American Association of Ocular Oncologists and Pathologists Companion Society Meeting

Inflammatory and Benign Orbital Lesions

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• No financial disclosures
• No off-label usage

INTRODUCTION

• Inflammatory orbital lesions are not uncommon
  • 10-15% of Mayo Clinic cases
  • 12% of AFIP series
  • 11% of Wills Eye Hospital series*
  • 29% of orbital lesions – Erasmus MC University (Netherlands)

* Shields JA et al. Ophthamol 2004;111:997-1008

INTRODUCTION

• Discussion of interesting cases
• Practical approach to the diagnosis of inflammatory and reactive lesions
• Pathologist point of view – morphology
  • Key histological feature(s)
  • Clinical and radiographic findings
  • Differential diagnosis
Inflammatory Orbital Lesions

“Predominant” histological features

*Granulomas* → *Fibrosis* → *Vasculitis* → *Fibroblastic Proliferation*

*Acute inflammation*

*Lymphocytic infiltrate*

*Necrosis*

*Foamy histiocytes*
Inflammatory Orbital Lesions

“Predominant” histological feature

- Granulomas
- Fibrosis
- Necrosis
- Foamy histiocytes
- Lymphocytic infiltrate
- Vasculitis
- Fibroblastic Proliferation
- Acute inflammation

LESIONS OF INFECTIOUS ETIOLOGY

- Acute inflammation
- Granulomatous inflammation
- Necrosis

CASE 1

CASE 2
ORBITAL CELLULITIS

- Infection of soft tissues posterior to the orbital septum
- 90% of cases follows an ethmoid sinus infection
  - *Streptococcus, Staphylococcus and Haemophylus influenzae*
- Increased incidence in the winter
  - Methicillin-resistant *S aureus* - USA

- Medial orbital wall is thin and perforated and venous drainage – mid third of face – orbital veins
- Lesser common causes
  - Secondary to maxillary/ dental infection – anaerobes
  - Direct inoculation - trauma or surgery
  - Direct spread from adjacent periocular/ ocular tissues
  - Hematogenous spread – bacteremia

Biopsies are infrequent
- Unusual presentation
- Need for surgical debridement

Good prognosis with prompt therapy
- Intracranial complications < 2%
- Blindness up to 11%

CASE 1

- 74 yo woman
- Breast cancer and diabetes
- 4 days history of left eye swelling and itching sensation
- Treated with antibiotics
- Diplopia

Clinical picture courtesy of Dr James Garrity
CASE 1

DIROFILARIASIS

- Worldwide helmintic zoonosis
- Natural hosts: dogs and wild canids
- Humans: accidental hosts
- Transmission through mosquito bite
- Species relevant to humans
  - *D. immitis*, *D. repens*, *D. tenuis*
  - Subcutaneous nodule, visceral form
- Treatment – surgical removal

Consultation case
Orbital mass – 70y woman
ORBITAL DIROFILARIASIS

- Dirofilaria – well-known to involve eye and periocular tissues
- Orbital dirofilariasis – case reports
  - Henderson B et al. Case Rep in Radiology 2012
  - Smitha M et al. Indian J Radiol Imaging 2008

CASE 2

- 18 years old woman
- Type 1 diabetes mellitus, insulin dependent
- 4 days history of progressive right sided headache and right blurred vision
- Eating disorder

MUCORMYCOSIS

Right posterior orbital biopsy
Rhino-orbital mucormycosis is rare
- Life threatening infection
  - Diabetes mellitus and other immunodeficiency diseases
- Inhaled airborne hyphae, spore
- Angioinvasive – ischemia, necrosis
- High mortality rate

Sarcoidosis
- Epithelioid granulomas
  - Non-necrotizing (common)
  - Focal necrosis (rare)

Granulomatosis with polyangiitis
- Necrobiosis
- Vague palisading granulomas
- Neutrophilic micro abscesses
- Small vessel vasculitis
- ANCA associated vasculitis
Always rule out an infectious etiology

LESIONS WITH XANTHOMA CELLS

- Foamy histiocytes
- Touton type giant cells
- Variable features
  - Lymphoid hyperplasia
  - Necrosis
  - Fibrosis

CASE 3

CASE 3
CASE 4

ORBITAL XANTHOGRANULOMATOUS DISEASE

- Group of entities with varying clinical manifestations and associations
- Not common and poorly understood
- Non-Langerhans histiocytic disorders
- Foamy histiocytes, Touton giant cells, varying degree of fibrosis, lymphocytic infiltrate and necrosis

ORBITAL XANTHOGRANULOMATOUS DISEASE

- Adult onset xanthogranuloma
- Adult onset asthma and periocular xanthogranuloma
- Necrobiotic xanthogranuloma
- Erdheim-Chester disease
ADULT-ONSET XANTHOGRANULOMA

• Isolated xanthogranulomatous lesion
• No systemic involvement
• Adult patients (38-79 years of age)
  • No sex predilection
• Anterior orbital soft tissues
• Self-limited, does not require aggressive treatment

ADULT-ONSET ASTHMA AND PERIOCULAR XANTHOGRANULOMA

• First recognized by Jakobiec in 1993
• Bilateral yellow-orange, indurated, non-ulcerated xanthomatous lids
• Anterior orbital masses
• Adults – 22 to 74 years of age; M>F
• Underlying mechanism correlating asthma and these lesions - unknown

CASE 3

• 51 year old man
• “Bulging” left eye – past year
• Diplopia - L > R
• Past medical history
  • autoimmune colitis
CASE 3

ERDHEIM-CHESTER DISEASE

- Middle age patients (50 yrs)
- Slight male predilection
- Involves long bones, orbital soft tissues, retroperitoneum, kidney, lung, brain, skin
- Bilateral and symmetrical lesions – posterior orbital involvement
- BRAFV600E mutation – target therapy
CASE 4

• 38 years old woman
• Bilateral progressive proptosis (1 yr)
• Yellow lids for past 2 months
• Sensation of pressure behind eye

Past medical history
• Lymph node biopsy – reactive
• No history of thyroid disease
• Normal TSH
CASE 4 - DIAGNOSIS

- Morphologically - Adult-onset asthma and periocular xanthogranuloma
- Radiographic – Erdheim-Chester Disease
- BRAF V600E immunostain and molecular testing – negative
- No systemic lesions
- Xanthogranulomatous inflammation with lymphoid hyperplasia

NECROBIOTIC XANTHOGRANULOMA

- Paraneoplastic syndrome
- Patients in 6th decade (17-85 years)
- Association with paraproteinemia and other hematological diseases
- It may involve the face, trunk, extremities
- Predilection for the periorbital region

DIFFERENTIAL DIAGNOSIS

- Adult orbital xanthogranulomatous diseases (4)
  - Subtle morphological differences
  - Differences in location of lesions
  - Correlation with systemic findings
- Rosai-Dorfman disease (SHML)
- Juvenile xanthogranuloma
- Langerhans histiocytosis

Clinical picture courtesy of Dr James Garrity
**ROSAI-DORFMAN DISEASE**

Young patients
Painless LN enlargement 43% extranodal
10% ocular involvement
Intraconal mass
Benign histiocytosis NL S100+, CD1a-
Emperipolesis
Lymphophagocytosis
Variable clinical course

**ORBITAL XANTHOGRANULOMATOUS DISEASE**

• Increased IgG4-positive plasma cells are a common histopathological finding in OXGD
  • Singh K and Eberhart C. Ocul Immunol Inflamm 2010; 18(5):373-8
  • Verdijk RM et al. Orbit 2014; 33 (1):17-22
  • McKelvie et al. Ophthal Plast Reconstr Surg 2016 (epub)

• IgG4-RD diagnostic criteria – ratio IgG4+/IgG+ plasma cells >40%
  • Deshpande V et al. Mod Pathol 2012;25:1181-1192

**LESIONS WITH FIBROSIS AND CHRONIC INFLAMMATION**

• Exclude a non diagnostic specimen in small biopsies

• Not to ignore other subtle or localized morphological features that might point to another diagnosis
  • Tissue reaction around neoplasm

*Many orbital lesions have xanthomatous cells*

Lake Louise, Canada
LESIONS WITH FIBROSIS AND CHRONIC INFLAMMATION

- Involvement of lacrimal gland and adjacent orbital soft tissues
- Variable amounts of fibrosis and chronic inflammation
- No necrosis, granulomas or vasculitis

CASE 5

- 33 years old woman
- Previously healthy
- “Lump” in the LUL
- No pain
- No visual symptoms
- No history of thyroid disease or autoimmune disease
IDIOPATHIC ORBITAL INFLAMMATION

CASE 6

- 30 year old man
- Eyelid swelling
- History of chronic sinusitis and cervical lymphadenopathy
- Past history of liver inflammatory pseudotumor

IgG IgG4
IgG4 Related Orbital Disease

IDIOPATHIC ORBITAL INFLAMMATION
- Inflammatory process with no recognizable local cause in the orbit or obvious underlying systemic disease
- 5-20% orbital biopsies for a mass
  - Lacrimal gland and extra-ocular muscles
- Diagnosis of exclusion

IDIOPATHIC ORBITAL INFLAMMATION
- Variable histopathology
  - Cases with marked lymphocytic infiltrate
    - Pseudolymphoma (past)
  - Cases with marked fibrosis
    - Idiopathic sclerosing orbital inflammation

Hsuan JD et al. Arch Ophthalmol 2006; 124:1244
IgG4-RELATED ORBITAL DISEASE

- IgG4-RD involving the orbit
  - Subset of cases previously diagnosed as idiopathic orbital inflammation
- Lacrimal gland and/or soft tissues
- Consensus document* - IgG4-RD
  - Dense lymphoplasmacytic infiltrate
  - Storiform fibrosis
  - >100 IgG4+ plasma cells/hpf or IgG4/IgG > 40%

*Ishihara V et al. Mod Pathol 2012; 25:1181-1192

IgG4-RELATED ORBITAL DISEASE - CLINICAL

- Equal sex distribution
- Bilateral involvement – 50%
- Infraorbital nerve involvement
- Involvement of non orbital sites
- Recurrent or persistent disease

Sato Y et al. Pathol Int 2008; 58:465-470
Plaza JA et al, Arch Ophthalmol 2011; 129:421-428

IgG4-RELATED ORBITAL DISEASE

- Fibrosis, chronic inflammation
- Florid lymphoid hyperplasia
- Eosinophils
- Rare obliterative phlebitis
- Lower absolute numbers IgG4+ cells

Andrew N et al. Mod Pathol 2013; 26:1150-1151

LESIONS WITH FIBROSIS AND CHRONIC INFLAMMATION

- Determine if biopsy is diagnostic
- Rule out diseases with specific etiology and/or treatment
  - Infectious
  - Vasculitis
  - Thyroid orbitopathy
- IgG4RD – Follow proposed diagnostic criteria - >40% IgG4/ IgG ratio
Idiopathic orbital inflammation is a diagnosis of exclusion.

Lesions with reactive features:
- Spindle cell lesions
- Fibroblast/myofibroblast proliferation

Case 7

Case 8
SPINDLE CELL LESIONS

- Edematous, myxoid stroma
- Spindle, elongated cells
- Scattered inflammatory cells
- A few red blood cells
- Occasional mitoses, typical

CASE 7

- 70 year old man
- No significant past medical history
- 3 days history of eyelid swelling
- No pain or visual symptoms

Reactive/ granulation tissue
NODULAR FASCIITIS

- 22 year old man
- Left orbital mass
- Consultation case

Until recently nodular fasciitis was considered a reactive lesion

- Self-limited clonal neoplastic process
  - Balanced translocation t(17;22)(p13;q13)
  - Resulting in MYH9-USP6 gene fusion
- Younger patients
- Fast growing nodule – 2-3 cm

Erickson-Johnson et al. Lab Invest 2011;91:1427-33

NODULAR FASCIITIS

- Benign appearing fibroblasts and myofibroblasts
- Myxoid stroma with extravasated rbc
- Tissue culture like pattern
- Mitosis often – not atypical
- No cellular atypia
- Immunostains – weak SMA+

NODULAR FASCIITIS

- 42 year old woman
- L medial orbit lesion
- Enlarging 2 months
- Consultation case
NODULAR FASCIITIS

DIFFERENTIAL DIAGNOSIS

- Spindle cell neoplasms
- Solitary Fibrous Tumor CD34+, STAT 6+
- Neurogenic neoplasms S100+
- Smooth muscle tumors SMA+, Desmin+

VASCULAR THROMBOSIS

- 32 year old man
- Craniofacial dysmorphism
- Left eyelid/ anterior orbital nodule

INTRAVASCULAR FASCIITIS?
Always think if a lesion could be reactive/benign
Lake Mallasia, WI

QUESTIONS?