with mild or focally limited cytologic atypia are designated as *atypical mixed tumors* and indicate an increased likelihood of malignant transformation if the tumor recurs.
- If prominent abnormal cytologic features are confined within the capsule, the term *intracapsular carcinoma, carcinoma in situ or noninvasive carcinoma ex mixed tumor* are appropriate.
- *Carcinoma-ex PA* displays capsular infiltration, hypercellularity, cellular atypia, hyalinization, increased mitosis (10 x HPF, 35% increased cells in cycle), necrosis, and vascular invasion.
- Malignant transformation occurs in 6.2 % of PAs, and incidence increases with length of history (1.5% at 5 years, 10% at 15 years).

**PLAG1 and HMGA2 Gene Fusions in PA**

- Translocations or intra-chromosomal rearrangements with breakpoints affecting 8q12 (>50% of cases) and 12q14-15 (10-15% of cases).
- Translocations lead to gene fusions involving the transcription factor genes *PLAG1* (PA gene-1) and *HMGA2*.
- *PLAG1* encodes a DNA-binding zinc protein (cell cycle progression).
- *HMGA2* (high mobility group) functions as an architectural transcription factor regulating AT-rich DNA (chromatin structure).
- These fusions have not been found in other histopathological subtypes of salivary gland neoplasms.
Gene Fusion in Carcinoma-Ex-PA

- Malignant component is usually a poorly differentiated adenocarcinoma or undifferentiated carcinoma. May be of any other subtype (MEC, salivary duct carcinoma, ACC).
- Express PAs specific gene fusions – PLAG1 and HMGA2 along with amplification of multiple genes within 12q13-15 (MDMs, HMGA2-WIF1, TP53 mutation, deletions of 5q21.3-23.1, gains of 8q12.1 (PLAG1) and 8q22.1-q24.1 (MYC) and amplifications of HER2).

Management

- Pleomorphic adenomas of the lacrimal gland are removed by superolateral orbitotomy through an eyelid crease incision with an extraperiosteal approach.
- Complete excision of the mass and its capsule is required; previous incisional biopsy is not recommended since it may impede complete removal of the lesion or subsequent tumor recurrence.

Clinical Presentation Case 3

- 98 y old female with a 3 year history of an orbital mass with decreased vision in her left eye.

CT Imaging

Left orbital mass displaying both solid enhancing and cystic components. The epicenter of the mass appears to be in the left lacrimal gland. There is left proptosis with medial displacement of the optic nerve and extraocular muscles. There is no definite osteolysis of the orbital walls; however, there is bone remodeling with depression of the orbital floor. No evidence of intracranial extension of the left orbital mass.

Histopathology

**Adenoid Cystic Carcinoma**

- Is more common in the lacrimal gland than mucoepidermoid carcinoma.
- Bimodal presentation in the second and fourth decades, with some occurring in the first decade.
- CKIT (CD117) overexpression does not appear to correlate in the clinic with the use of imatinib (shows low efficacy).

**MYB-NFIB Gene Fusion in ACC**

- Translocation of t (6;9)(q22-23;p23-24) leads to fusion of the MYB oncogene to the transcription factor NF1B.
- MYB belongs to a family of proteins that functions as transcriptional regulators.
- The fusion gene results is the over-expression of the MYB protein.

**Management**

- If a lesion is small and circumscribed it can be completely removed.
- If extensive involvement orbital exenteration and possible bone removal maybe necessary.
- Supplemental radiation and chemotherapy in advanced cases.
- Poor prognosis.

**Selected References**