7.5.6. Orbital Neoplasms and Malformations (VI): Lymphoproliferative Disorders

- **Xanthogranuloma**
  - 4 syndromes
    - **necrobiotic xanthogranuloma (NBX)** 1
      - eyelids and anterior orbit
      - may occur throughout the body
      - subcutaneous lesions
      - have a propensity to ulcerate and fibrose
      - systemic findings
        - paraproteinemia
        - multiple myeloma
    - **adult-onset asthma with periocular xanthogranuloma (AAPOX)** 2
      - periocular xanthogranuloma
      - asthma
      - lymphadenopathy
      - increased immunoglobulin G levels
      - most devastating of the adult xanthogranulomas
        - death frequent
          - despite aggressive therapy!
    - **Erdheim-Chester disease (ECD)** 3
      - dense, progressive, recalcitrant fibrosclerosis of
        - orbit
        - internal organs
        - mediastinum
        - pericardium
        - pleural space
        - perineghric space
        - retroperitoneal space
      - bone involvement is common
      - diffuse xanthogranuloma of the orbit and adnexa
        - xanthogranuloma of the orbit and adnexa tends to be anterior in NBX, AAPOX, and ACIX
        - leads to vision loss
    - **adult-onset xanthogranuloma (ACIX)** 4
      - isolated xanthogranulomatous lesion without systemic involvement
      - juvenile xanthogranuloma
        - focal subcutaneous disease of childhood
        - self-limited
        - corticosteroid-sensitive
  - adult xanthogranuloma of the adnexa and orbit is often associated with systemic manifestations

- **Histiocytic Disorders**
  - classification
    - Langerhans cell histiocytosis
    - rare disorders of mononuclear phagocytic system
    - pathogenesis
      - abnormal immune regulation
      - accumulation of proliferating dendritic histiocytes
    - most commonly in children
      - peak incidence between 5 - 10 years
    - varies in severity from benign lesions with spontaneous resolution to chronic dissemination resulting in death
    - unifocal eosinophilic granuloma of bone 1
    - multifocal eosinophilic granuloma of bone 2
    - diffuse soft tissue histiocytosis 3
  - clinical presentation
    - most frequent presentation in the orbit is a lytic defect
      - superotemporal orbit
      - sphenoid wing
      - may cause proptosis
    - relapsing episodes of orbital inflammation
      - often initially misinterpreted as infectious orbital cellulitis
    - younger children
      - more often present with significant overlying soft-tissue inflammation
      - more likely to have evidence of multifocal or systemic involvement
        - younger patients require regular observation for detection of subsequent multiorgan involvement
  - prognosis
    - survival rate
      - only 50%
        - <2 years
      - 87%
        - >2 years
    - spontaneous remission has been reported
    - involved bone usually reossifies completely
  - treatment
    - localized orbital disease
      - confirmatory biopsy with debulking
      - intralesional steroid injection
      - low-dose radiation
    - systemic disease
      - aggressive chemotherapy

- **Plasma Cell Tumors**
  - much less common
  - composed predominantly of mature plasma cells
    - plasmacytomas
    - localized plasma cell–rich pseudotumors
  - some lesions are composed of lymphocytes and lymphoplasmacytoid cells
  - multiple myeloma should be ruled out
    - particularly if there is
      - bone destruction
      - immaturity or mitotic activity among the plasmacytic elements
  - display the same spectrum of clinical involvement as do lymphoproliferative lesions

- **Lymphoid Hyperplasia and Lymphoma**
  - Introduction
    - 20% of all orbital tumors
    - % of orbital lymphoproliferative lesions designated as malignant lymphoma
      - 70%–80% on the basis of monoclonal cell-surface markers
      - 90% based on molecular genetic studies
    - over time, some conjunctival lymphoid lesions fluctuate between being monoclonal and polyclonal
    - incidence of non-Hodgkin lymphoma (NHL) of all anatomical sites has been increasing
      - 3–4% /year
      - 50% over the last 20 years
      - NHL is the 4th most common malignancy among men and women
      - incidence of orbital lymphomas has been increasing at an even greater rate
    - risk factors for NHL
      - older adults
      - patients with chronic autoimmune diseases
      - long-term exposure to bioactive solvents and reagents
  - Classification of NHL
    - largely based on nodal architecture
    - Revised European-American Lymphoma (REAL) classification
      - includes extranodal sites, including orbit
    - orbital extranodal NHL appears to represent a biological continuum and to behave unpredictably
      - extraorbital lymphoma can develop in patients with orbital lymphoid infiltrates that appear benign histologically
      - patients with malignant lymphoma of ocular adnexa may respond satisfactorily to local therapy without subsequent systemic involvement
    - cell of origin
      - most orbital lymphomas are derived from B cells
        - Hodgkin lymphoma
          - rarely metastasize to the orbit
        - non-Hodgkin lymphoma
          - malignant B-cell NHL accounts for >90% of orbital lymphoproliferative disease
      - T-cell lymphoma is rare
        - more lethal
  - 4 most common types of orbital lymphomas
    - mucose-associated lymphoid tissue (MALT) lymphomas
      - 40%–80%
      - originally described as occurring in the gastrointestinal tract
      - proliferation of early MALT tumors may be antigen driven
        - therapy directed at the antigen (eg, against Helicobacter pylori in gastric lymphomas) may result in regression of early lesions
        - some conjunctival MALT lymphomas are associated with chronic chlamydial infection
      - in contrast to MALT lymphomas occurring in other areas of the body, those in the ocular adnexa do not appear to be preferentially associated with mucosal tissue (ie, conjunctiva, lacrimal gland)
      - low grade of malignancy
      - systemic disease at 10 years
        - ≥ 50%
      - spontaneous remission
        - 5%–15%
      - transformation to a higher-grade lesion (usually of a large cell type)
        - 15%–20%
        - occurs after several years and is not related to therapy
    - chronic lymphocytic lymphoma (CLL)
      - low-grade lesion of small, mature-appearing lymphocytes
    - follicular center lymphoma
      - low-grade
      - follicular centers
    - high-grade lymphomas
      - large cell lymphoma
      - lymphoblastic lymphoma
      - Burkitt lymphoma
  - Clinical presentation
    - gradually progressive, painless mass
      - low-grade lymphomas & reactive lymphoid hyperplasias show slow expansion over a period of months to years
    - ≈ 17% bilateral
      - does not necessarily indicate presence of extraorbital disease
    - location
      - anterior orbit
        -
        - Figure 7.5.13 (© 2020 American Academy of Ophthalmology)
      - beneath the conjunctiva
        - salmon-patch appearance
        -
        - Figure 7.5.14 (© 2020 American Academy of Ophthalmology)
    - mold to surrounding orbital structures rather than invade them
      - disturbances of extraocular motility or visual function are unusual
    - ≤50% of orbital lymphoproliferative lesions arise in the lacrimal fossa
    - orbital imaging
      - characteristic pulty/like molding of the tumor to normal structures
      - bone erosion or infiltration is usually not seen
        - except with high-grade malignant lymphomas
    - lymphomas in the retrobulbar fat may appear more infiltrative
    - systemic lymphoma
      - 1/2 of periocular lymphomas
        - 20%–30% have a history of previous or concomitant systemic disease
        - 30% develop it over 5 years
      - anatomical site of origin is predictive of systemic lymphoma
        - eyelid-orbit-conjunctiva
          - lymphoid lesions in the lacrimal fossa may carry a greater risk of systemic disease
      - bilateral periocular involvement markedly increases the risk of systemic disease
        - not a definitive evidence of systemic disease
      - the risk of systemic disease is increased for decades after the original lesion is diagnosed, regardless of the initial lesion's location in the orbit or its clonality
  - Diagnosis
    - technique
      - open biopsy is preferred
        - light microscopy (fixation)
          - may reveal a continuum from reactive hyperplasia to low-grade lymphoma to higher-grade malignancy
          - hypercellular proliferations with sparse or absent stromal components
            - both reactive hyperplasia and malignant lymphoma
        - majority of the specimen should be sent fresh to a molecular diagnostics laboratory
          - for possible flow cytometry and polymerase chain reaction analysis
      - fine-needle aspiration biopsy
        - can provide adequate sample volume to establish all but the morphologic characteristics of the lesion
    - immunologic identification of cell-surface markers on lymphocytes
      - B cells
      - T cells
      - monoclonal
      - polyclonal
      - specific monoclonal antibodies directed against surface light-chain (κ or λ) immunoglobulins
    - DNA hybridization
      - extracting, amplifying, and hybridizing tumor DNA with radioactively labeled nucleotide probes
      - more sensitive than cell-surface marker typing
        - allow more precise identification of tumor clonality
          - 90% of orbital lymphoproliferative disease is monoclonal
          - 10% is polyclonal
      - more time-consuming
      - expensive
      - DNA genetic studies have shown that most lymphoproliferative lesions that appear to be immunologically polyclonal actually harbor small monoclonal proliferations of B lymphocytes
        - does not predict which tumors will ultimately result in systemic disease
  - Management
    - all patients with hypercellular lymphoid lesions should be examined by an oncologist
      - general physical examination
      - complete blood count
      - bone marrow biopsy
      - liver and spleen scan
      - chest radiograph
      - serum immunoprotein electrophoresis
      - CT of the thorax and abdomen
        - to check for mediastinal and retroperitoneal lymph node involvement
      - patient should be reexamined periodically
      - whether monoclonal or polyclonal!
    - systemic corticosteroids
      - are not recommended in the treatment of lymphoproliferative lesions
    - radiotherapy
      - treatment of choice
        - achieves local control in virtually all cases
      - 2000–3000 cGy
    - surgical excision
      - usually cannot be achieved because of the infiltrative nature of lymphoid tumors
    - indolent lymphomas
      - treatment of low-grade lymphoid lesions that have already undergone systemic dissemination is somewhat controversial
      - generally refractory to chemotherapy
      - are associated with long-term survival, even if untreated
      - many oncologists take a watchful waiting approach
        - treat only symptomatic disease
    - agressive lymphomas require treatment
      - radiotherapy
      - aggressive chemotherapy
      - ≤1/3 can be cured

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