ILD Collaborative

Project ECHO

Sarcoidosis: Overview, Diagnosis, and Monitoring

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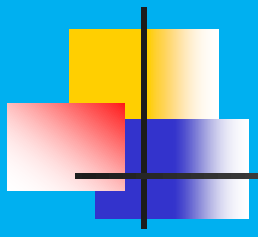


Sarcoidosis

- Epidemiology
- Etiology
- Pathophysiology
- Organ System Involvement
- Clinical and Laboratory Findings
- Radiology
- Diagnosis
- Treatment

Sarcoidosis

- Generalized granulomatous disease primarily affecting the lung and lymphatic system
- Frequently involves multiple organ systems (extra-pulmonary sarcoid)

Sarcoidosis – an old disease

- **1808** Robert Willan describes **erythema nodosum**, found in 1946 to be related to sarcoid
- **1877** Sir Jonathan Hutchinson describes the skin lesions associated with sarcoid
- **1899** Caesar Boeck describes the first case of sarcoidosis with skin changes and involvement of the **lymph nodes** and termed it "**sarkoid**"
- **1919** Jorgen Nilsen Schaumann recognizes the **systemic nature** of the disease
- **1941** Morten Ansgar Kviem publishes test to differentiate sarcoidosis from tuberculosis

Sarcoid - Epidemiology

- Both sexes, but women > men
- All races
- Usually < 40 yo, peaks ages 20-29
- Scandinavian countries and Japan – another peak incidence in women > 50 yo
- In US: lifetime risk whites 0.85%, blacks 2.4%
- World: prevalence is highest in Swedes, Danes, and US blacks
- Rare in Spain, Portugal, India, Saudi Arabia, South America

USA – Racial Disparity

Sarcoidosis incidence estimates reported in the literature

References	Country	Sex, race/ethnicity	Time period	Incidence per 100,000	Data source
Baughman et al. (4)	USA	Male and female, multiracial	2010–2013	Black: 17.8 White: 8.1 Hispanic: 4.3 Asian: 3.2	Optum Health Care Database
Cozier et al. (6)	USA	Female, black	1995–2007	71	Black Women's Health Study, self-reported sarcoidosis
Dumas et al. (8)	USA	Female, multiracial	1989–2011	Overall: 11 Black: 43 White: 11	Nurses' Health Study II, self-reported
Rybicki et al. (10)	USA, Detroit, MI	Male and female, multiracial	1990–1994	Black: 35.5 White: 10.9	Health Alliance Plan HMO

Hena, KM Front Immunol. 2020; 11: 537382.

Sarcoidosis – Racial Disparity

- Black patients have more extrapulmonary sarcoid
- Whites – calcium dysmetabolism
- Pulmonary involvement is the only organ involvement independent of age, sex, race

Sarcoidosis - Epidemiology

- Whites
  - more benign asymptomatic disease
- Blacks
  - more chronic w/uveitis, lupus pernio
- Europeans
  - more erythema nodosum
- Japan
  - more cardiac and ocular sarcoid

Sarcoidosis – Severity at Dx

- Lower income
- Absence of private/Medicare insurance
- Black race
- Female sex

Sarcoidosis - Mortality

- Overall mortality 1-5%
- Black females: 10 per million
- Black males: 3 per million
- White males & females: 1 per million

Seasonal Clustering

- Japan: increased cases in June and July between 1963-1972
- Finland 354 pts – 64% diagnosed first half of the year
- Barcelona – 186 pts ~50% pts noted first symptoms b/w April and June
- New Zealand – 21 pts w/ EN – Peak clustering in August, Sept, October (spring in NZ)
- Recent retrospective analysis of US veterans 2000-2007 found no seasonality, even when divided by north v. south

Environmental Exposures

- Isle of Man study – 18.8% pts were health care workers v. 4.2% controls
- Firefighters – increased incidence and prevalence compared with health care workers and historical controls
- WTC – increased incidence of sarcoid or sarcoid-like granulomatous pulmonary disease in 5 yrs after 9/11 compared with 15 yrs before
- US Navy aircraft carrier – increased risk of sarcoid

Environmental Etiology

- Transmissible agent – 1964 sarcoid reported in recipients of transplants from sarcoid pts and vice versa
- Bacteria: Proprionibacterium acnes, mycobacteria, Mycoplasma, Borrelia Burgdorferi
- Implicated viruses: HSV, EBV, CMV, retrovirus, coxsackie B

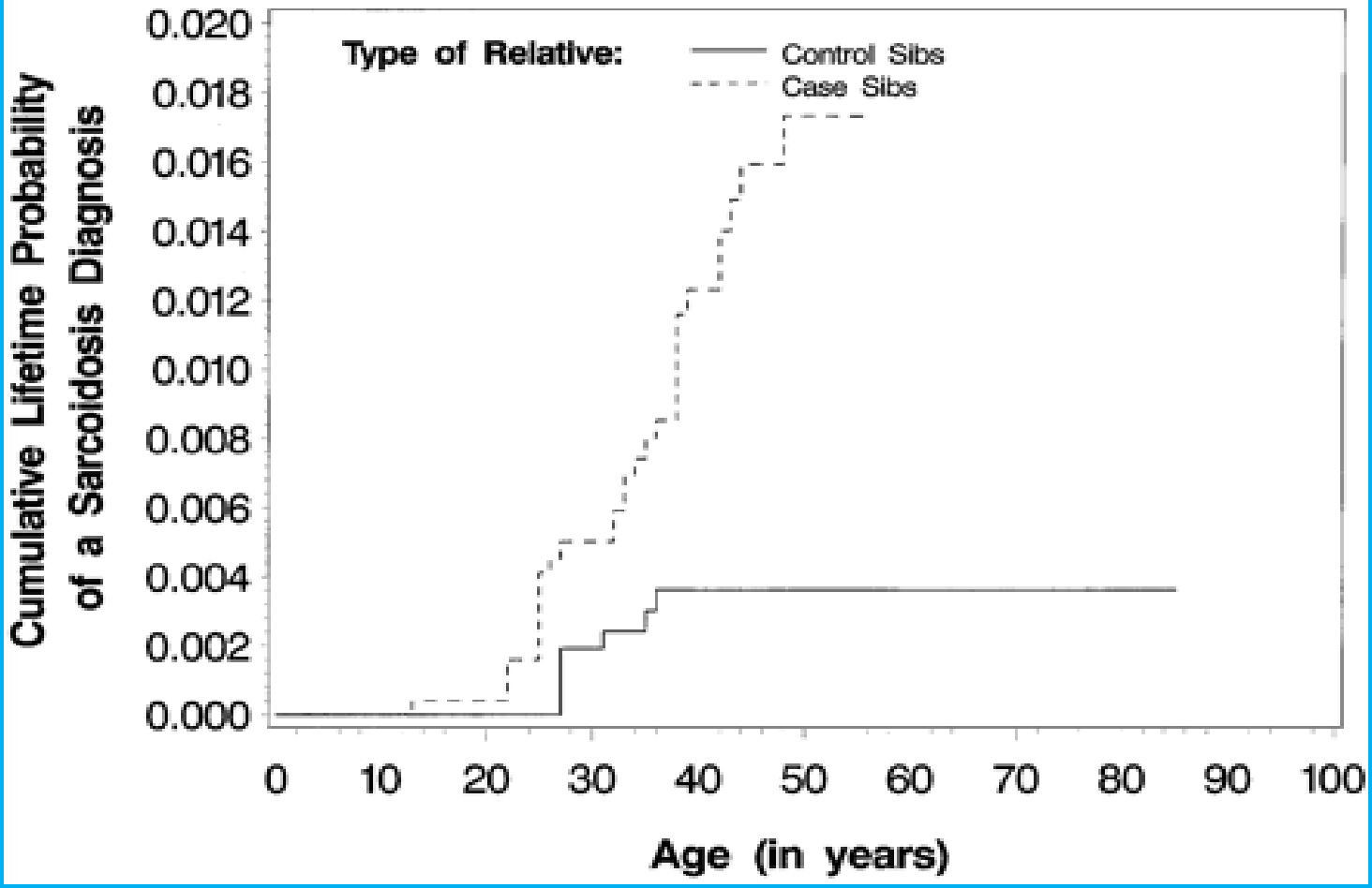
Genetic Etiology: ACCESS

- 706 sarcoid case-control prs: 10K first degree relatives & 17K second degree relatives
- Relative risk for familial aggregation
  - OR that an individual has a sarcoidosis history and is a relative of a case / OR that an individual has no sarcoidosis history and is a relative of a control

Genetic Etiology

- OR of relative with history of sarcoid being related to case: $\geq$ 4 in 1st and 2nd degree relatives
- Highest OR was for sibs with h/o sarcoid being related to a case
- No positive association for non-blood relatives, close contacts, or spouses of patient with sarcoid

Siblings


Type of Relative:
Control Sibs
Case Sibs
Cumulative Lifetime Probability of a Sarcoidosis Diagnosis
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
0
10
20
30
40
50
60
70
80
90
100
Age (in years)

Genetic Etiology

- HLA-B7 significantly increased in AA
- Löfgren's syndrome (acute disease) strongly associated with HLA-DR3, good prognosis
- HLA-DRB1*1501/DQB1*0602 haplotype is associated with chronic course and severe pulmonary sarcoidosis
- HLA allele DQB1*0602 confers increased susceptibility in black families, and risk of radiographic progression

Immunology

- Sarcoid granulomas form in response to a persistent and poorly degradable antigenic stimulus
- Cytokine and chemokine release seen in sarcoid is c/w antigen triggering

Immunology

- CD4+ helper cells > CD8+ T cells
- CD4+ cells release INF-γ and IL-2
- Alveolar macs release TNF-α, IL-12, IL-15, and growth factors

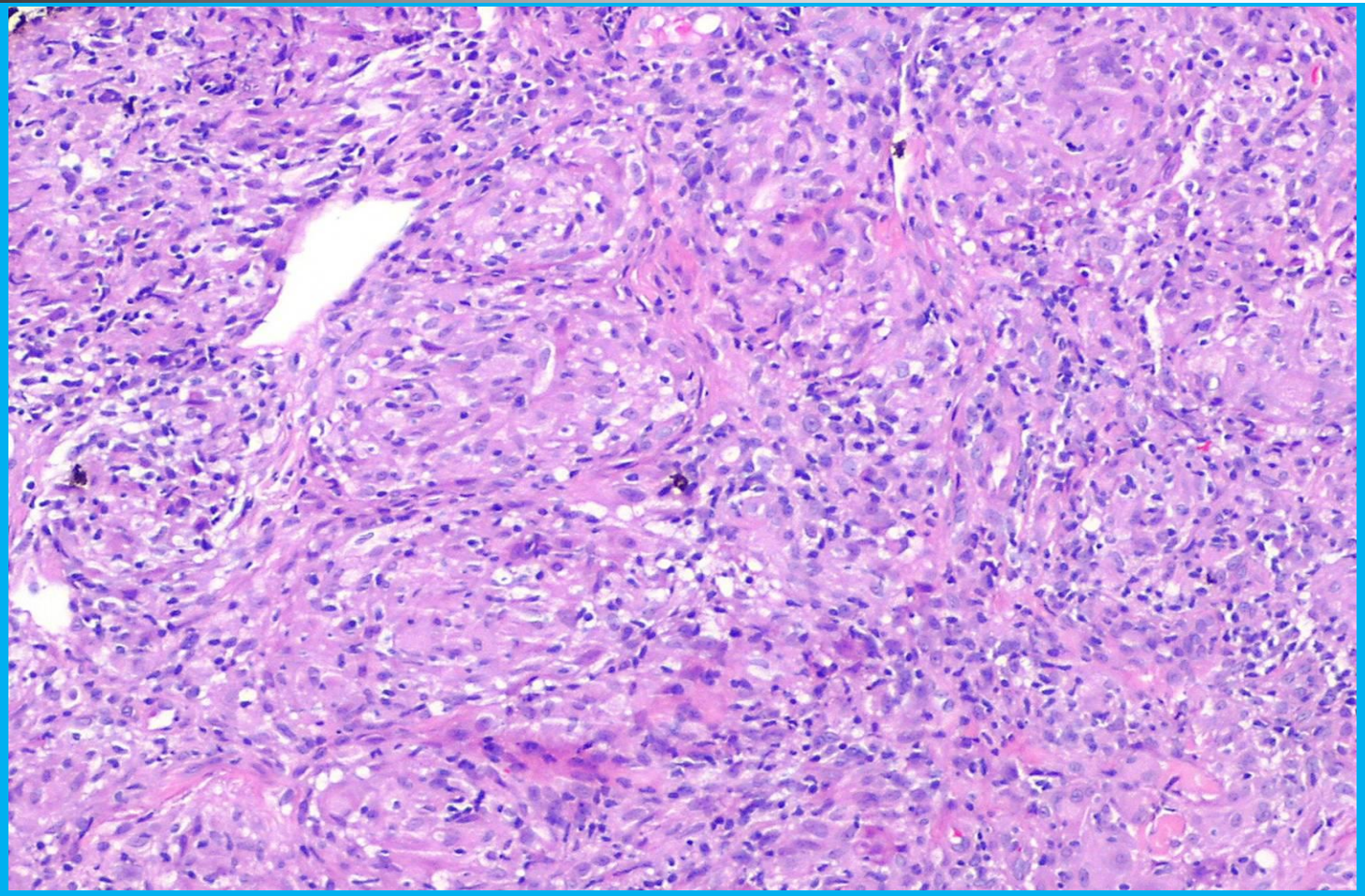
Granuloma Formation

- Central cell: activated CD45RO+ Th1 cells
- Redistribution of cytokines from peripheral blood to lung (IL-8, IL-15, IL-16, RANTES)
- *In situ* proliferation mediated by IL-2
- Th0 cells differentiate into Th1 cells
- IFN-γ is elevated

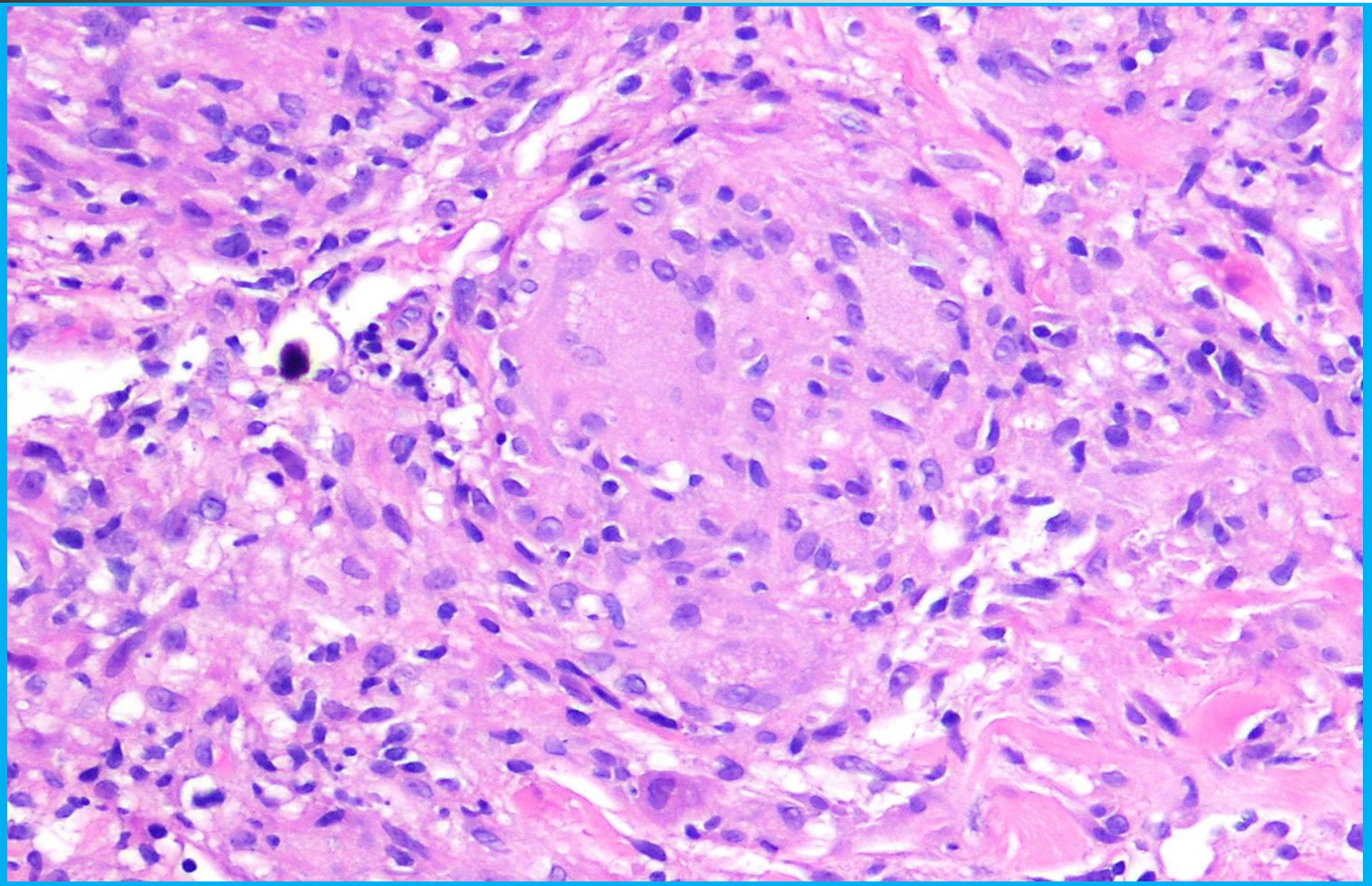
Sarcoidosis - Histology

- Compact, noncaseating epithelioid granuloma (epithelioid cells, giant cells, lymphs)
- Central portion: CD4 + lymphs
- Periphery: CD8+ lymphs
- Fibrosis begins peripherally and spreads centrally
- Occasional necrosis
- 75% are close to or in the connective tissue sheath of the bronchioles
- Nodules -subpleural or perilymphatic distribution

Multiple granulomas - tattoo



Giant Cells



Clinical Symptoms

- Non-specific constitutional symptoms 1/3 (fever, fatigue, malaise)
- Dyspnea, dry cough, chest pain 1/3-1/2
- May involve the sinuses, larynx, trachea, bronchi
- Peripheral Lymphadenopathy 1/3
- Cardiac Sarcoid 5% (25% at autopsy)
- Liver in 50-80% on biopsy

Extrapulmonary Organs

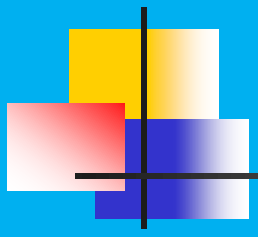
- Skin in 25% (erythema nodosum & lupus pernio)
- Ocular lesions 26%
- Neurosarcoid < 10% (4.6% ACCESS)
- Musculoskeletal system: joints (25-39%), myopathy
- GI tract <1%; Liver (12% abn lft, 96% +bx)
- Bone marrow: anemia, leukopenia (40%)
- Parotid glands (Heerfordt's syndrome)
- Hypercalcemia (6%), renal failure 42%, hypercalciuria (5-15%)
- Kidneys (interstitial nephritis) – 7%
- Endocrine organs – DI, hypo/hyperthyroid
- Reproductive organs

Laboratory Findings

- Anemia – uncommon
- Leukopenia 5-10%
- Eosinophilia 25%
- Thrombocytopenia – rare
- ESR elevation
- Hypercalciuria > hypercalcemia
- Hypergammaglobulinemia 30-80%
- Decreased skin test reactivity
- Alk phos, LFT abnormalities
- ACE +75%; False positive rate <5%

Sarcoidosis: Mechanisms of Hypercalcemia

- Over-production of 1,25-dihydroxyvitamin D3 (calcitriol) by activated macrophages and sarcoid granulomas
- 1,25-OH-Vit D increases the intestinal absorption of calcium
- Hypercalcemia– 5-11%
- Hypercalciuria (absorptive, resorptive, osteoclast activating factor) - 30%
- PTH level is normal or suppressed



PFTs

- Restriction with low DLCO
- Normal
- Obstruction (endobronchial sarcoid in 40% Stage I, 70% Stage II-III)
- Airway hyperresponsiveness – 20%

Radiology Staging

- Developed > 40 years ago based on plain films, not CT scans
- CXR indicates extent of involvement; cannot measure disease activity or assess functional defects
- It does have some prognostic value

Sarcoid Stages

- Stage I: Adenopathy
- Stage II: Adenopathy + Infiltrates
- Stage III: Infiltrates alone
- Stage IV: Fibrosis

Diagnosis

- Compatible clinical and radiographic manifestations
- **Exclusion of other diseases** which cause a similar histologic or radiologic picture
- **Histologic evidence** of noncaseating granulomas
- **Systemic**: Evidence of more than one organ involvement

Diagnosis

- In many series, the yield of EBUS-TBNA is > 70%
- Diagnostic accuracy of EBUS-TBNA in 643 patients was 84%, which increased to 89% with the addition of standard techniques such as TBLB and EBBX

Initial Evaluation

- CXR or Chest CT
- Full PFTs
- Eye exam – baseline (v. low quality evidence)
- Creatinine and alk phos CBC with diff
- Calcium & Vit D (25OH & 1,25 OH)
- U/A
- EKG
- If no cardiac symptoms, no echo/Holter
- PPD

Screening Continued

- Suspected cardiac involvement, get MRI rather than PET or echo
- If no MRI, then cardiac PET rather than echo
- Suspected PH: Echo
- +Echo, proceed to RHC
- - Echo, RHC on case-by-case basis

Monitoring

- Most intense first 2 years. Stage I every 6 months, higher stages every 3-6 months
- Monitor vigilantly for minimum of 3 years after treatment is stopped due to high rate of relapse, longer if extrapulmonary sites are involved
- Stage II-IV monitor indefinitely at least annually regardless of treatment or not
- Periodic chest radiographs and spirometry, eye exams, periodic labs