Adult Orbital Xanthogranulomatous Disease

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Lynn Schoenfield
Associate Professor, Ohio State University Wexner Medical Center
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Goals

- Be familiar with the rare entity of Adult orbital xanthogranulomatous disease (AOXGD)
- Know the 4 subtypes
- List the differential diagnosis
- Know what clinical and histopathologic/immunohistochemical features are important in the diagnosis
Case

- 46 year old male with 9 year history of diplopia, proptosis, and papilledema
- Orbit MRIs: diffuse intraconal masses with encasement of optic nerves bilaterally, L>R
- Brain MRI: non-specific lesions, particularly involving the brain stem
- PMH:
  - Malignant melanoma of right shoulder 2 years prior (in 2011) with previous dysplastic nevi in various locations
  - Pericardial effusion
  - Renal function deteriorating
  - Denies bone pain
Case - PMH

- Dyslipidemia
- Hypertension
- Obesity
Laboratory findings

- HgB = 10.4 g/dl
- Serum protein = 6.1 g/dl
- BUN = 39 mg/dl, Creatinine = 1.97 mg/dl, Estimated GFR decreased
- Calcium = 9.9 mg/dl
- ALT = 8 U/L
- Cholesterol = 212 mg/dl, Triglycerides = 479 mg/dl
- Normal immunoglobin levels; specifically normal IgG4
- No paraproteinemia
Histopathology
Histopathology – Pertinent Immunohistochemical Stains

- Negative for S-100, CD1a, MelanA, AE1/3
- CD3 and CD20 (kappa and lambda light chains showed polyclonal population)
- Only occasional IgG4 positive plasma cells
Histiocytic Disorders
(Histiocyte Society Writing Group – 1987)

- Class I: Langerhans cell histiocytosis – histiocytosis X spectrum
- Class II: Histiocytoses of mononuclear phagocytes other than Langerhans cells
- Class III: Malignant histiocytic disorders
Adult orbital xanthogranulomatous disease (AOXGD)

- Type II - Non-Langerhans type of histiocytosis
- Rare and poorly understood heterogeneous group of syndromes
AOXGD

- Age range: 17-85 (usually middle age)
- No sex preference, except for Erdheim Chester disease (male>female, 3:1)
- Clinically:
  - Bilateral firm, indurated, rubbery, yellow masses: subcutaneous, subconjunctival, or periocular
  - CT scan demonstrating preseptal anterior or diffuse intraconal orbital infiltration
AOXGD: 4 Subtypes

- Adult onset xanthogranuloma (AOX)
- Adult onset asthma and periocular xanthogranuloma (AAPOX)
- Necrobiotic xanthogranuloma (NBX)
- Erdheim-Chester disease (ECD)
Histopathology

- Sheets of foamy histiocytes (xanthoma cells)
- Fibrosis
- Touton giant cells
- Dispersed aggregates of lymphocytes
- Necrobiosis of collagen (in necrobiotic xanthogranuloma)
Histopathology

Xanthoma cells:
- cytoplasm positive for lipid stains (Oil red-O or adipophilin)
- Lack atypia and high mitotic rate (or Ki-67)
- Positive by IHC for CD68, CD163, XIIIa
- Negative for CD1a and usually S-100
- Negative for IHC markers for melanoma, carcinoma, etc.
Adult onset xanthogranuloma (AOX)

- Solitary lesion
- Adult onset juvenile xanthogranuloma (JXG) of the orbit
- No systemic findings
Adult onset asthma and periocular xanthogranuloma (AAPOX)

- Syndrome described by Jakobiec et al in 1993 based on small number of cases
- In addition to asthma, patients may have lymphadenopathy and increased IgG levels (polyclonal)
Necrobiotic xanthogranuloma (NBX)

- Subcutaneous skin lesions in eyelids and anterior orbit (and sometimes throughout body or internally)
- Skin lesions have strong propensity to ulcerate and then become fibrotic
- Frequent systemic findings:
  - Paraproteinemia and multiple myeloma
Erdheim Chester disease (ECD)

- Most devastating subtype

- Dense, progressive fibrosclerosis of orbit and internal organs
  - Bone involvement common
  - Mediastinum, pericardium, pleura, retroperitoneum, and perinephric region
Erdheim-Chester Disease

Frequency of clinical and radiologic features:

- Bone pain (50%)
- Periaortic infiltration (60%)
- Pericardial involvement (45%)
- Exophthalmos (27%)
- Diabetes insipidus (27%)
- Xanthelasma (19%)
- “Hairy kidney” appearance on CT
- CNS involvement (15-25%)
- Pulmonary involvement (22%)
- Death (60%)
Orbital involvement in AOXGD

- Anterior orbit/adnexal:
  - AOX
  - AAPOX
  - NBX

- Diffuse or intraconal orbit:
  - ECD
Differential Diagnosis

- Adult xanthogranulomatos disease
- Langerhans histiocytosis
- Extranodal Rosai-Dorfman disease
- Inflammatory pseudotumors including inflammatory myofibroblastic tumor and IgG4 related sclerosing disease
- Juvenile xanthogranuloma (JXG)
- Lymphoma
- RA
- Sarcoid
- Infection
- Melanoma
- Metastatic carcinoma
Diagnosis

- May not be apparent until the disease process evolves

- Sometimes overlap of subtypes as well as syndromes (ECD with LCH or ECD with Rosai-Dorfman disease)
Erdheim-Chester Disease

Treatment:
- Interferon α
- Cyclophosphamide
- Vemurafenib (BRAF inhibitor) in severe multisystem disease when $BRAF^{V600E}$ mutation exists
- Steroids
Recent update on patient’s condition

- Treated with cyclophosphamide and prednisone
- FDG PET/CT: soft tissue prominence around origin of great vessels and pericardium, as well as around kidneys; also increased FDG uptake of long bones
- Stroke/Carotid artery stenosis
Summary

- AOXGD is a non-Langerhans type of xanthogranulomatous disease (type II), typically affecting middle age adults
- May or may not be part of systemic disease
- Several disease entities should first be ruled out (metastasis, melanoma, inflammatory processes, etc.)
- Histopathologic findings alone cannot be used alone to subclassify the 4 subtypes (except perhaps if necrobiosis is present)
- Clinical correlation required because of the non-specific findings
References

Thank you