Advances in retinitis pigmentosa and allied diseases

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Retinitis pigmentosa, congenital retinal blindness, histopathology, photoreceptor, neuronal degeneration, gene, rhodopsin, RPE65, gene therapy
This presentation will review the published histopathologic findings of patients with retinitis pigmentosa or an allied disease in whom the responsible gene defect was identified, with the outline as follows.

1. Mutations at any of over 150 genes cause forms of retinitis pigmentosa and allied retinal degenerations in humans.

2. Retinitis pigmentosa can be inherited as a dominant, recessive, or X-linked trait. Different genes can cause retinal degeneration with the same inheritance pattern.

3. The classic funduscopic features of retinitis pigmentosa can occur in patients with different gene defects because the fundamental histopathologic abnormality is the loss of rod and cone photoreceptors. Associated with these neurons’ loss are attenuated retinal vessels (due to a reduction in oxygen needs when fewer neurons are present) and intraretinal pigment deposits (from pigmented macrophages accumulating in the retina in response to the cell death).

4. A survey of cases of photoreceptor degeneration in which both histopathology was available as well as knowledge of the responsible gene defect found 24 cases with defects in a total of 12 different genes.

5. Remarkably, no reports could be found of the histopathology of recessive retinitis pigmentosa with a known gene defect, nor of an individual with common color vision deficiencies (red/green color blindness).

6. The histopathology of 8 patients with dominant retinitis pigmentosa due to rhodopsin gene mutations has been reported. Membranous swirls in the remaining rod
photoreceptors has been observed, as well as inclusion bodies possibly containing aggregates of misfolded proteins.

7. An example is provided of the histopathology of the retina and the cerebellum in a patient with spinocerebellar ataxia 7 and a defect in the SCA7 gene.

8. Three cases demonstrating persistent survival of some photoreceptor cells in patients with retinitis pigmentosa. These are the types of patients in whom therapies have a chance of preserving or restoring visual function long after symptoms of reduced vision.

9. Additional studies of the histopathology of patients with retinal degeneration with known gene defects are to be encouraged to learn at which age photoreceptors or other neurons are still available for rescue. The disease is not so rare that cases are not available (1.7 patients with retinitis pigmentosa die each day in the U.S).
ADVANCES IN ORBITAL INFLAMMATION

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Learning objectives

1. To discuss the most important inflammatory orbital lesions and their clinical frequency.

2. To familiarize the audience with the most prevalent infectious orbital pathologies.

3. To compare and contrast the most important inflammatory orbital lesions, including Grave’s orbitopathy, inflammatory pseudotumor, infections and other diseases.

I. INTRODUCTION

The orbit is the bony cavity that contains the eye, eye muscles, lacrimal gland, and neural and vascular structures that serve eye function. Numerous diseases occur in the orbit that can affect visual function. While the human globe reaches its adult size by about age 3, the full adult orbital size in terms of volume is not attained until about age 16.

A mass lesion of the orbit may cause proptosis, displacement of the eye, lid asymmetry, conjunctiva and eyelid congestion, changes in ocular motility and even decreased visual acuity. Orbital lesions may be the presenting sign of systemic diseases, such as metastatic cancer. Demographics such as age, sex, and location within the orbit may be helpful in making a specific diagnosis. Treatment of orbital lesions may be medical, such as the use of steroids or radiotherapy for inflammatory disease, and does not always require surgery.

Inflammatory conditions of the orbit, whether they be focally tumefactive or diffusely infiltrating, are the result of blood-borne inflammatory cells, since there are no indigenous lymph nodes or lymphoid aggregates in the orbit. Some orbital inflammations have a known cause (such as fungus or bacterium), and others are idiopathic (such cases would be Grave’s disease, and orbital pseudotumor). Inflammatory conditions of the orbit include both infectious and non-infectious etiologies. Inflammations and tumors comprise about 10-20% of orbital lesions (see Table 1). Inflammatory and lymphoid lesions of the lacrimal gland are seen at about 5 x greater frequency than glandular epithelial tumors. The lacrimal gland is a modified salivary gland, and therefore similar inflammatory processes and tumors occur as in the major salivary glands (i.e. sarcoid, Sjögren’s, viral adenitis, etc.). The lacrimal gland is the only location in the orbit that under normal circumstances contain lymphoid inflammatory cells. Inflammatory processes of the deeper orbit are blood-borne, and lymphoid proliferative diseases (i.e. lymphomas) are by-definition primary extra-nodal.
Table 1. Frequency of Orbital Lesions by Major Diagnostic Group

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid orbitopathy</td>
<td>50</td>
</tr>
<tr>
<td>Cystic lesions</td>
<td>10</td>
</tr>
<tr>
<td>Inflammatory lesions</td>
<td>11</td>
</tr>
<tr>
<td>Vascular neoplasms</td>
<td>4</td>
</tr>
<tr>
<td>Vascular, structural</td>
<td>1</td>
</tr>
<tr>
<td>Lacrimal gland lesions</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoproliferative lesions</td>
<td>5</td>
</tr>
<tr>
<td>Secondary tumors</td>
<td>4</td>
</tr>
<tr>
<td>Mesenchymal lesions</td>
<td>4</td>
</tr>
<tr>
<td>Metastatic tumors</td>
<td>2</td>
</tr>
<tr>
<td>Optic nerve tumors</td>
<td>3</td>
</tr>
<tr>
<td>Other and unclassified</td>
<td>5</td>
</tr>
</tbody>
</table>

**Major Causes of Orbital Inflammatory Lesions**

- **Infectious Orbital Lesions**
  - a. Orbital cellulitis
  - b. Fungal infections
  - c. Parasitic infections
  - d. Other orbital infections

- **Inflammatory Orbital Lesions**
  - e. Grave’s orbitopathy
  - f. Orbital Inflammatory Pseudotumor
  - g. Sarcoidosis
  - h. Amyloid deposition
  - i. Vasculitis
  - j. Benign lymphoepithelial lesion
  - k. Histiocytic disorders
  - l. Reactive lymphoid hyperplasia
  - m. Lymphoma
  - n. Angiolymphoid hyperplasia with eosinophilia

- **Secondary Orbital Inflammations**
  - o. Necrotic orbital tumor
  - p. Orbital foreign body
  - q. Orbital metastases
  - r. Ruptured dermoid cyst
  - s. Mucocele
  - t. Orbital blood cyst
II. CASE PRESENTATIONS

CASE NUMBER 1

Clinical Presentation: Painful left eye of 15 hour duration

A 65-year old Asian female presented to ER with acute painful, swollen left eye of 15 hour duration. The patient noticed an insidious onset of discomfort in the left eye (OS) over 3 days. The patient denied trauma or recent illness. She did not have a significant past ocular history, and was not taking any medications. She had a clinical history of hyperthyroidism and hypertension for which she was taking tapazole, rocaltrol, and atenolol. The patient had emigrated from China 5 years prior to presentation. She did not suffer from any known allergies, was a febrile and had moderate distress from pain. Her non-corrected visual acuity was 20/50 in her right eye (OD) and 20/100 in her left eye. The intraocular pressures were 16 (OD) and 74 (OS). The pupils were reactive in the right eye and sluggish but reactive in her left eye. The motility was intact OD; there were no extraocular movements OS, with a color vision of 12/12 OD; 1/12 OS and an estimated proptosis of 5mm in her left eye. Her anterior segment exam showed an edematous and ecchymotic left upper eyelid with some conjunctival inflammation present. The cornea, anterior chamber, and iris were normal. A CBC w/diff lab study was normal. She was immuno-competent; she did not have diabetes mellitus. Imaging showed a focal soft tissue lesion involving the orbit with a characteristic and subtle focal bony destruction.

The differential diagnosis included:
- Trauma
- Neoplasia
  - Secondary (metastatic, contiguous spread)
  - Primary intracranial
    - Lacrimal gland tumors
    - cavernous hemangioma
- Inflammatory/Infectious
  - Vasculitis and granulomatous (Wegener’s, Sarcoid, Temporal arteritis)
  - Fungal (Mucormycosis, Aspergillosis)
  - Bacterial (sinusitis, mucocele, periostitis)
  - Viral (Herpes)
  - Acute and subacute idiopathic inflammation
    Orbital pseudotumor
    Tolosa-Hunt syndrome
- Lymphoproliferative disorder (lymphoma)
- Vascular
  - Carotid cavernous fistula
  - cavernous sinus thrombosis
- Neuro-ophthalmic disorders
  - Cranial nerve palsies
- Thyroid eye disease.

The patient underwent an anterior orbitotomy for orbit debulking; a tissue biopsy was obtained and cultures were done.
CASE NUMBER 2

Clinical presentation: Worsening proptosis of 5 months duration.

A 42-year old man inpatient from the Shattuck Hospital in Boston presented with a left eye proptosis of 4 to 5 month duration. The patient’s clinical history included schizophrenia. He denied pain. His visual acuity in the left eye was 20/200, color 0/10, with a positive afferent papillary defect due to a compressive optic neuropathy. He had 6 mm of proptosis with a frozen globe, with no external ocular movement present. Computed tomographic (CT) scanning showed a diffuse infiltration of the orbit, with involvement of the optic nerve. The orbital mass showed poorly defined margins.

The differential diagnosis of this lesion included:

- Malignancy
  - Metastasis, lymphoproliferative disorder
- Idiopathic orbital pseudotumor
- Ruptured dermoid cyst
- Cellulitis
- Systemic vasculitis (Wegener’s)
- Sarcoidosis
- Infections (tuberculosis)

A diagnostic orbital biopsy was performed.
III. INFECTIOUS ORBITAL LESIONS

A. Orbital Cellulitis

The major causes of orbital cellulitis are sinusitis (58%), eyelid or face infection (28%), foreign body (11%), and hematogenous (4%). *Staphylococcus* and *Streptococcus* are the most common causative organisms in adults, *Haemophilus influenzae* in children. Less common organisms are *Pseudomonas* and *Escherichia coli*. Children are affected more than adults, and in children the primary focus is generally an ethmoiditis because the ethmoid sinus pneumatizes before all of the other sinuses and has a very large ostium into the nasal cavity.

Orbital symptoms include pain, eyelid edema and erythema, chemosis, and axial proptosis if diffuse disease occurs or abaxial displacement if an abscess forms. Decreased ocular motility is common, and intraocular pressure may be elevated. A rapid loss of vision from optic nerve compression, optic neuritis, or vasculitis may ensue. Orbital abscess (subperiosteal abscess) may occur, and is an emergency situation. Surgical drainage is often necessary (or CT-guided urgent aspiration may be employed to save vision). With posterior extension, cavernous sinus thrombosis, subdural empyema, and intracranial abscess may develop potentially causing a catastrophic event.
One third of patients with orbital cellulitis will have positive blood cultures. Systemic symptoms may include malaise and fever. If the cavernous sinus is involved, headache, nausea, vomiting, and decreased consciousness may supervene. The warning signs of orbital cellulitis are a dilated pupil, marked ophthalmoplegia, loss of vision, afferent pupillary defect, papilledema, perivasculitis, and violaceous eyelids.

B. Fungal Infections

Two fungal infections commonly involve the orbit, usually by invasion from the sinuses. There are the ubiquitous organisms *Aspergillus* and *Mucor* (Phycomycosis), which exist in air and soil, on skin, and as common food molds. They produce two clinical syndromes.

The first is a life-threatening infection of the sinuses involving the orbit and brain in patients with poor controlled diabetes, or in cases of underlying systemic immuno-compromising conditions such as leukemia, carcinomatosis, or burns. A tissue biopsy is necessary to establish a diagnosis. Histopathology shows necrotic tissue due to invasion of vessels by the fungus, causing infarction. The inflammatory infiltrate may be minimal in pancytopenic patients or may consist of numerous neutrophils. The organism may be identified by the size of the hyphae, the branching pattern and the presence of septa. *Mucor* shows broad, irregularly shaped nonseptate hyphae measuring 30 to 50 um in diameter and branching at right angles. *Aspergillus* species are narrower, measuring 5-10 um in diameter, they are septate, are more regular, and branch at acute angles. Culture of the biopsy material is necessary for exact speciation. Early diagnosis and aggressive therapy are necessary for survival.

The second infection is limited to the nose, orbit and sometimes brain in otherwise healthy patients. In these cases, biopsy specimens show well-formed granulomatous inflammation, often with necrotizing centers surrounded by neutrophils, histiocytes, giant cells, lymphocytes and plasma cells. The organisms are usually located in the center of the granulomatous inflammation and may not be easily found requiring fungal stains for easy identification (PAS and GMS stains). Aspergillosis is the most common fungal infection of the paranasal sinuses (causes approximately 90% of the cases). The pathogenesis is related to the fungus ability to binds to laminin and fibrinogen. The treatment depends on the presence of invasion of surrounding structures; if bone or blood vessel invasion is present, the prognosis is poor with high mortality, usually 2-6 months after the initial presentation. Five of 17 reported cases in the literature of sino-orbital aspergillosis occurring in immuno-competent patients survived the infection.

Other fungi may rarely involve the orbit including *Sporothrix schenckii* and *Blastomyces dermatitidis* among others.

C. Orbital Parasites

Many parasites may involve the orbit, but examples in North America are few and usually occur in individuals who have lived or traveled in the Middle East, Africa, Asia, Central and South America. All of these infections require excision of the affected tissues and histopathological examination for diagnosis. Cysts due to *Echinococcus Granulosus* (hydatid cyst) are probably the most frequent (up to 30% of patients with proptosis in Iraq have this infection). Other cystic infections are cysticercosis, produced
by the larval stage of the pork tapeworm *Taenia solium*. Microfilaria of *Onchocerca volvulus, Loa Loa* and adult worms of *Dirofilaria* species have been seen in the anterior orbit. *Trichinella spiralis* may localize in the extraocular muscles. Eggs of *Paragonimus* and *Schistosoma haematobium* have been reported.

Histopathological evaluation shows granulomatous inflammation, with numerous eosinophils, surrounding the residue of parasite. The Splendore-Hoeppli phenomenon refers to radiating eosinophil deposits around helminths (or fungi), attracted by the Ag-Ab complexes that form on the cuticular walls of these parasites.

**D. Other orbital infections**

**Tuberculosis** may rarely involve the orbit, spreading from the paranasal sinuses or lacrimal gland or via the blood system. On histopathological examination, typical non-necrotizing granulomatous inflammation is present. A single or few acid fast positive stain bacilli may be found in most cases (if immunosuppression is present, then numerous bacilli are found).

**Syphilitic** orbital involvement is extremely rare. A syphilitic peri-ostitis with superior orbital fissure inflammation and external ophthalmoplegia has been described.

**Dacryo-adenitis** are usually infectious and of viral etiology and is seen in children and adults. The eyelid can present with erythema laterally, and a swollen “S-shaped” deformity, and lacrimal gland enlargement on CT projecting beyond the orbital rim (in contrast to epithelial tumors, which rarely project beyond rim).

**Rhinoscleroma** is an endemic, chronic, slowly progressive granulomatous disease caused by *Klebsiella rhinoscleromatis*. The rate of occurrence is probably associated with poverty, poor hygiene, and prolonged contact with infected individuals. Rhinoscleroma is endemic in some parts of Africa, Asia, eastern Europe, South America, and Central America. The disease most frequently affects persons in the 20- to 40-year age range. The nose is the most common site of infection, although the nasopharynx, paranasal sinuses, pharynx and orbit may be involved as well. On histologic examination these masses are formed of plasma cells cells with Russell bodies and Mikulicz cells (foamy histocytes containing *K. rhinoscleromatis* as seen on gram stain). Treatment of rhinoscleroma is antibiotic therapy.

**IV. INFLAMMATORY ORBITAL LESIONS**

**A. Grave’s Orbitopathy / Thyroid-Related Orbitopathy (TRO)**

Thyroid orbitopathy is an immunological disorder that affects the orbital muscles and fat. Hyperthyroidism is seen with orbitopathy at some point in most patients, although the two are commonly asynchronous. Thyroid orbitopathy is seen most frequently in middle-aged adults (30–50 years), more commonly in women than in men (ratio of 3–4:1): it is always a bilateral process but is often asymmetrical; and multiple muscles are involved simultaneously, most commonly the inferior and medial rectus. There are no known endocrinologic or immunologic parameters to predict which patients will have ocular involvement. The disease has an immune etiology, with an anti-thyroid immunoglobulin produced called TSI (thyroid-stimulating Ig); this immunoglobulin
interacts with the receptor on the thyroid follicular cell for TSH. The thyroid gland thereby becomes autonomous.

The systemic signs of Grave’s disease include diffuse hyperplastic goiter, tachycardia, sweating, weight loss, and pre-tibial edema. Ocular symptoms and signs include dry eyes, conjunctival injection, eyelid retraction, exophthalmos, diplopia, corneal exposure, and rarely optic nerve compression (see Table 2). Graves’ disease usually runs a progressive course for 3–5 years and then stabilizes. Less than 10% of patients have evidence of infiltrative myopathy, where enlargement of the extra-ocular muscles occurs, leading to the more serious ophthalmic signs including proptosis, diplopia with extra-ocular motility imbalances, and optic nerve compression.

Orbital imaging shows increased fat lucency, as well as extraocular muscle enlargement confined to the bellies, but with sparing of the insertions and origins. On MRI the T1 is isointense and the T2 isointense to slightly hyperintense to muscle. Thickened muscles with medium to high internal reflectivity and an irregular acoustic structure are seen on echography.

Histopathological examination shows the enlarged, rubbery muscles with variable amounts of edema and infiltration with inflammatory round cells. An increased amount of acid mucopolysaccharides infiltrates the orbital tissue.

Symptomatic therapy is given until the disease stabilizes. Systemic corticosteroids or radiotherapy may be indicated for acute orbital inflammation and congestion. The orbital disease is usually progressive over 1–5 years, followed by stabilization. Eyelid recession, strabismus surgery, or orbital decompression may be offered after stabilization, as needed, to improve function and cosmesis.

**Table 2. Werner Classification** of eye changes with Grave’s disease, based on the mnemonic “no-specs”

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
<th>Mnemonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No signs, symptoms</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>Only signs, no symptoms</td>
<td>O</td>
</tr>
<tr>
<td>2</td>
<td>Soft tissue involvement</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Proptosis</td>
<td>P</td>
</tr>
<tr>
<td>4</td>
<td>EOM involvement</td>
<td>E</td>
</tr>
<tr>
<td>5</td>
<td>Corneal involvement</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
<td>Sight loss</td>
<td>S</td>
</tr>
</tbody>
</table>

**B. Orbital Inflammatory Syndrome (OIS) / Idiopathic Orbital Inflammation/ Orbital Pseudotumor**

Diffuse orbital pseudotumor is a nongranulomatous acute to subacute onset inflammatory disease with no systemic manifestations that may affect teenagers to the elderly. Most commonly it occurs in the anterior or mid orbit, and it frequently involves the lacrimal gland. It is typically unilateral but rarely may be bilateral. Uveitis and retinal detachment may be associated with scleritis.
Clinical symptoms include abrupt pain, conjunctival injection, chemosis, eyelid edema, exophthalmos, and motility restriction. A palpable mass is detected in 50% of cases. The disease should be distinguished clinically from infectious orbital cellulitis. In children, bilaterality is present more commonly (40%), with evidence of papillitis or iritis. In adults, if the presentation is bilateral, a systemic disease such as lymphoma or Wegener’s should be ruled out.

On CT scan, the posterior Tenon’s capsule shows thickening and enhancement. Extra ocular muscle swelling typically extends to involve the tendons, and orbital fat shows increased intensity (either from edema or inflammatory cell infiltration). A shaggy orbital infiltrate or discrete mass is present, which may mold to the globe or optic nerve sheath. The lacrimal gland may be enlarged. On MRI the T1 signal is hypointense and the T2 signal is hyperintense to muscle. Moderate enhancement occurs with gadolinium. On echography, the lesion has a variable shape and borders, with low to medium reflectivity, a regular acoustic structure, and weak sound attenuation. Edema in Tenon’s capsule may appear as an area of lucency behind the globe.

Histopathological evaluation shows widespread polymorphic infiltrate of lymphocytes, eosinophils, plasma cells, and polymorphonuclear leukocytes involving extraocular muscles, fibro-fatty tissues and the lacrimal gland. In the sclerosing type, the dominant feature is scarring and collagen deposition. Eosinophils can be seen (and may be accompanied by peripheral blood eosinophilia, especially in children). Lymphoid follicles and germinal centers are not typically seen (more typical of Grave’s Disease). As the disease progresses, there is fibrous replacement of muscles, fat, and lacrimal gland acini. In the sclerosing pseudotumor variant increased fibrosis and wall-to-wall congealing of all orbital contents leads to a “frozen orbit”. If the disease is specifically localized to the apex, a Tolosa Hunt syndrome is produced, with complete painful external ophthalmoplegia.

This disease is exquisitely responsive to high dose systemic corticosteroids, and can show remarkable clinical resolution within 48 hours. Slow taper over 4-6 weeks recommended, because rebound can occur. Intractable cases with progressive fibrosis respond less well to corticosteroids. Radiotherapy has some advocates. Prognosis generally is excellent, with complete resolution of disease.

C. Sarcoidosis

Sarcoidosis is a multi-system disease manifest in ocular adnexa, uvea, lacrimal and salivary glands, lungs, skin etc. The disease has a predilection to involve lacrimal gland and it is a cause of acute and sub-acute lacrimal gland enlargement or inflammation. Histopathological examination shows characteristic non-necrotizing granulomatous inflammation, giant cells and a lymphoplasmacytic infiltrate. The disease is mostly bilateral, but may be asymmetric.

D. Amyloid Deposition

Amyloid deposition may be related to systemic or localized disease. If systemic, it may be associated it with a plasma cell dyscrasia, a chronic inflammatory condition or a familiar neuropathy. Localized disease may be due to a local lymphoid proliferation, a chronic inflammatory condition or an organ-limited disease. Histopathological evaluation
of amyloid on H and E stain shows eosinophilic amorphous deposition, often situated around blood vessels. The material stains with Congo Red stain and shows apple-green dichroism under polarized light.

E. Vasculitis
   a. Wegener’s Granulomatosis

Wegener’s granulomatosis is a necrotizing granulomatosis of the upper respiratory tract, characterized by vasculitic pneumonitis, glomerulonephritis, sinusitis, and mucosal ulcerations of the nasopharynx. A limited form does not involve the kidney. The cause is T-cell immune complex formation secondary to inhaled antigens. The key features of this condition are a) a peak incidence in adults 40–50 years of age; b) men are more commonly affected than women, in a ratio of 2:1; c) the classic antineutrophil cytoplasmic antibody (c-ANCA) is positive in 80% of cases; d) 40–50% of patients may have ocular involvement (mostly contiguous from the sinus or pharynx, but it may be isolated); of those 18–22% of patients demonstrate orbital involvement, usually bilateral as a result of extension of the sinus process through a lytic bony lesion, or as a result of a vasculitis of the orbital vessels.

Symptoms are chemosis, exophthalmos, motility restriction, papilledema, and decreased vision. Ocular tissue involvement may include scleritis and episcleritis (20–38%), uveitis (10–20%), peripheral corneal guttering (14–28%), and retinal vasculitis (7–18%).

The pathology is a necrotizing granulomatous vasculitis with giant cells. However, the inflammatory infiltrate may or may not show granulomas, but mononuclear histiocytes seen (along with lymphocytes and plasma cells) with vasculitic involvement of arteries, veins and interstitial connective tissue inflammation.

The treatment consists of administration of systemic corticosteroids plus cyclophosphamide or azathioprine. Radiotherapy is of doubtful value. Improvement with systemic therapy is usual, with up to 90% remission. Patients who have the more limited form of the disease have a better prognosis.

b. Giant Cell Temporal (Cranial) Arteritis

The clinical presentation may be varied with systemic symptoms (myalgias, weight loss, jaw claudication, fatigue, headaches) and ophthalmic symptoms (transient or permanent vision loss, visual field loss – AION, ophthalmoplegia). This disease usually affects the elderly and presents with elevated ESR. The ophthalmic artery and posterior ciliary arteries may be involved. Histopathology shows a mononuclear cellular infiltration of all layers of the blood vessel wall with histiocytes and/or giant cells seen at the muscularis media and internal elastic lamina. Destruction and or loss of the internal elastic lamina, and destruction of muscularis media with fibrosis are findings that are detectable even in healed arteritis. Inflammation in orbital vessels is not a prominent feature of the disease.

   c. Polyarteritis Nodosa

This form of vasculitis affects smaller arteries (orbital as well as other). There is vessel wall necrosis, with numerous PMN’s and eosinophils present. Usually it affects
males more than females (unusual among the auto-immune diseases). Serum p-ANCA is positive in most patients.

d. Orbital Thrombophlebitis
Elderly individuals may be affected by an inflammation centered almost exclusively around the orbital veins. The inflammation is idiopathic or associated with a visceral malignancy (for example mucinous carcinoma), or and infection of the eyelids. It is considerably painful, with hemorrhage and suffusion of the lids and orbital contents. On histological evaluation PMN’s and lymphocytes are localized to the walls of veins, causing thrombosis.

F. Benign Lympho-epithelial Lesion of Lacrimal Gland

Historically, bilateral parotid and lacrimal gland enlargement was characterized by the term Mikulicz’s disease if the enlargement appeared apart from other diseases. If it was secondary to another disease, such as tuberculosis, sarcoidosis, lymphoma, and Sjögren's syndrome, the term used was Mikulicz’s syndrome.

The lesion occurs mostly in adult (50 years of age) females (60-80% of cases). The lacrimal gland shows diffuse swelling that can be asymptomatic or with mild pain. Most cases of benign lymphoepithelial lesions appear in conjunction with Sjögren's syndrome. When Sjögren's syndrome is present, the swelling is usually bilateral. In most cases, a biopsy is needed to distinguish benign lymphoepithelial lesions from chronic sialadenitis.

Histopathology shows a marked lymphoplasmacytic infiltration. Lymphoid follicles surround solid epithelial nests, giving rise to the 'epimyoepithelial islands', that are mainly composed of ductal cells with occasional myoepithelial cells. Excess hyaline basement membrane material is deposited between cells, and there is also acinar atrophy and destruction.

Treatment usually consists of surgical removal of the affected gland. Prognosis is usually good, however occasionally this condition may evolve into lymphoma, or represent occult lymphoma from the outset.

G. Histiocytic Diseases

G. Eosinophilic Granuloma (Langerhans’ Cell Histiocytosis)

Eosinophilic granuloma is the most common and benign form of the histiocytosis X group. The disease affects primarily children and teenagers (from birth to 20 years of age). It consists of a unifocal, granulomatous proliferation in the bone. Orbital involvement occurs in up to 20% of cases, most commonly in the superotemporal orbit.

Clinically, a rapid onset of displacement of the globe occurs, and painful superolateral swelling. Erythema and inflammatory signs are seen in the overlying skin. Unifocal disease is termed eosinophilic granuloma. Multifocal disease may present with multiple orbital lytic lesions and diabetes insipidus (Hand-Schuller-Christian disease),
and a multifocal disease with visceral, skin and nodal involvement (Letter-Siwe disease). A spectrum of these diseases used to be termed “Histiocytosis X”.

Orbital imaging usually shows a lytic orbital rim lesion (near the superotemporal bony rim), orbital extension may look pink and inflammatory. Histopathological examination shows numerous binuclear histiocytes, eosinophils, and giant cells with characteristic Langerhans' granules are seen in the cytoplasm. Immunohistochemical stains used to aid the diagnosis include CD1a stain and S100.

Surgical curettage generally is curative, but radiotherapy at 900–1500 cGy also may be used. The prognosis is very good.

**Orbital Xanthogranuloma (Erdheim-Chester Disease)**

The disease is characterized by subcutaneous eyelid, anterior or posterior orbital lesions presenting as indurated, waxy yellow, erythematous nodules. The patients are usually in the 6th decade of life. The disease is associated with systemic disease (plasma cell dyscrasias, multiple myeloma). On histopathology, the characteristic Touton giant cells, and foamy lipid-laden xanthoma cells are present. Necrobiosis (dissolution of collagen as a central nidus) may be present.

**Kimura's Disease**

Also called Angiolympoid Hyperplasia with Eosinophilia is a rare disease involving primarily the skin of head and neck. The inflammatory lesion is usually present in superior orbit, well-circumscribed but edges “trail off” into surrounding orbital connective tissue. In general blood eosinophilia or asthma is found more frequently in patients with skin involvement than with orbital disease.

**H. Benign Reactive Lymphoid Hyperplasia**

This disease constitutes a benign proliferation of lymphoid follicles that contain polymorphic lymphocytes that are immunohistochemically polyclonal. Benign reactive lymphoid hyperplasia (BRLH) occurs most commonly in the anterior superior orbit, with a predilection for the lacrimal gland (15%). The clinical course is indolent, with painless exophthalmos, globe displacement, and typically normal vision. A firm, rubbery mass is often palpable beneath the orbital rim, and there may be a pink subconjunctival “salmon-patch” infiltrate. Imaging shows an infiltrative mass seen in the eyelids or anterior orbit. It typically molds to the globe and other adjacent structures and may extend along the rectus muscles. On MRI the T1 signal is hypointense and the T2 signal hyperintense to muscle. On histopathology there is typically a polymorphous population of small lymphocytes and plasma cells, with mitotically active germinal centers. Treatment involves systemic corticosteroids or local radiotherapy at 1500–2000 cGy. Some lesions may require cytotoxic agents (chlorambucil) for control. There is a 15–25% chance of developing systemic lymphoma within 5 years.

In contrast, orbital lymphoma is usually a low-grade malignancy characterized by a proliferation of monoclonal B cells (non-Hodgkin's). Most commonly affected is the older age group (50–70 years). Clinically, a palpable mass may be present in the
anterior orbit. Symptoms include exophthalmos, occasional diplopia, eyelid edema, and ptosis. In 75% of cases the process is unilateral, and in 25% it is bilateral; 40% of cases are associated with systemic disease at the time of diagnosis. Imaging shows a well-defined mass that molds to encompass adjacent structures. Most lesions are located in the anterior, superior, and lateral orbit and frequently involve the lacrimal gland. A specific form of lymphoma, the MALT (mucosa-associated lymphoid tissue) lymphoma or marginal zone lymphoma has the highest frequency of occurrence in the orbit. This lymphoma is characterized by an extranodal location, a localized disease, and a distinctive histopathology of lymphoplasmacytic infiltrates, foci of follicle center cell and lympho-epithelial lesions. Most ocular adnexal lymphomas are localized at presentation and radiation therapy provides excellent local control.

V. DIAGNOSIS

Case number 1 diagnosis: Sino-Orbital Aspergillosis infection in an immunocompetent patient.

References

Case number 2 diagnosis: Inflammatory pseudotumor

Advances In Orbital Neuropathology

Charles G. Eberhart, MD PhD
Associate Professor of Pathology, Ophthalmology and Oncology
Johns Hopkins University School of Medicine
Overview

• Non-neoplastic lesions
  – Microphthalmos/pseudoglioma
  – Cephaloceles
  – Neuroma

• Tumors
  – Neurofibroma
  – Schwannoma
  – Meningioma
  – Optic Nerve Glioma

• Genetic advances in Pilocytic Astrocytoma
The ophthalmic artery and nasociliary nerve enter the orbit intraconally and, wrapping around the lateral aspect of the optic nerve, travel to the medial wall where they both give off their ethmoidal branches.

• **Non-neoplastic lesions**
  - Microphthalmos/pseudoglioma
  - Cephaloceles
  - Neuroma

• **Tumors**
  - Neurofibroma
  - Schwannoma
  - Meningioma
  - Optic Nerve Glioma

• **Genetic advances in Pilocytic Astrocytoma**
Microphthalmia

- Caused by incomplete closure of fetal cleft
- Usually unilateral
- Often with large cyst
- May be associated with chromosomal deletions (13q or 18)
- Eye can be relatively normal or totally disorganized.
- Proliferating neuroectodermal tissue in the cyst can simulate neoplasm (pseudogliomatous hyperplasia)
Microphthalmia with cyst
Cephaloceles

- Developmental malformations with brain or meninges present in orbit.
- Sometimes retain communication with brain, but this often closes.
- **Meningocele** – only meninges
- **Encephalocele** – only brain
- **Meningoencephalocele** – both present
Amputation Neuroma

- Rare
- Haphazardly entangled regenerating nerve fibers growing from end of disrupted peripheral ciliary nerve(s)
• Non-neoplastic lesions
  – Microphthalmos/pseudoglioma
  – Cephaloceles
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• Tumors
  – Neurofibroma
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• Genetic advances in Pilocytic Astrocytoma
Neurofibroma

- Sporadic or NF1 associated
- Localized, diffuse and plexiform types
- Usually arise from sensory nerves
- 6 of 1,264 (<1%) of orbital lesions (Shields)
- Localized lesions can be well circumscribed, but are not encapsulated
- Treatment is surgical excision; recurrence is frequent with larger lesions
Neurofibroma
Plexiform Neurofibromas
Schwannoma (Neurilemoma)

- Often arise from trigeminal nerves; less often from ocular motor nerves
- 14 out of 1,264 (1%) of orbital lesions (Shields). Presentation at 10-85 years of age (median 37)
- Mostly sporadic, but can be NF2-associated
- Encapsulated, and can sometimes be separated from the nerve
Schwannoma

Slow progression of proptosis (several years)
Schwannoma
Cystic Schwannoma

Dr. PS Rosenbaum EOPS 2003
Schwannoma

In contrast to neurofibroma and meningioma, schwannomas tend to “roll” along the slide and do not smear well. They also have distinctive elongated nuclei.
Orbital Meningioma

- Can be derived from optic nerve sheath (primary) or extend into the orbit from the brain (secondary)
- 29 of 1264 (2%) of cases in one orbital tumor series were primary optic nerve meningiomas (Shields)
- In the same series, 24 (2%) were secondary intraorbital meningiomas
- Primary tumors unilateral in 95% of cases; bilateral cases usually in young adults
- Primary tumors may be localized or extend along much of orbital-canalicular optic nerve length
Diffuse Process with “Tram-Tracking”

Dr. N Miller
Primary ONSMs usually not surgically curable unless accompanied by removal of optic nerve.

Dr. N Miller
Review of Johns Hopkins Cases 1968-2008 (Jain et al)

• 51 cases (21 Primary, 30 secondary)
• Mean age 45 years; 5 in children
• 2 patients with NF2
• 25 Meningothelial, 23 Transitional, 2 Angiomatous 1 Chordoid,
• 4 WHO grade II (elevated mitotic activity, brain invasion, Chordoid subtype)
Mitotic Activity In Grade II Tumor
Invasion of Lacrimal Gland and Muscle
Invasion of Optic Nerve

Equivalent to brain invasion?

Probably not
Chordoid Intraorbital Mengioma (Secondary)
Meningioma Frozen Section Diagnosis

Menigiomas smear easily and have crisp nuclear outlines with delicate chromatin.

Dr. P Burger
Optic Nerve Gliomas

- Almost all Pilocytic Astrocytomas
- 48 of 1,284 (4%) of orbital lesions (Shields)
- Can arise from orbital, optic canal or intracranial portions of the nerve
- Most in children in first decade of life
- 25% or more have evidence of neurofibromatosis type 1 (can be bilateral)
- 15% of children with NF 1 have ONGs
Anterior Orbital Presentation: Proptosis and optic disc swelling
Posterior Orbital/Canalicular Presentation

- Decreased vision (variable)
- No (minimal) proptosis
- Relative afferent pupillary defect

Asymptomatic

- Found during screening for NF1
- Found during evaluation for pale disc
CT scans showing diffuse enlargement of optic nerve
MRI Showing Intracranial Extension
Diffuse involvement of optic nerve parenchyma
Subarachnoid Proliferation of Tumor
Rosenthal Fibers
Eosinophilic Granular Body (EGB)
Natural History of PA

- Treatment generally not required
- Most remain stable throughout life and do not produce progressive visual loss
- Some spontaneously regress, often with improvement in visual function
- Rare cases increase in size associated with worsening vision
- Sporadic (non-NF1) tumors generally arise earlier and are more likely to grow
- Virtually no risk of spontaneous malignant transformation
Pilomyxoid Astrocytoma

- WHO grade II entity that is clinically more aggressive than Pilocytic Astrocytoma
- Frequently involves hypothalamus/chiasm
- Relatively monomorphous cells with mucoid background
- Perivascular orientation
- No Rosenthal fibers or EGBs
Malignant Optic Nerve Glioma

- 55 year old man
- Presented with visual Sx
- Chiasmal/optic nerve mass
- Died within 1 year of intracranial spread.
• Non-neoplastic lesions
  – Microphthalmos/pseudoglioma
  – Cephaloceles
  – Neuroma

• Tumors
  – Neurofibroma
  – Schwannoma
  – Meningioma
  – Optic Nerve Glioma

• Genetic advances in Pilocytic Astrocytoma
BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas


SHORT COMMUNICATION

High-resolution, dual-platform aCGH analysis reveals frequent HIPK2 amplification and increased expression in pilocytic astrocytomas

H Deshmukh, TH Yeh, J Yu, MK Sharma, A Perry, JR Leonard, MA Watson, DH Gutmann and R Nagarajan
Frequent Gains at Chromosome 7q34 Involving BRAF in Pilocytic Astrocytoma

Eli E. Bar, PhD, Alex Lin, MS, Tarik Tihan, MD, PhD, Peter C. Burger, MD, and Charles G. Eberhart, MD, PhD
17 of 25 PA had 7q34 gains

3 cases had activating BRAF mutations (V600E)

Bar et al, JNEN 2008
Activation of BRAF/MEK/ERK Signaling in Pilocytic Astrocytoma

Bar et al, JNEN 2008

81%
The BRAF gene duplication/amplification forms a fusion gene with unregulated kinase activity.
Tandem Duplication Producing a Novel Oncogenic BRAF Fusion Gene Defines the Majority of Pilocytic Astrocytomas

David T.W. Jones, Sylvia Kociatkowski, Lu Liu, Danita M. Pearson, L. Magnus Bäcklund, Koichi Ichimura, and V. Peter Collins

A

~2Mb

KIAA1549 (144kb)

BRAF (190kb)

Duplication

KIAA1549

BRAF 3': KIAA1549 5'

B

L  PA48  PA28  PA49  PA25  NB -ve

710bp
536bp
392bp

KIAA1549 Ex1-16
20 cases

KIAA1549 Ex1-15
7 cases

C

KEx16BEx9

5247bp, 1749aa

1158bp, 386aa

KEx16BEx11

5247bp, 1749aa

984bp, 328aa

KEx15BEx9

4929bp, 1643aa

1158bp, 386aa

D

KIAA1549Ex16

BRAFEx9

TCCCTG

GAGTG

ACTTG

ATTA

7 cases
We have identified BRAF/KIA fusion transcripts in all PA with 7q34 gains.

Sample 23
Ras/Raf Signaling Can Be Activated At Multiple Points In PA

Bar et al, JNEN 2008
Advances in Orbital Tumors

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Take-Home Points:

- A wide variety of benign and malignant neoplasms, inflammatory, and non-neoplastic conditions occur within the orbit
- Primary orbital neoplasms include epithelial tumors, bone and soft tissue tumors, lymphoid tumors, melanocytic tumors, vascular tumors, tumors of the central nervous system and its meningeal coverings, germ cell tumors, and others
- Secondary orbital tumors are either metastatic in origin, or they may secondarily invade the orbit from adjacent structures including the eyelid, conjunctiva, intraocular structures, paranasal sinuses, and nasopharynx
- The lacrimal gland is the only epithelial structure normally present within the orbit. Its epithelial tumors are identical to epithelial salivary gland tumors

Orbital Tumors:

- Orbital tumors and simulating lesions are not very common. However, the orbit is a location where a wide spectrum of neoplastic surgical pathology can occur. The Wills Eye Hospital Oncology Service reviewed 1,264 consecutive patients with a space-occupying orbital lesion over a 30-year period:
  - 810 (64%) were benign
  - 454 (36%) were malignant
  - Rhabdomyosarcoma was the most common malignancy in children (median age 7 years)
  - Lymphoma was the most common malignancy in older adults (median age 71 years)
  - Epithelial tumors of the lacrimal gland were more common in middle-aged patients (median age 40 years)
The general categories of orbital tumors are listed here, and they can be further subcategorized into specific diagnoses:

- Inflammatory lesions that simulate neoplasms;
- Cystic lesions;
- Lacrimal gland primary epithelial tumors;
- Metastatic cancer;
- Secondary tumors.
- Lymphoid tumors and leukemias;
- Osseous, fibrous, and cartilaginous tumors;
- Vascular and hemorrhagic lesions;
- Primary melanocytic tumors;
- Peripheral nerve tumors;
- Myogenic tumors;
- Fibrous connective tissue tumors;
- Lipomatous and myxomatous tumors;
- Histiocytic tumors and pseudotumors;
- Optic nerve, meningeal, and other neural tumors.

The Orbit: Normal Anatomy and Components:

- The human adult orbit measures approximately 40 mm in height, 45 mm in depth, and has a volume of 30 mL.
- The posterior and peripheral borders of the orbit are defined by seven bones of the skull, face, and nose: the frontal, zygomatic, palatine, lacrimal, sphenoid, ethmoid, and maxillary.
- The major intraorbital components are:
  - The globe;
  - The lacrimal gland;
  - Extraocular muscles;
  - Smooth muscle;
  - Fibroadipose tissue;
  - Blood vessels;
  - Peripheral nerves and sympathetic ganglia;
  - The optic nerve and its meningeal coverings; and,
  - The cartilaginous trochlea.

The Lacrimal Gland:

- The lacrimal gland is situated anteriorly in the superotemporal quadrant of the orbit. It is mostly a serous gland, and is divided into two parts, the larger orbital lobe and the smaller palpebral lobe.
- Ducts from the gland open into the superior conjunctival fornices and transmit their secretions into the tear film.
Lacrimal gland tumors account for approximately 5%-10% of orbital tumors. The histopathologic classification of these tumors is similar to the World Health Organization’s classification of salivary gland tumors. They can be divided into epithelial and non-epithelial, benign and malignant tumors. Pleomorphic adenoma (benign mixed tumor) is the most common benign tumor of the lacrimal gland. They have a propensity to recur, and they can undergo malignant transformation into carcinoma ex-pleomorphic adenoma. Non-invasive carcinomas have an excellent prognosis after complete excision, while the prognosis is guarded for invasive carcinomas. Adenoid cystic carcinoma is the most common malignant epithelial tumor of the lacrimal gland. Mucoepidermoid carcinoma are the next most common, while acinic cell carcinoma, salivary duct carcinomas, adenocarcinomas, and epithelial-myoepithelial carcinomas are exceedingly rare.

Lymphoproliferative Lesions:

- The orbit normally lacks lymphoid tissue but contains scattered lymphocytes, especially within the lacrimal gland tissue. These cells presumably are the progenitors of orbital inflammatory and neoplastic lymphoid proliferations.
- Orbital lymphoproliferative lesions involve the spectrum of benign/reactive processes (reactive lymphoid hyperplasia), to malignant lymphomas.
- The differential diagnosis may include orbital inflammatory disease.
- Orbital lymphomas are similar to those elsewhere in the body, presenting as primary tumors or as a manifestation of systemic lymphoma.
- The majority of orbital lymphomas are low-grade, non-Hodgkin lymphomas including B-cell chronic lymphocytic leukemia and marginal zone / mucosa-associated lymphoid type (MALT) lymphoma.
- Hodgkin lymphoma is rare in the orbit.

Secondary Tumors:

- Orbital metastases may involve the globe, optic nerve, intraconal and extraconal compartments.
- Secondary tumors may invade the orbit from adjacent structures including the eyelid, conjunctiva, intraocular structures, paranasal sinuses, and nasopharynx.
- Lung carcinoma, breast carcinoma, prostate carcinoma, and malignant melanoma, are the most common metastatic tumors to the orbit in adults.
- Adrenal neuroblastoma, Wilms tumor, and Ewing sarcoma are more common in children.
Reference List


