SARCOIDOSIS UPDATE

Who gets sarcoidosis? Despite years of clinical observation, inadequate case definitions, have led to extremely variable results, with many remaining questions.

- Incidence: annual in US and Western Europe estimated at 10/100,000
- Host factors: age predilection 20-40 y.o. (peak 20-29), second peak noted in Japan and Scandinavian countries in women over 50; slight female > male distribution; African Americans, Swedes and Danes have highest prevalence rates in the world, while much lower in South Americans, Southern Europeans; familial clustering has been observed.
- Time and space factors: exposures—small studies have reported some associations with navy ship work, firefighting, rural living (pine pollen); geographic clusters (mid-Atlantic states in US); seasonal variation (cool summer/mild winter zones of Europe).

Why do you get sarcoidosis? Still unknown, thought to result from an exposure (?) in a genetically susceptible individual that results in an immunologic/inflammatory response.

- Some HLA associations have been observed: HLA-B8 with EN, HLA-D3 with spontaneous resolution, less clear associations with HLA-B22, B13, A1.
- Some exposures have been suggested as etiologic agents: infections (HSV, EBV, CMV, coxsackie, Borrellia burgdorfei, Propiobacterium, Mtb/Mac, Mycoplasma); organic (pine tree pollen, clay) and inorganic (aluminum, zirconium, talc). None proven.
- Early activation of T cells, most notably Th1 (CD4), and macrophages, which release cytokines (IFN-gamma, IL-2, TNF-alpha, IL-12, IL-15) causing local inflammation. If antigenic stimulus persists, T-cell proliferation and cytokine production persist, likely with TCR oligoclonality, with continued macrophage recruitment and eventual granuloma formation and lung destruction.

What are the stages of pulmonary involvement? Clinical variability in presentation from symptomatic to non-specific complaints of fever, malaise and weight loss, to mild complaints of dyspnea, dry cough and pleurisy to severe pulmonary compromise, depending on extent of involvement. Affected in 90% cases. Rare clubbing, hemoptysis.

- Stage 1: bilateral hilar LAN (BHL)
- Stage 2: BHL and parenchymal infiltrates
- Stage 3: parenchymal infiltrates without BHL.
- Stage 4: advanced fibrosis with honey combing, hilar retraction, bullae, cysts
- May involve the airways (trachea, bronchi, larynx, nasal septum)causing obstruction and the pleural space causing effusion, chylothorax, pneumothorax, thickening.

What are the extra-pulmonary manifestations? The fun begins, almost every organ can be affected, remember to look closely.

- Lymphoid system: 30% patients with palpable peripheral nodes (cervical, axillary, epitrochlear and inguinal), spleen can enlarge
- Skin: 25% patients with findings-erythema nodosum (seen mostly in acute disease with European, Puerto Rican and Mexican women; rarely in AA); lupus purnico (seen in chronic disease, in AA women with bone cysts and fibrosis); other skin findings are subcutaneous nodules, maculopapular rash, alopecia, changes in old scars….these latter are not painful, do not itch or ulcerate.
- Eyes: 10-80% patients with findings-acute or chronic uveitis, lacrimal gland enlargement, keratoconjunctivitis sicca, retinal vasculits
- Musculoskeletal: 40% patients with some form of arthralgias, not destructive. Acute arthritis of ankles, knees, wrist and elbows; chronic arthritis may also affect MCP and PIP (esp. in AAM).
- Cardiac: 5% clinical, 30% autopsy involvement, conduction disorders and restrictive cardiomyopathy.
- Others: more rarely affected-GI (<1%, malabsorption, bleed), liver, heme (4-20%, mild anemia and leukopenia), parotid (<6%, painful enlargement), endocrine (<10% with hypercalcemia and hypercalciuria, central DI, hypopituitary), reproductive organs, neurologic (<10% with cranial nerve palsies, mononeuropathy, basilar meningitis, pituitary mass lesions), renal (interstitial nephritis, rare MPGN, stones)
- The syndromes to watch for: Heerfordt’s—fever, parotid, uveitis and facial n.; Lofgren’s—fever, BHL, EN with acute arthritis.

**How do you make the diagnosis?** Histologic confirmation of diagnosis should be obtained in all cases except in cases that are made without a reasonable doubt, goals are to get pathology, assess disease severity and prognosis, exclude other diagnosis.
- Biopsy: transbronchial bx is recommended (4-5 pieces) with 50-90% sensitive, mediastinoscopy next line if BHL with normal lung fields, has 60% yield, VATS may be next option, if needed. Remember, look for extra-pulmonary evidence of disease to biopsy such as parotids, skin (not EN) to help with dx, but may not be enough.
- BAL: may be helpful, CD4/CD8 ratio > 3.5 has a sensitivity of 50%, specificity of 94%. This ratio is c/w alveolitis, may also be seen with TB, HP.
- Gallium scan: may be diagnostic with classical uptake in parotid and bilateral hilar areas (panda and lamda signs), however in the absence of this, parenchymal uptake is seen in other diseases with activated macrophages and granulomas. May be used better as marker for active disease with good sensitivity.
- Serum ACE levels: very high levels are c/w sarcoi, but again, as ACE is made by granulomas, may be seen with other diseases, does not correlate will with disease activity
- Remember: need PFT’s, serum lytes/LFT/Calcium, EKG, check 24 hour urine for calciuria, eye exam, good neuro exam, HRCT if abnormal parenchyma on CXR and if abnormal PFT’s with normal CXR. As of now, NOT clear which tests, if any, correlate with disease activity the best.

**When do you decide to treat and with what?** Treat early for ocular, cardiac, neurologic, renal, hypercalciuria manifestations. For the lung, there is controversy, probably for symptomatic pulmonary stage 2 and definitely for stage 3. Concern that if you wait too long, irreversible damage may have occurred.
- Spontaneous remissions are common in early pulmonary stages: stage 1 (55-90%), stage 2 (40-70%), stage 3 (10-20%), stage 4 (none).
- Excellent prognosis in patients with acute inflammatory reactions, presenting with fever, arthritis and EN. (80% spontaneous remission)
- Poor prognostic factors include: lupus pernio, chronic uveitis, late age of onset, black race, hypercalcemia, progressive pulmonary, cardiac or neuro involvement.
- Therapeutic options: steroids are first line, a response must be seen within 3 months, if not, not likely to respond to long term therapy. Next line are cytotoxic agents such as methotrexate, azathioprine. Recent negative study comparing cyclosporine to prednisone. Future therapeutic may include immunomodulators (TNF-alpha inhibitors).