Primary Orbital Tumors
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• No financial disclosures

Orbital Tumors

• Vascular Tumors
• Neural Tumors
• Fibrous/Mesenchymal
• Lacrimal Gland
• Lymphoid
• Optic Nerve Tumors

Cavernous Hemangioma
Cavernous Hemangioma

- Is the most common primary orbital neoplasm
- Benign vascular tumor
- Middle age women
- Low-grade proptosis
- Spares vision and ocular motility

CT

Well circumscribed, smoothly margined with increased density

B Scan

A Scan
- Well circumscribed
- High reflectivity that correspond to the intralesional septa

Cavernous Hemangioma

Well-circumscribed, encapsulated lesion

Orbital Tumors. Henderson 1994
Cavernous Hemangioma

Pathology
• Large, round, oval vascular spaces lined by endothelium
• Thick fibrous septa that may contain smooth muscle.

Management
• Indications for surgery:
  – Diplopia
  – Compression of the optic nerve (Visual field loss)
  – Optic nerve swelling
  – Optic atrophy
• Small lesion can be monitored

Capillary Hemangioma
• “Strawberry birthmark”
• Benign tumor
• May present at birth or appear within the first 6 months of life
• Begin to decrease in size between 12 and 15 months of age
Capillary Hemangioma

- Benign proliferation of CD 31 positive endothelial cells
- Concern for amblyopia
- Treatment: Propranolol, surgical resection

Orbital Lymphangioma

- Clinical onset in children younger that 10 years of age
- It may diffusely involve the orbit, conjunctiva and lids
- Slow growing lesion
- Presents with proptosis, blepharoptosis and restriction of eye movements
- May enlarge during URI
Vertical/Axial
ON
Posterior to Equator
Cross-section
ON
Irregular Structure
Low-medium reflectivity
Irregular lobulated mass
Cystic components
No central enhancement of mass to suggest solid structure

Lobular lesion with fluid levels

Orbital Lymphangioma

- Lymph-filled spaces of different sizes
- Lined by endothelium
- Septated by thin delicate walls
- Hemorrhage in the lesion produces a “Chocolate Cyst”
Orbital Lymphangioma

Management

• Complete orbital excision is usually not possible
• Limited excision indicated for ocular damage or severe cosmetic deformities
• Treatment with oral sildenafil (experimental)

Schwannoma/Neurilemmoma

Neurilemmoma

• Schwannomas account for about 1–2% of all tumors in the orbit.
• They occur mainly in individuals between 20 and 50 years of age
• Predilection for the head and neck
• Slowly growing
• Well-tolerated proptosis and extraocular motility disturbance
Schwannoma

- Encapsulated by perineurium
- Nuclei of spindle-shaped Schwannoma cells show a tendency toward palisading.
- Two growth patterns:
  - **Solid Antoni A**: Bands of nuclear palisading
    - Verocay bodies
  - **Loose Antoni B**: Myxomatous background
- Complete surgical excision should be performed
Plexiform Neurofibroma

- First decade of life
- Infiltrating lesion that may affect all aspects of the orbital soft tissues
- Overgrowth of the orbital peripheral nerves
- Enlarged orbit and excessive eyelid skin
- “Bag of worms”
- Most common manifestation of von Recklighousen disease - NF1

Histology

- Not encapsulated
- Hyperplasia of the peripheral nerve terminal branches

Plexiform Neurofibroma

- S-shaped eyelid lesion
- “Bag of worms”
- Bundles of nerve fibers
Solitary Fibrous Tumor

• Originally considered a neoplasia of the mesothelium due to their propensity to arise from the pleura and mediastinum
• Mostly benign, but malignant forms of the tumor can occur de novo
• Middle-aged patients with gradual unilateral progressive proptosis and mass effect

CT scan typically reveals a mild to moderately enhancing, well-circumscribed mass with or without local bony remodeling

Representative Picture

Solitary Fibrous Tumor

Representative Picture
Solitary Fibrous Tumor

- Patternless architecture of hypo and hypercellular areas separated by thick collagen with cracking artifact and staghorn vessels
- Perivascular sclerosis
- Bland and uniform oval to spindle cells dispersed along thin parallel collagen bands
- Minimal cytoplasm, small elongated nuclei and indistinct nucleoli

Histology

Solitary Fibrous Tumor

- Some have myxoid change, mast cells, adipose tissue and indistinct nucleoli
- Minimal pleomorphism
- No atypia no/rare mitotic figures

Solitary Fibrous Tumor

- Malignant SFT: hypercellular, moderate to marked atypia and nuclear pleomorphism, hyperchromasia, tumor necrosis, 4+ mitotic figures/10HPF
  - Including atypical mitoses
  - Infiltrative borders
SFT: Immunohistochemistry

- CD34 + (90-95%)
- CD99 : 70%
- 1/3 positive for bcl-2, EMA and actin
- Negative for: Desmin, keratin, S100, CD32, vessels CD-40 negative.

Management and Treatment

- *En bloc* surgical excision with complete tumor removal is the treatment of choice
- Malignant SFT and malignant transformation of a recurrent SFT are uncommon but have been reported.
- There is increasing evidence that supports the notion that aggressive tumor behavior does not necessarily correlate with the histologic grade, and the most important predictor of tumor recurrence is subtotal resection.

Stat-6

- NAB2-STAT6 gene fusion, resulting in a chimeric protein in which a repressor domain of NGFI-A binding protein 2 (EGR1 binding protein 2) is replaced with carboxy-terminal transactivation domain from Signal transducer and activation of transcription 6, interleukin-4 induced (STAT-6) recently identified as a consistent finding in SFT.
- 98% of cases showed nuclear expression of STAT6
- All other tumors negative except three dedifferentiated liposarcomas and one deep fibrous histiocytoma.

Granular Cell Tumor
Hertel: Base – 102; 16mm OD, 21mm OS

EOM: full OD; -2 superiorly and -2 inferiorly OS, full in medial and lateral gaze.

Granular Cell Tumor

MRI Orbits with and without contrast

2.8 x 1.7 x 1.9 cm ovoid enhancing mass in the medial orbit extending into the apex. Intraconal. Displaces ON laterally. Indistinct from medial rectus. Hypointense on T1 and T2 with enhancement

GCT Imaging Characteristics

- Hypointense on T1 and T2
  - Unlike cavernous hemangioma, hemangiopericytoma, schwannoma, and fibrous histiocytoma (iso-hyperintense on T2)

- +Enhancement with contrast
GCT Imaging Characteristics

- Hypointense on T1 and T2
  - Unlike cavernous hemangioma, hemangioendothelioma, schwannoma, and fibrous histiocytoma (iso-hyperintense on T2)

Ultrasound Characteristics

- Medium to high reflectivity
- Lack of cystic spaces
- None with bony erosion
- Tend to be Intraconal (5/6)
- Muscle involvement (5/6)
Granular Cell Tumor

Historical Background
- First described by Russian pathologist Abrikossoff in 1926 as “myoblastic myoma”
- Presents as a single, painless mass
- Histiogenesis not well understood
- Synonyms: granular cell myoblastoma, granular cell histiocytoma, granular cell neuroma, granular cell neurofibroma, and granular cell schwannoma

Granular Cell Tumors (GCTs)
- Soft tissue neoplasms of neural crest origin
- Head and neck region accounts for 45-65% of all sites
- Tongue is most commonly affected anatomic location
- Usually small (<3 cm), benign, solitary lesions located in dermis or subcutis regions of skin
- Typical age 40-60; slight female predominance, more common in African decent
- Extremely rare in orbit and ocular adnexa

GCT Histopathological Features
- Grossly, may be poorly circumscribed; tumor often removed with adjacent adipose tissue or muscle
- Cut section pale yellow-tan
- Association with marked acanthosis or pseudoepitheliomatous hyperplasia of overlying squamous epithelium (mistaken for SCC)
GCT Histopathological Features

- Cells round, polygonal, ovoid, slightly spindled in structure
- Nuclei range from small dark to large with vesicular chromatin
- Mild to moderate nuclear atypia seen (not indicative of malignancy)
- Eosinophilic cytoplasm is fine to coarsely granular
- Granules - phagolysosomes that are strongly PAS-positive, diastase-resistant

GCT Histopathological Features

- Growth pattern varies;
  - ribbons or nests divided by slender fibrous connective tissue or
  - large sheets in no particular cellular arrangement
- Older lesions may exhibit marked desmoplasia – nests of granular cells dense mass of collagen
- May involve or replace musculature; grow along muscle fibers even extend within sarcolemmal sheath
- Schwannian features on EM (postulated origin)

GCT Histopathological Features

- Immunohistochemistry: S-100, Neuron-specific enolase, laminin, and CD68 positive (lysosomal in nature),
- Tumors stain positive for myelin proteins (PO and P2), myelin-associated glycoproteins (suggests granules are myelin or myelin breakdown products)
- Do not react with antibodies for neurofilament proteins or GFAP
- Negative for HMB-45, CK, EMA and desmin

GCT Histopathological Features

- Rare usually benign lesion of the orbit; (1/52 malignant in orbit from metastasis)
- Average age 42; slight female predominance
- Diplopia and gaze restriction
- Imaging: well circumscribed often inferior orbit with muscle involvement
- Hypointense on T1 and T2
- Pathology: Granular cytoplasm, PAS+, S100+, CD68+, NSE+
- Treatment: complete surgical excision

Summary
Rhabdomyosarcoma

- Most common soft tissue sarcoma of the head and neck in childhood; 10% present in the orbit
- Presents on average at age 7 (birth to 7th decade)
- More common in boys
- Rapid growth
- Can cause fulminant proptosis
- Can mimic inflammatory disease

Imaging/Presentation

- Rapid proptosis over weeks
- Superior orbit most frequently involved
- Deceptively well-circumscribed lesion
- Subtle bone erosion can be present
- Metastatic spread uncommon but goes to lung, bone and bone marrow hematogenous if untreated
Presentation

- Local spread to orbital bones
- Can extend intacranially

Imaging

- Usually extraconal (37-87%)
- Intra and extraconal (13-47%)
- Superonasal (esp embryonal)
- Inferior (alveolar)
- No enlargement of muscle belly
- Early stages well circumscribed, later pseudocapsular invasion

Biopsy

- Incisional or excisional based on clinical and imaging findings
- Fine needle aspiration can be performed but limited material may be insufficient for diagnosis
MRI: extension through orbital septum, homogeneous enhancement, globe displacement laterally and inferiorly

Pathology

- Three histologic subgroups
  - Embryonal: majority of cases
    - 50-70% of cases
    - Basophilic cells with tapered cytoplasmic processes
    - May be interlacing fascicle
    - Cross striations may be seen
  - Pleomorphic: almost exclusively in adults (6th decade median)
  - Alveolar
Rhabdomyosarcoma

- Three types: embryonal, alveolar, pleomorphic

Embryonal

Botryoid

- Histopathology similar to embryonal
- Conjunctival fornix appears “grape like”

Pleomorphic
Pathology

- Alveolar (20-30%) of orbital cases
  - Ill defined aggregates of poorly differentiated cells loosely arranged and separated into irregular ovoid spaces by thin fibrovascular septa in alveolar pattern
  - Any focus of alveolar morphology is sufficient to classify as alveolar

Immunohistochemistry

- Desmin (90%)
- Muscle specific actin, myoD1 (71-91%)
- Myogenin (90%) more in the alveolar
Genetics

- RMS occurs more commonly in familial syndromes like Li-Fraumeni familial cancer syndrome (associated with p53 mutation), neurofibromatosis, Noonan, Beckwith-Wiedemann and Costello syndromes.
- Alveolar t(2;13)(q35-37;q14): most common resulting in 5’PAX3 sequences fused to 3’FKHR sequences unfavorable
- T(1;13)(p36;q14)

Staging

- Essential to treatment approach
- Most common staging classification established by Intergroup Rhabdomyosarcoma Study Group
  - Group 1: completely resected, no microscopic spread
  - Group 2: microscopic residual disease
  - Group 3: gross disease residual after disease
  - Group 4: distant metastasis at presentation
    - Since most have small incisional biopsy most Group 3
    - Orbit is a favorable site

Treatment

- Group 1: chemotherapy (vincristine + actinomycin D) without radiation
- Group 2: chemotherapy (vincristine + actinomycin D) and a reduced dose of 41.4-Gy conventional fractionated radiation
- Group 3: (vincristine + actinomycin D + cyclophosphamide or vincristine + actinomycin D + ifosfamide or vincristine + actinomycin D + etoposide) and 50.4-Gy conventional fractionated irradiation
- Group 4 patients: Intensivised chemotherapy

Prognosis

- 3 year survival rate
  - Group 1: 91%
  - Group 2: 94%
  - Group 3: 80%
- Histopathology
  - Embryonal: 94% five year survival
  - Alveolar: 74% five year survival
  - Orbital in infants less 1 year: more aggressive
  - Paranasal RMS that secondarily invades orbit is lower than pirmary
Lacrimal Gland Lesions

Pleomorphic Andenoma/Benign Mixed Tumor

Benign Mixed Tumor
- Accounts for 50% of epithelial tumors of the gland
- Male predominance
- Painless proptosis
- Rarely produces diplopia or visual decrease
- Eye is displaced inferonasally

Echography
- Medium to Medium-high reflectivity
- Moderate Attenuation
CT scan

- Pressure indentation and accentuation of the lacrimal fossa region
- Rounded ovoid lesion flattening the sclera.

Benign Mixed Tumor

- Macroscopically the tumor is well circumscribed and pseudoencapsulated
- Fleshy bosselated appearance

Pleomorphic Adenoma

- Locally invasive tumor
- Indents globe
- Composed of areas of epithelial differentiation interposed with areas of myxoid metaplasia
- Excise in toto to reduce risk of malignant transformation
Micro

Epithelial elements

Mesenchymal elements

Keratin-filled cysts

Proteinaceous material

Ducts, cords, tubules

Courtesy Dr. Dubovy

Courtesy

Proteinaceous material
Mesenchymal section – cartilaginous elements

Intact capsule

Area of tumor breaking through capsule
Prognosis and Management

- Mortality rate is less than 10%
- Deaths due to multiple recurrences and intracranial extension
- Treatment: En bloc excision
- Rupture of pseudocapsule may lead to recurrence and malignant transformation

Malignant Mixed Tumor
Malignant Mixed Tumor

- Represents a pleomorphic adenoma that has undergone malignant degeneration
- Patients tend to be older than those with pleomorphic adenoma

Malignant Mixed Tumor of the Lacrimal Gland in a Teenage

Malignant Mixed Tumor

- May manifest in three ways:
  - Incompletely excised, recurrent pleomorphic adenoma
  - Evolve from a previously unrecognized pleomorphic adenoma
  - Rapidly developing symptoms in a patient with unremarkable clinical history

Malignant Mixed Tumor

- Globoid, well-circumscribed mass
- Bony excavation of the fossa of the lacrimal gland.
- Computed tomography is the imaging modality of choice to investigate for bony involvement
Malignant mixed tumor with disorganized elements

Malignant mixed tumor with disorganized elements

Adenoid Cystic Carcinoma

- Second most common epithelial neoplasm of the lacrimal gland
- 60% of cases occur in women
- Average at presentation is 40 years
- Biphasic age distribution
- Occasionally develop in children
Adenoid Cystic Carcinoma

- Propensity for perineural invasion and can present with pain and/or numbness, blepharoptosis and ocular motility deficits
- Patients are generally symptomatic for a short period of time (Less than a year)

CT SCAN

- Generally reveals a globular, rounded lesion
- More irregular and serrated borders that those seen in pleomorphic adenoma
- Infiltrating character of the lesion
- Bone changes in 80% of cases

Adenoid Cystic Carcinoma

Histology

- Five histologic patterns:
  - Cribriform (Most common)
  - Sclerosing
  - Basaloid (Solid)
  - Comedocarcinoma (Areas of central necrosis)
  - Tubular
Adenoid Cystic Carcinoma

- Most lesions composed of nests of basaloid cells

Cribriform

- Myxoid and hyalinized elements trapped in the centers of the nests of cells
- Swiss Cheese

Sclerosing

- Elongated cords of epithelial cells with a dense hyalinized stroma

Basaloid/Solid

- Poorly differentiated with large basophilic nuclei and scant cytoplasm in solid epithelial lobules
- Worse prognosis
- 5 year survival rate of 21% vs. 71% if not basaloid
- More frequently in patients older than 40.
Comedocarcinoma

Areas of central necrosis

3/28/2016
Perineural invasion

Prognosis and Management

• Biopsy through the lid without violating the periorbit
• Exenteration of orbital contents with removal of potential bone involvement (Survival rate 20% at 10 years)
• Patients die of intracranial spread due to perineural invasion
• Pulmonary metastasis are frequent

Treatment

• Controversial
• Surgery with or without bone removal and adjuvant radiotherapy
• Radiotherapy is often initiated in cases of perineural invasion

Treatment

Long-Term Outcomes of Neoadjuvant Intraarterial Cytoreductive Chemotherapy for Lacrimal Gland Adenoid Cystic Carcinoma

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\(^2\)Department of Otolaryngology, University of Miami Miller School of Medicine, Miami, Florida

• Eight patients with an intact lacrimal artery had significantly better outcomes for survival (100% vs. 28.6% at 10 years), cause-specific mortality, and recurrences (all \(p<0.002\), logrank test) than conventionally treated patients from this institution
• Neoadjuvant IACC appears to improve overall survival and decrease disease recurrence.
• An intact lacrimal artery, no disruption of bone barrier or tumor manipulation other than incisional biopsy are factors responsible for favorable outcomes
Mucoepidermoid Carcinoma

Mucoepidermoid Carcinoma arising in ocular or ocular adnexal structures is rare and has been reported to occur in the conjunctiva, lacrimal gland, and lacrimal sac.
- Median age group 53 years
- Male predominance

Histology
- Tumor contains epidermoid (squamous) and mucin producing cells
- Mucoepidermoid carcinoma is locally aggressive;
- Metastases have not been described in any of the conjunctival or lacrimal sac cases and only rarely occur in patients with the tumor arising in the lacrimal gland

Management
- Attempt local cure by wide local excision or exenteration
- Very poor prognosis
Salivary Gland Tumors

Table I. Histology types for benign salivary gland tumors.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>43</td>
<td>72</td>
</tr>
<tr>
<td>Warthin’s tumor</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>Mucous metaplasia adenoma</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>74</td>
<td>100</td>
</tr>
</tbody>
</table>

Table II. Histology types for malignant salivary gland tumors.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucoepidermoid carcinoma</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>3</td>
<td>21</td>
</tr>
<tr>
<td>Acinic cell carcinoma</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>Carcinoma ex pleomorphic ade.</td>
<td>4</td>
<td>21</td>
</tr>
<tr>
<td>Epithelial-myoepithelial carcinoma</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>100</td>
</tr>
</tbody>
</table>

Ocular Adnexal Lymphoma

- Group of lymphoid neoplasms arising in the adnexa:
  - Eyelids, conjunctiva, lacrimal gland and orbital soft tissue
- Most common primary orbital malignancy in adults
  - 10% of all adult orbital neoplasms vs. 1.5% of conj. tumors
  - 2% of all non-Hodgkin lymphomas (NHLs)
  - 8% of all extranodal lymphomas
- Epidemiology
  - Increasing incidence
    - 6.3% annual increase in the incidence between 1975 and 2001
Ocular Adnexal Lymphoma

- **Classification**
  - Working Formula (1982)
  - Revised European American Lymphoma / REAL (1990’s)
  - REAL / WHO (2008):
    - Cell type, morphology, immunophenotype and cytogenetics
    - Precursor & peripheral B-cell, precursor & peripheral T-cell, NK cell and Hodgkin lymphoma
    - Majority of ocular adnexal lymphomas are neoplasms of peripheral B-cells
    - Rarely arise from peripheral T-cells, NK-cells or as a Hodgkin lymphoma

- **Clinical presentation**
  - Orbital or conjunctival masses with associated signs:
    - proptosis, ptosis, diplopia, extraocular muscle restriction
    - +/- salmon-colored conjunctival patch
  - Imaging
    - Masses mold to globe and orbital bone on CT

CT Comparison

Lymphoid Proliferations

- **Lymphoproliferative disease spectrum**
  - *Reactive lymphoid hyperplasia*
    - Reversible proliferation due to antigenic stimulus
    - Follicular and diffuse patterns
  - *Atypical lymphoid infiltrate*
    - Not classified as reactive hyperplasia or lymphoma
  - *Malignant lymphoma*
    - Neoplasms of lymphocytes: B-cells, T-cells and natural killer cells
    - “Lymphoma” is used to describe lymphoid neoplasms that present as solid tissue masses
    - Whereas “leukemia” denotes a presentation consisting of extensive bone marrow and peripheral blood involvement
Lymphoid proliferations

Benign (reactive) vs. Malignant?

- Anatomic location
  - 30% of orbital, 26% of conjunctival and only 10% of eyelid lymphoid proliferations are lymphoid hyperplasias (Knowles & Jakobiec)

- Morphology – nuclear margins, nucleoli, mitoses

- Colonality - polyclonal vs. monoclonal
  - Flow cytometry (κ or λ light chain restriction)
  - Immunohistochemistry
  - Gene rearrangements (PCR, Southern Blot)
    - Immunoglobulin heavy chain (IgH), κ or λ light chain

- Cytogenetics (Fluorescent In Situ Hybridization / FISH studies)
  - t(14;18) - IgH/BCL2 (follicular lymphoma)
  - t(11;14) – CCND1/IgH (mantle cell lymphoma)

Gene Rearrangement

- Detects monoclonality via PCR or Southern blot with primers for the variable (V) and joining (J) regions of the IgH, κ and λ genes

Flow Cytometry

- Yellow fusion signals demonstrate the presence of:
  - IgH/CCND1 (t(11;14)(q13;q32)) rearrangement (mantle cell lymphoma)
OAL Subtypes

• Vast majority are NHL of B-cell origin:
  – Extranodal marginal-zone lymphoma
  – Follicular lymphoma
  – Diffuse large B-cell lymphoma
  – Chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL)
  – Mantle cell lymphoma

• Other:
  – Burkitt lymphoma
  – T-cell lymphomas (NK cell, peripheral NOS)

Extranodal Marginal-Zone Lymphoma

– Derived from peripheral B-cell neoplasms that resemble the cells comprising the marginal zone of lymphoid follicles

• Most common ocular adnexal lymphoma
  – 40-70% of all orbital lymphomas
  – MALT (mucosa associated lymphoid tissue) type lymphoma when involving the conj, lacrimal sac or gland
    • Analogous to the MALT lymphomas originally described in 1983 by Isaacson and Wright

Extranodal Marginal-Zone Lymphoma

– Typically presents in the 5th to 7th decade of life
– Median age of 65 years
– M:F ratio of 1:1.5
– Bilateral in 10-15% of patients
  • The majority (85-90%) present with Stage I disease
– Median duration of symptoms between onset and diagnosis – 7 months
– The most frequent sites of involvement:
  • Orbit (40%)
  • Conjunctiva (35-40%)
  • Eyelid (10%)
Extranodal Marginal-Zone Lymphoma

• Pathophysiology:
  – Thought to be secondary to chronic antigenic stimulation through infectious or autoimmune disease with subsequent genetic changes
    • Conjunctiva normally devoid of MALT
  • Reported infectious agents include:
    – H. pylori in gastric MALT lymphoma
    – C. jejuni in immunoproliferative small intestine disease (MALT variant)
    – B. burgdorferi in the skin (primary cutaneous B-cell lymphoma)
    – C. psittaci in the ocular adnexa
    • (although this association has not been corroborated in other studies, suggesting a possible varying geographic distribution)

Extranodal Marginal-Zone Lymphoma

• Morphology:
  – Follicular colonization
  – Lymphoepithelial lesions
  – Dutcher bodies

• Immunophenotype:
  – pan B-cell marker positivity (CD19+, CD20+, CD22+, CD79a+)
    • BCL-6, CD5 and CD10

• Cytogenetics:
  – Affect the NFκB signaling pathway
  – translocations t(11;18) and t(1;14) are often seen
  – t(14;18) involving IGH and MALT1 is more frequently seen in the ocular adnexa
Extranodal Marginal-Zone Lymphoma

- **Outcomes** are typically favorable as a large portion of patients have localized disease and low lymphoma associated mortality rates
- **Prognosis** and risk of systemic dissemination has also been found to be related to the initial anatomic site of involvement:
  - The conjunctiva has the lowest risk of systemic spread (20%), followed by orbital (35%) at intermediate risk and eyelid (65%) with the highest risk.
  - Presence of bilateral disease has not been shown to increase risk of systemic disease

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Follicular Lymphoma

• Peripheral B-cell neoplasm derived from normal germinal center B-cells
• 2nd / 3rd most common ocular adnexal lymphoma
  – Most common secondary ocular adnexal lymphoma
• Presents in middle age
• No gender predilection
• Originally described in 1925
  – Only lymphoma that was accurately diagnosed by way of morphology alone via light microscopy
    • Centrocyes – small lymphocytes with irregular nuclear borders
    • Centroblasts – large cells with prominent nucleoli

Case

• HPI: 56 year-old male with history of right orbital mass involving right lacrimal sac for 6 months
  – Firm palpable lesion beneath the lower eyelid skin and overlying the lacrimal sac.
Follicular Lymphoma

- Graded according to the number of centroblasts per high power field (HPF)
- Cytogenetics:
  - t(14;18) - Involves the IgH enhancer element on chromosome 14 and BCL-2 on chromosome 18.
- Indolent outcome with a difficult cure
- Risk of transformation into diffuse large B-cell lymphoma

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Diffuse Large B-cell Lymphoma

- Peripheral B-cell neoplasm that is derived from germinal or post-germinai center B-cells
  - High grade NHL, 30-40% of adult NHLs
  - Slight male predominance
  - Median age at presentation is 60 years
  - 50% of large B-cell lymphomas appear to be primary
  - Diagnosis is by morphology and CD20 positivity
    - Large B lymphoid cells with nuclei at least 2x size of lymphocyte

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Diffuse Large B-cell Lymphoma

- **Cytogenetics:**
  - Heterogeneous but generally consist of dysregulation of BCL-6
  - The most common gene rearrangements include BCL-6 (30%), BCL-2 (20%) and c-MYC (5-10%)
- **Treatment:**
  - Chemotherapy with CHOP was the gold standard until the introduction of anti-CD20 therapy

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  – Extranodal marginal-zone lymphoma
  – Follicular lymphoma
  – Diffuse large B-cell lymphoma
  – Chronic lymphocytic leukemia / small lymphocytic lymphoma (CLL/SLL)
  – Mantle cell lymphoma

• Other:
  – Burkitt lymphoma
  – T-cell lymphomas (NK cell, peripheral NOS)

CLL/SLL

• Peripheral B-cell neoplasm derived from naïve (pre-germinal) B-cells or post-germinal center B-cells
• Originally recognized in 1903 by Turk
  – Clinical features subsequently described by Minot and Isaacs in 1924
• M:F ratio is approximately 2:1
• Median age at presentation of 60 years
• Presents with nonspecific symptoms including easy fatigability, weight loss and anorexia.

CLL/SLL

• Immunophenotype:
  – CD5+, CD19+, CD20+, CD23+, CD10+, Cyclin D1 and BCL-6.
• Cytogenetics:
  – Trisomy 12, deletions of 11q, 13q and 17p
OAL Subtypes

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Mantle Cell Lymphoma

• Mature B-cell neoplasm derived from naive B-cells surrounding the germinal center within the mantle zone
• Median age at onset is 68 years
• 4:1 male to female ratio
• 6% of all NHLs
• First described by Mann et al in 1979
• Immunphenotype
  – Characteristically Cyclin D1 positive
• Cytogenetics:
  – (t11;14) involving IgH and cyclin D1
OAL Subtypes

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Orbital Lymphoma

• Most common in 5th to 7th decades
• Female > Male (2:1)
• Location: orbit > conjunctiva > lids
• Typically, superior/anterior orbit
  – 30% w/in lacrimal gland
• Bilateral in 10 – 17 %
  – Simultaneous: 80%
  – Subsequent: 20%

Biopsy

• FNA Bx
  – May be performed
• Open anterior approach preferred
  – Transcutaneous/transconjunctival
  – Subperiosteal brow
  – Lateral orbitotomy for posterior lesions
• Conjunctival lymphoma:
  – Both eyes should be biopsied
  – Inferior fornical biopsy is performed in the clinically uninvolved eye
• Specimen handling
  – Formalin-fixed tissue → Pathology
  – Fresh tissue → flow cytometry and DNA analysis

Staging

• Complete history
• Complete blood count
• Metabolic panel
• Serum lactate dehydrogenase levels
• B2-microglobulin
• CT of neck, chest, abdomen and pelvis
• MR of brain and orbit
• Bone marrow biopsy
Follicular lymphoma

- Second most common lymphoma in US & Europe
- Presents in middle-aged Caucasians
- Painless peripheral adenopathy
- Arises from germinal center B cells
- Nodular growth pattern
- Course is variable

Orbital Lymphomas and Chlamydia

- Chronic antigen stimulation proposed secondary to chronic *Chlamydia psittaci* infection
  - Ferreri et al, Italy, 2004
- Ruiz et al performed PCR for *Chlamydia psittaci* on 34 patients with ocular adnexal EMZB lymphoma
  - All cases negative for *C. psittaci*
- Geographic heterogeneity

Orbital Lymphomas, Chlamydia, and Doxycycline

- Ferreri et al tested 27 patients with orbital lymphoma for *C. psittaci* with PCR
  - 11/26 were positive
- All patients were treated with doxycycline, 100mg BID, x 3 weeks
  - 6/26 with complete regression (4 with Cp)
  - 7/26 with partial response (3 with Cp)

Orbital Lymphoma and Other Infectious Agents

- Hepatitis C
  - Found in up to 13% of patients with orbital lymphoma
  - May be associated with more disseminated disease and more aggressive subtypes
- *Chlamydia pneumoniae*
  - Shen et al reported on a 47 yo Chinese man with bilateral orbital MALT lymphoma
  - *C. pneumoniae* was detected by PCR
### Treatment

- **Localized disease:**
  - **External-Beam Radiotherapy (EBRT):**
    - 30 to 36 gray (Gy)
    - 20 daily fractions of 1.8 Gy
    - Excellent local control in most patients
  - **Interferon alfa-2b:**
    - Several cases with complete remission in patients after 8 weeks of intralesional injections
    - Limited to low grade lymphomas
    - Flu-like symptoms during first week after injection
  - **Intralesional injections of rituximab**
    - Have led to complete remission in several cases of MALT and follicular lymphoma
    - Follow-up is necessary

### Primary tumors of the ON

#### Intrinsic Tumors
- Optic nerve glioma (Benign)
- Malignant ON glioma
- Ganglioglioma
- Medulloepithelioma
- Hemangioblastoma

#### Tumors of the Sheath
- Optic nerve sheath meningioma
- Hemangiopericytoma

### Optic Nerve Glioma (Benign)

- 1% of all intracranial tumors
- Unilateral occurring more commonly in females
- Can occur at any age, but 75% of symptomatic gliomas occur in the 1st decade
  - Avg age 10.9
- Most are sporadic, but a strong association with NF-1
  - Neurofibromin mutation (Chr17); normally downregulates p21 ras oncoprotein
- Loss of tumor suppressor function of neurofibromin leads to proliferation of neural tumors.

(Miller, NR 2004)
Optic Nerve Glioma

Clinical
- Usually ages 0-9
- Females > males
- Unilateral proptosis often infradisplacement
- Painless
- Optic disc swelling or pallor
- Strabismus
- Associated with NF1 (25-50%)
- 1-5% of intracranial tumors
- 1% of all orbital tumors

Optic Glioma Clinical Features
Optic nerve glioma presentation:
- Visual loss/VF defect
- Proptosis, rarely gaze induced TVOs or pain

On clinical exam:
- pallor of optic disc
- swollen disc,
- rarely optociliary shunts
- choroidal folds

Optic Nerve Glioma

Imaging
- Orbital segment of ON
- CT scan: Fusiform/round enlargement of ON
- May enlarge optic canal
Optic Nerve Glioma

- Pilocytic Astrocytoma
- Circumscribed, slow growing hamartoma from neural crest tissue
- Proliferation of pilocytic glial cells and astrocytes
- Benign
- Rosenthal fibers

Management and Follow-up

- **Treatment:**
  - Excisional biopsy although margins not cleared
  - Post-op Chemotherapy with oral Temodar and stereotactic radiotherapy treatment

- **8 Month Follow-up exam**
  - Va: OD NLP OS 20/15
  - Color Va: OS 15/15
  - HVF 30-2: OS Full fields

- Repeat MRI: post-operative changes, no new enhancing lesion in the chiasm.
- Close Follow-up with guarded prognosis

Malignant ON Glioma

**Clinical**
- Adults 2nd to 8th decade
- Males > Females
- Rapid progressive ↓ Vision
- Posterior pole hemorrhage
- Neurological deficits
- Death

**Imaging**
- Nonspecific
- Diffusely thickened
- Marked enhancement
- +/- Cyst-appearing areas
“Malignant Optic Glioma of Adulthood”
- Case study of 5 patients found to have aggressive adult optic nerve gliomas
- Described the clinical presentation, natural history, and histopathology to define the syndrome of “Malignant optic Glioma of Adulthood”
- “An unusual but remarkably uniform neuro-ophthalmic syndrome that: (1) usually involves middle-aged adult males; (2) begins with signs and symptoms mimicking optic neuritis; (3) Progresses within 5-6 weeks to total blindness, and (4) ends fatally several months thereafter”

(Hoyt et al 1973)

Anaplastic Astrocytoma
18 yo female with vision loss in the right eye over 2 weeks
- OD: NLP vision
- Optic edema; Central artery and vein occlusion with significant neovascularization
- MRI of the Orbits – Diffuse enhancement and thickening of OD optic nerve, otherwise normal brain
- Normal CSF analysis and serologies
MRI

Impression:
Diffuse enhancement and thickening of the right optic nerve extending from the orbital to the intracranial segment, but not involving the chiasm

Optic nerve and Sheath biopsy

Chronic inflammatory infiltrates and changes
No pathological diagnosis!!!

Frontal-orbital craniotomy and excisional optic nerve biopsy
H&E, 40x

Mitotic Figure
Clinical Pathology

Intracranial portion of the right optic nerve specimen

- Large pleomorphic and hyperchromatic atypical cells infiltrating the nerve
- Atypical cells were strongly GFAP (+)

Clinical Pathology

Intracranial portion of the right optic nerve specimen

- The Ki67 index of the posterior margin of the tissue was 4-5%
- Olig and IDH1 stains negative; weak p53 staining

Anaplastic Astrocytoma WHO Grade III

Case Presentation

CC: 54 yo female presents with a 5 mo h/o progressive painless visual loss of the left eye with intermittent headaches.

HPI

- Symptoms began with intermittent blurred vision
- “Jelly in front of eye” with “black spots” in central vision
- Subjective change in color vision OS
- No eye pain
- Worsening left sided Headaches for past year
- MRI Brain from 11 months prior reviewed and nondiagnostic (3/2014)
CT Orbit w/o contrast

MRI Orbit post contrast

20x H&E
Optic nerve sheath meningioma

- ONSM is the 2nd most common primary ON tumor and present with painless vision loss in middle age adults
- Primary originate from optic nerve sheath (10%)
- Secondary originate from an intracranial source (90%)
- Females > males
- Triad of vision loss, optic atrophy, and retinociliary collateral vessels should point to the possibility of an ONSM “MADS”
- Management includes observation, stereotactic radiation and surgical resection +/- radiation in certain situations
- ONSMs may masquerade as more common causes of optic neuropathies

Newman et al. 2004
Management of ONSMs

Demonstrates visual loss?

No

Yes

Any of the following features present?

• Intracranial spread
• Threat to contralateral visual pathway
• Disfiguring proptosis

Observation

• Regular clinical exams 3-6 mo
• Repeat CT/MR q 6-12 mo

Radiation Therapy

• Conformal fractionated radiation therapy
• Regular clinical exams q 6 mo
• Repeat CT/MR q 12 mo

Surgical resection

• Craniotomy, transnasal or transorbital approach to debulk tumor
• +/- radiation therapy

Future Directions

Improved RT

• Reduce radiation induced damage to ON

Medical

• Progesterone receptor inhibition
  – *Mifepristone*: Small studies demonstrate improvement in 25-30%
  – Phase III trials fail to demonstrate benefit (lack of expression in late dx?)
• Next generation sequencing of meningiomas has revealed that approximately 8 percent of grade I meningiomas have AKT1 mutations.
  – Mechanism: Prevents signaling pathway that blocks apoptosis
• Trials with agents targeting these mutations are planned

Prognosis

Life

• Excellent, essentially 0% mortality

Vision

• Poor, without treatment visual loss progresses slowly
• Eventual blindness in affected eye
• Surgery offers no benefit, most cases accelerate process
• Radiotherapy beneficial in stabilizing or improving visual symptoms, >90% stable or improve
• Long-term complications of RT include dry eyes, cataracts, and radiation retinopathy in 15, 9, and 12 percent of cases

Metastatic Breast CA to Orbit (Scirrhous)
Thank You