Sarcoidosis

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Overview

- Definition
  - Multisystem non-caseating granulomatous disease of unknown etiology
  - Ocular involvement in 30%, mostly chronic granulomatous anterior uveitis, but may involve posterior structures, retinal vessels, optic nerve
  - Criteria for ocular sarcoidosis:
    Definite – uveitis with biopsy positive
    Presumed – uveitis with bilateral hilar lymphadenopathy (BHL), no biopsy
    Probable – 3 suggestive intraocular signs *and* 2 labs, BHL negative, no biopsy done
    Possible – 4 suggestive intraocular signs *and* 2 labs, biopsy negative
- Symptoms
  - Blurring
  - Redness
  - Floaters, flashes
  - Pain, irritation
    May be deep orbital pain
  - Photophobia
  - Scotomas
  - Diplopia (with orbital involvement)
- Laterality
  - Unilateral or bilateral
- Course
  - Acute or chronic

C. S. Foster et al. (eds.), *Uveitis*, https://doi.org/10.1007/978-3-030-52974-1_6

- Age of onset
  - Two peaks of incidence:
    20s to 30s (typically acute form)
    50s to 60s (typically chronic form)
  - Early onset sarcoidosis (first decade) is actually sporadic form of Blau syndrome (*NOD2* mutation)
- Gender/race
  - No specific gender predilection, but females may have more eye and neurologic involvement
  - More common in US blacks (often presents earlier, more severe) and northern European whites
  - Less common in Asians
- Systemic association
  - Multisystem non-caseating granulomas involving one or several organ systems including primarily lungs, but also lymph nodes (hilar and mediastinal most common), eyes, skin, heart, joints, spleen, liver, and nervous system
  - Hypercalcemia
  - Ocular symptoms may precede systemic signs

Exam: Ocular

Anterior Segment

- Granulomatous anterior uveitis (22–70%)
  - Bilateral, chronic
  - Mutton-fat keratic precipitates
    May also present with fine keratic precipitates
- More common
  - Conjunctival nodules (variable %)
    Solitary, yellow, "millet-seed," often on bulbar surface
  - Posterior synechiae
  - Iris nodules
    Busacca (iris stroma)
    Koeppe (pupil margin)
  - Peripheral anterior synechiae
  - Cataract
  - Orbital inflammation, myositis, lacrimal gland enlargement
  - Nasolacrimal duct obstruction
- Less common
  - Band keratopathy
    Associated with hypercalcemia
  - Scleritis (rare), anterior or posterior
    Angle closure (due to annular ciliochoroidal detachment)

Posterior Segment

- Vitritis or intermediate uveitis
  - Inferior vitreous (snowballs*) or pars plana exudates (snowbank*)
  - * not to be confused with inactive fibrotic changes along pars plana
  - String of pearls – vitreous exudate strands in chains
  - May also be posterior uveitis or panuveitis
- Cystoid macular edema
- Retinal vasculitis (very common)
  - Segmental phlebitis
  - "Taches de bougie" or candle wax drippings
    Creamy white perivascular exudate or sheathing
- Papillitis (may be only posterior manifestation)
- Retinal vein occlusion
  - Ischemic retinopathy with neovascularization, less common
- Glaucoma
- Choroidal nodules
- Multifocal punctate mid-peripheral chorioretinal scars
  - "Punched-out lesions," very characteristic
- Choroidal neovascularization, peripapillary or subfoveal
- Exudative retinal detachment (less common)
  - Posterior scleritis with annular ciliochoroidal detachment (angle closure)

Exam: Systemic

- Acute disease (weeks)
  - Fever, erythema nodosum, arthralgia, parotid enlargement
- Pulmonary (90%)
  - Hilar and mediastinal lymphadenopathy
    Mediastinal without hilar LAD is rare, alternative diagnosis
  - Pulmonary nodules
  - Calcification
  - May also involve upper respiratory mucosa
- Skin (9–37%)
  - Erythema nodosum
  - Plaque-like lesions
    Lupus pernio – indurated, chronic violaceous, often on face
  - Subcutaneous nodules
  - Glandular enlargement (salivary, parotitis)
- Neurologic (5–26%)
  - May involve any part of nervous system
    Occurs in 37% of patients with ocular involvement
  - Cranial neuropathies, most common
  - Hypothalamic or pituitary lesions may lead to endocrinologic disease

  - Meningeal
  - Spinal cord
- Cardiac (up to 25%)
  - Cardiomyopathy
  - Pericardial effusion or pericarditis
  - Conduction abnormalities
  - Cor pulmonale (with severe pulmonary disease)
- Hepatosplenic enlargement with granulomas/nodules (>50%)
- Musculoskeletal
  - Arthritis – ankles, other joints
  - Bone resorption in marrow of phalanges
- Renal (uncommon)
  - Interstitial nephritis
  - Calculus
  - Renal failure

Imaging

- OCT: CME, disc edema
- ED-OCT: choroidal granuloma
- OCT-A: retinal ischemia, microvascular disease
- FA: venule (very common) or capillary leakage or staining, CME, diffuse chorioretinal leakage, disc leakage, peripapillary or subfoveal choroidal neovascularization, ischemia, retinal vein occlusion, choroidal granuloma
- ICG: early lobular hypolucence, choroidal vasculitis, focal and diffuse late hyperlucence
- VF: glaucoma, optic neuropathy, craniopathy
- B-Scan: orbital inflammation, posterior scleritis, choroidal granuloma, papillitis

Laboratory and Radiographic Testing

- ACE or lysozyme may be elevated in active disease, often normal, nonspecific
- Elevated soluble interleukin-2 receptor (sIL2R)
- Hypercalcemia, hypercalciuria
- Chest CT – occult or symptomatic pulmonary findings, cardiomyopathy
  - Chest X-ray often negative, nonspecific
- MRI brain/orbits – CNS involvement, orbital inflammation
- Gallium scan
  - Panda sign – bilateral symmetric lacrimal and parotid uptake
  - Lambda sign – para- and infrahilar bronchopulmonary lymph nodes and right paratracheal (azygous) mediastinal lymph nodes
- Biopsy – conjunctiva, vitreous (high levels of HMGB1), transbronchial lung, lacrimal gland, skin

- Other testing
  - Cutaneous anergy
  - Pulmonary function testing
  - Bronchoalveolar lavage
  - PET imaging

Differential Diagnosis

- Anterior uveitis
  - HLA-B27 associated uveitis
  - Fuchs' heterochromic iridocyclitis
  - Herpes simplex or varicella zoster
  - Syphilis
  - Tuberculosis
  - Juvenile idiopathic arthritis
- Intermediate uveitis
  - Pars planitis
  - Multiple sclerosis
  - Lyme disease
- Posterior uveitis
  - Toxoplasmosis
  - Toxocariasis
  - Tuberculosis
  - Syphilis
  - Birdshot retinochoroidopathy
  - Multifocal choroiditis and panuveitis
  - Vogt-Koyanagi-Harada disease
  - Intraocular lymphoma
  - Sympathetic ophthalmia
  - Adamantiades-Behçet's disease
  - Whipple's disease

Treatment

- Acute AU: frequent topical corticosteroid +/− cycloplegia
  - Q1h steroid and atropine 1% BID with hypopyon
- Severe AU or any posterior involvement
  - Systemic corticosteroids, oral or intravenous
  - Initiation of immunomodulatory therapy
    Coordination with other specialists if necessary
- Immunomodulatory therapy
  - Antimetabolites
    Methotrexate particularly effective

  - Azathioprine or mycophenolate
  - Calcineurin inhibitors (supplemental)
    - Cyclosporine, tacrolimus
  - Biologics (especially with RV)
    - TNFα inhibitors – adalimumab, infliximab
    - Anti-IL6 - tocilizumab
    - CD20 inhibition – rituximab
    - Anti-IL1β – anakinra, canakinumab (used in some cases)
  - Alkylating agents
    - Chlorambucil or cyclophosphamide
- Intravitreal therapy
  - Anti-VEGF
  - Corticosteroid injections, implants
- Pan-retinal photocoagulation
- Other therapeutic measures
  - Hydroxychloroquine
  - IV-Ig
  - Subcutaneous corticotropin gel
  - Thalidomide

Referral/Co-management

- Pulmonology
- Rheumatology
- Neurology
- Cardiology
- Dermatology
- Endocrinology