Sarcoidosis

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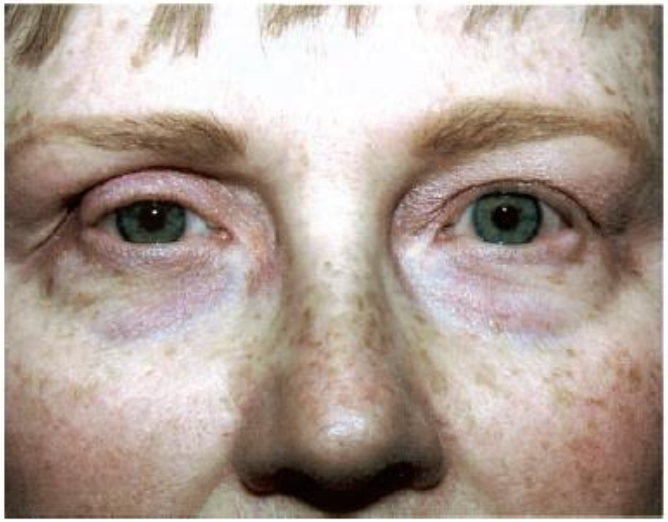
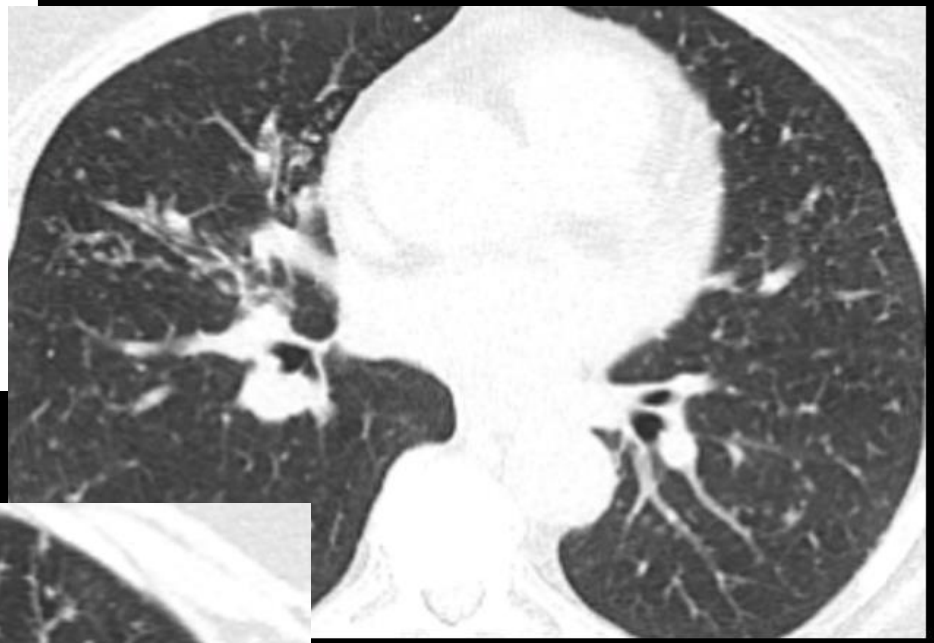
Housekeeping

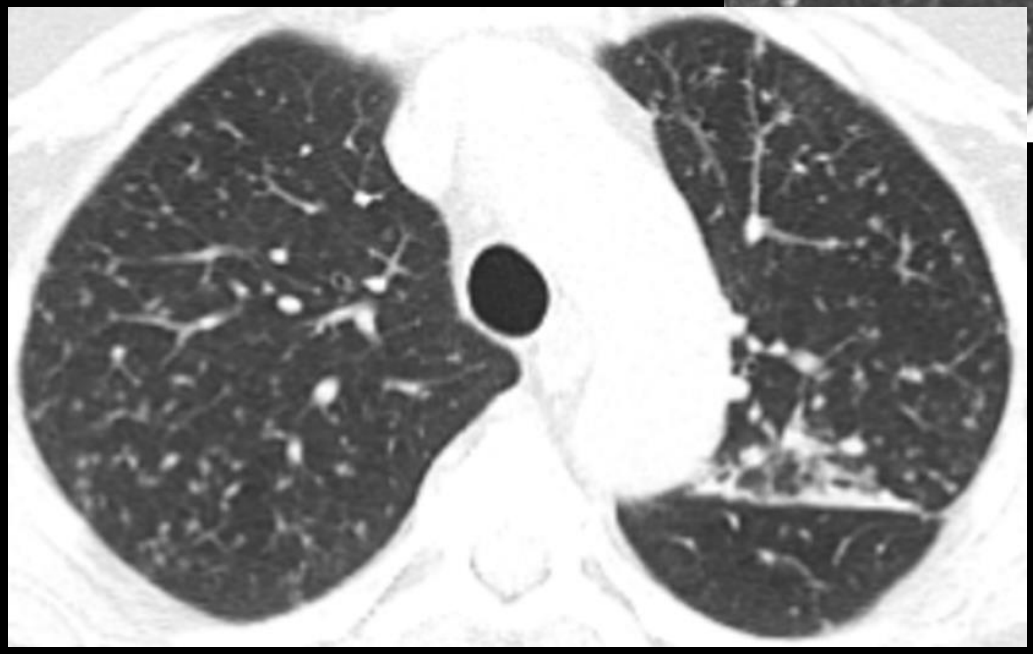
- No disclosures
- One FDA approved medication for sarcoidosis
- Funding
  - NIH/NHLBI/NIA
    - Lung immune response to HIV and Pulmonary microbiome
    - Virome “burden” and Aging
  - ADHS
    - Lung on a Leaf, modeling and platform for drug discovery and granuloma modeling

Objectives

- To understand sarcoid pathogenesis
- To appreciate sarcoidosis as a complex systemic disease
- To recognize the difficulties associated with diagnosing sarcoidosis
- To determine when to treat sarcoidosis







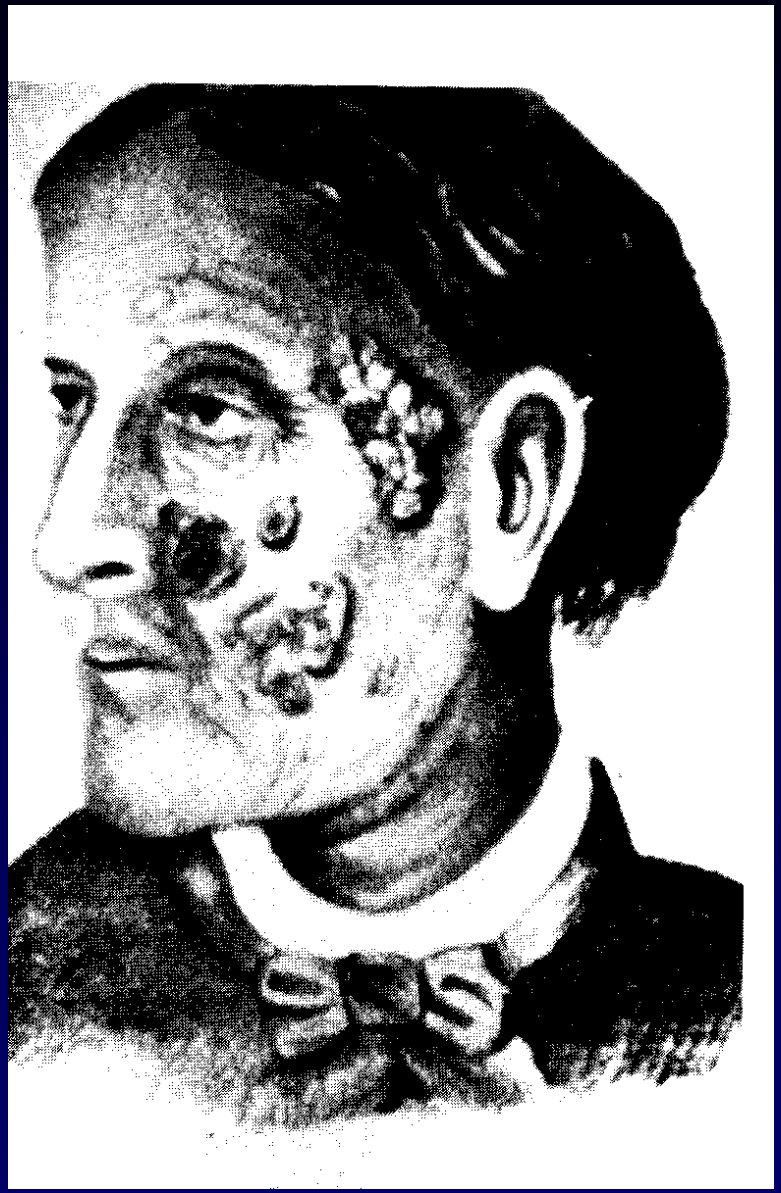
63 yo
Nonsmoker
Cough
Fatigue

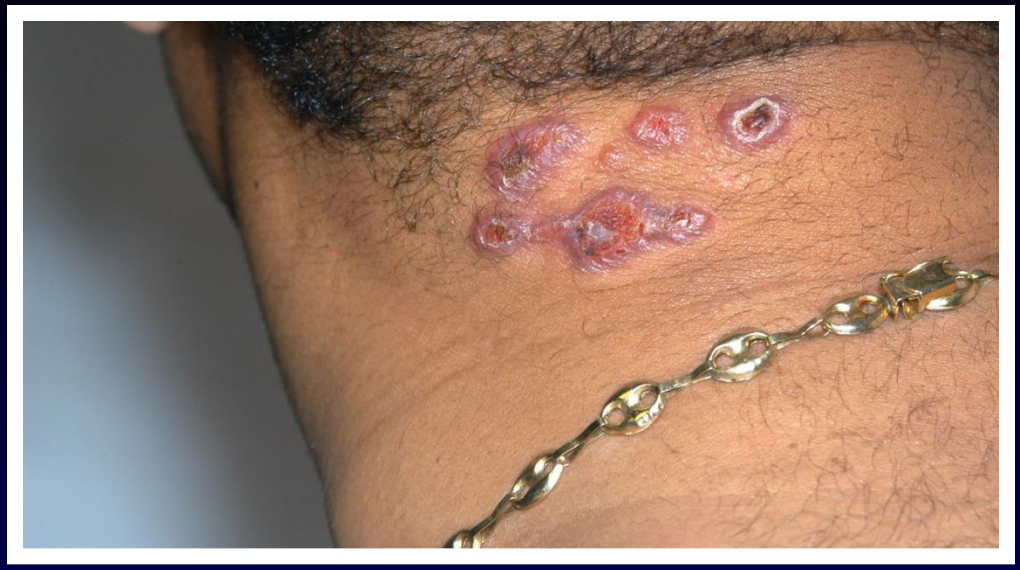
What is Sarcoidosis ?

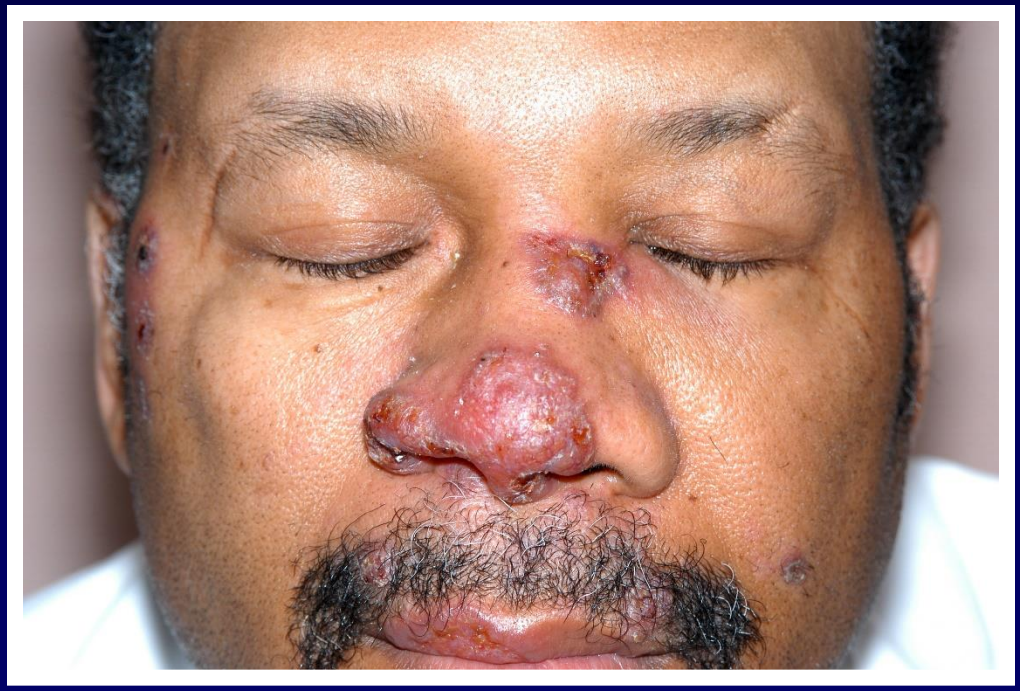
- Systemic inflammatory/immunologic disorder
- Affects any organ, but lung in over 90% of patients, Liver almost as much
- Hallmark is granulomatous inflammation (noncaseating)
- It is diagnosis of *exclusion*
- Thought to be in response to inhaled trigger

History- Sarcoid is a skin disease…

- First described by Hutchinson in 1878 and in 1898 as Mrs. “Mortimer’s Malady” (she had “gout”)
- Besnier described a patient in 1889 and termed skin findings “lupus pernio”
- Tenneson in 1892, second patient with lupus pernio, first report with histology
- Boeck in 1899 reported a patient with “Multiple Benign Sarkoid of Skin”
- In 1914 Schaumann first identified that Boeck’s sarkoid and Besnier’s pernio were same- termed it “lymphogranuloma benignum”





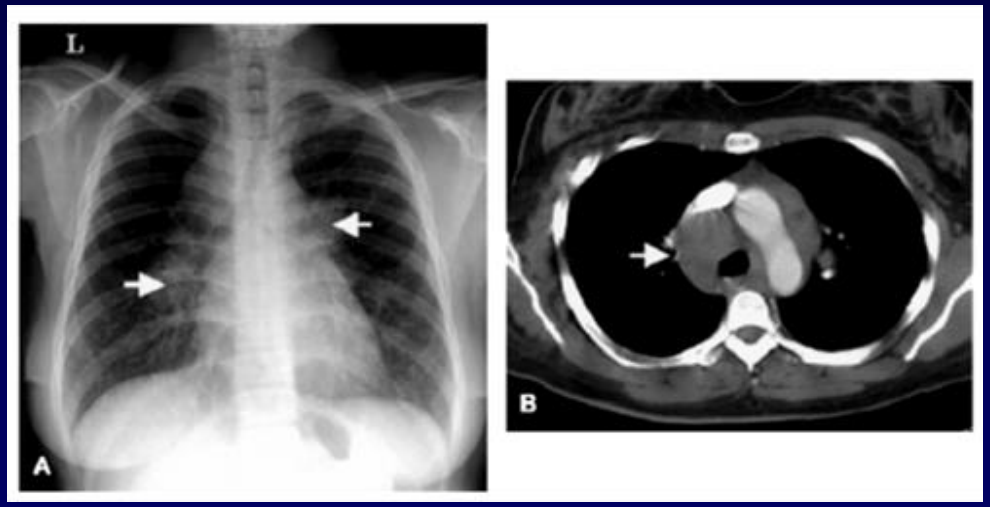


History- Sarcoid is systemic…

- Mikulicz in 1892, salivary and lacrimal gland involvement
- Heerfordt in 1909 (uveoparotid fever) uveitis, salivary gland, and cranial nerve palsy
- Boeck in 1916 showed sarcoidosis to be a systemic disease with “benign miliarlupoids”, also cutaneous anergy to crude tuberculin.
- Kreibich 1904 and Jungling 1921- bone

History- Where's the lung?

- In 1932, Schaumann pioneered lung involvement as the first stage in the natural course of sarcoidosis
- In 1946 Lofgren first described the constellation of erythema nodosum, febrile arthropathy, and bilateral hilar adenopathy



- 1952 Myers described migratory polyarthritis as presenting feature of sarcoidosis

Sarcoid: An inflammatory disease

- Israel in 1954 pioneered the idea of sarcoidosis as an immunologic disease
- From about 1975 on, sarcoidosis recognized as a “hyperactive” disease of inflammation
- 1980 Hunninghake examined inflammatory T cells in bronchoalveolar lavage (BAL)
- 1984 Kataria describes cell-mediated granulomatous response to Kveim-Siltzbach “particulate” skin test.

Who gets Sarcoidosis ?

Sarcoidosis = Genetic X Antigen X Immunologic

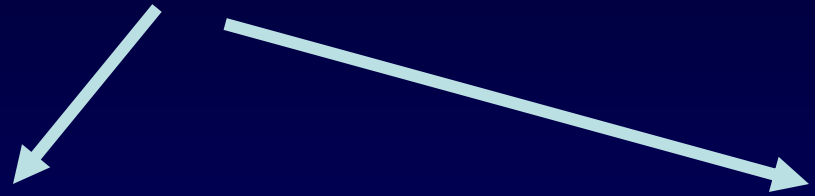
Susceptibility
ie: HLADRB1,
5q,BTNL2

Infection,
Environment

Autoantigen
Amyloid
Vimentin

Severity
ie: TNF,HLA,TCR

Immunogenetics



Sarcoidosis = Genetic X Antigen X Immunologic

Genetics- SAGA, African American

Iannuzzi et al

- Sarcoidosis Genetic Analysis consortium performed genome wide sib-pair multipoint linkage analysis in 229 African American families

- Possible susceptibility gene on 5q11
- Associations with severity phenotypes, different loci

Genetics- German cohort

Valentonyte et al

- SNP scan of 16.4 Mb on chromosome 6p21 in as many as 947 independent cases of familial and sporadic sarcoidosis and found that a 15-kb segment of the gene butyrophilin-like 2 (BTNL2) was associated with the disease

- BTNL2 is a member of the immunoglobulin superfamily and has been implicated as a costimulatory molecule involved in T-cell activation on the basis of homology to B7

- Less so when validated in SAGA, ACCESS- AA population

Genetics- Scandanavia

Wahlstrom et al- Scandanavian sarcoid study

- Characterized HLA DRB1*0301 and cell expansion of CD4+ Va2.3T cells
- Eluted antigen and found 78 aa sequences from self proteins associated with BAL cells (ie: vimentin and ATP-synase) as possible "autoantigen"

Wahlstrom J et al. Identification of HLA-DR-bound peptides presented by human BAL cells in sarcoidosis. J Clin Invest. 2007 Nov 1;117(11):3576-3582.

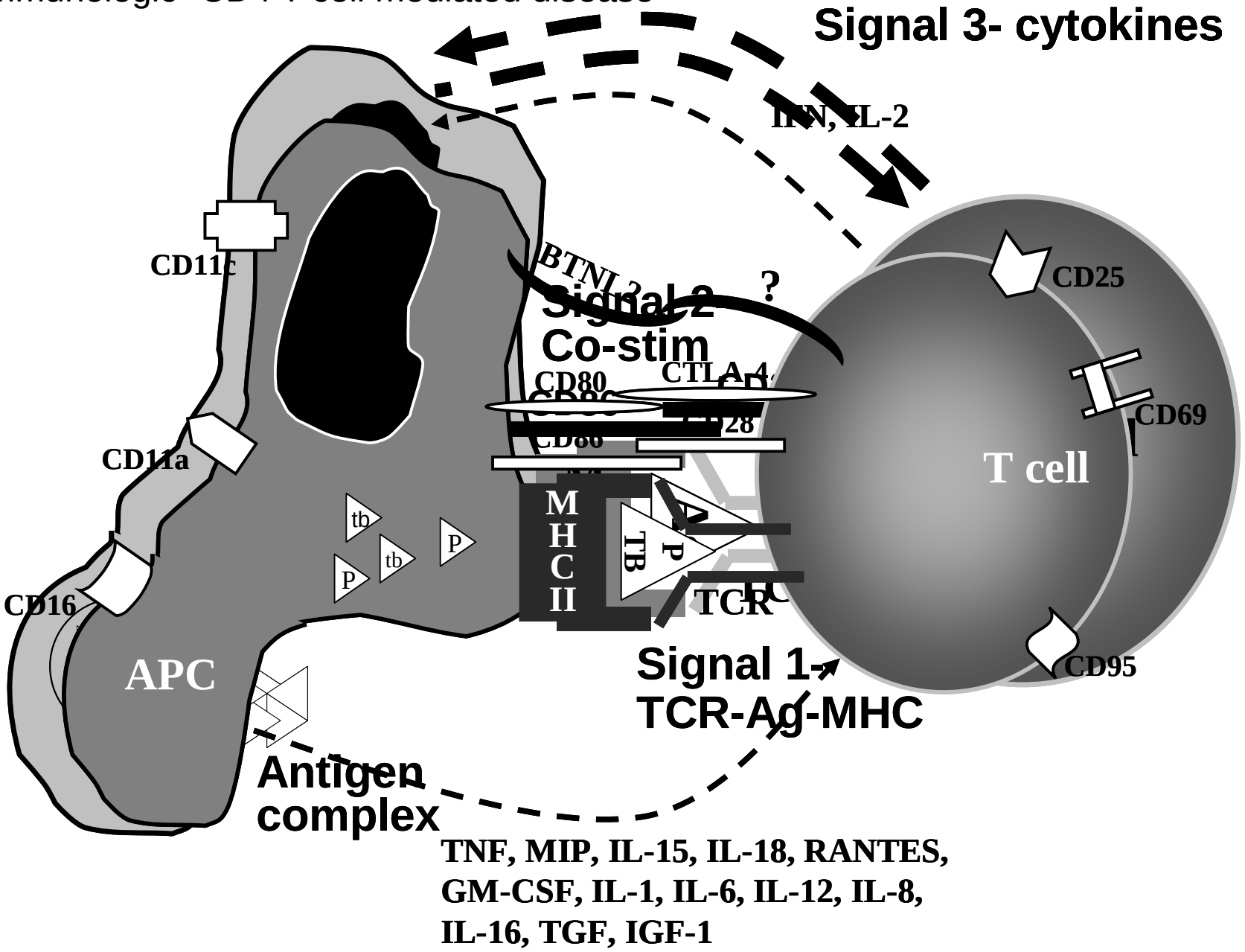
Genetic Factors

Disease Risk Phenotype	Allele	Population	OR	CI	*P*
Increased risk of Lofgren syndrome	DRB1*03	White UK/Dutch	7.97	4.16–15.26	<.0001
	DRB1*0301	White Spanish	3.52	1.83–6.79	.0004
	DRB1*0301	White Swedish	7.71	4.63–12.84	<.0001
	DRB1*03	White Swedish	6.71	NR	<.0001
	DRB1*03-DQB1*0201	White Dutch	12.5	5.69–27.52	<.0001
	DRB1*0301	Finnish	2.46	1.11–5.45	.044
	DRB1*0301	Portuguese	4.01	1.88–8.56	<.01
	DRB1*1501	Finnish	2.16	1.06–4.41	.037

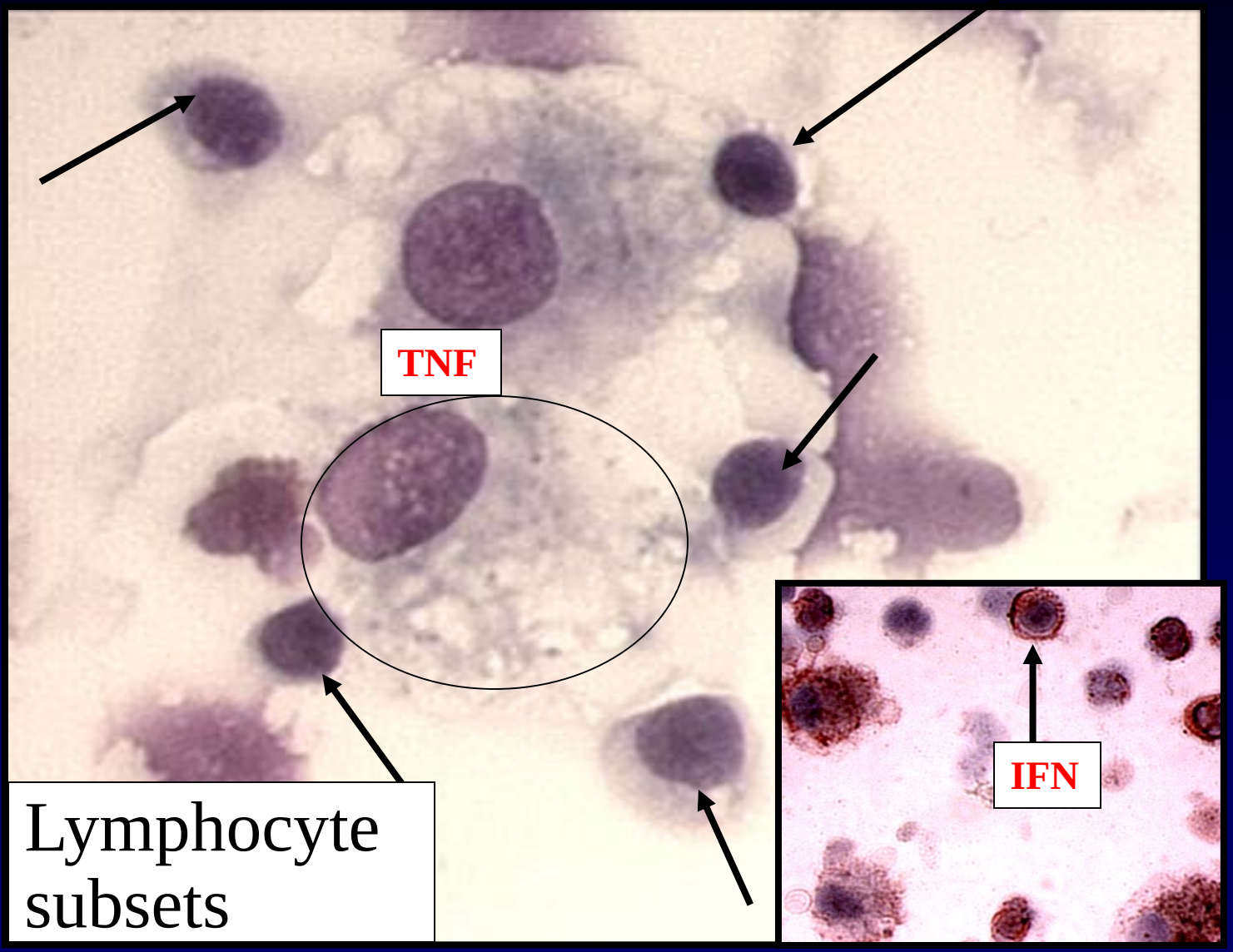
Fingerlin TE. et al. Genetics of Sarcoidosis. Clinics in Chest Medicine. Dec 2015

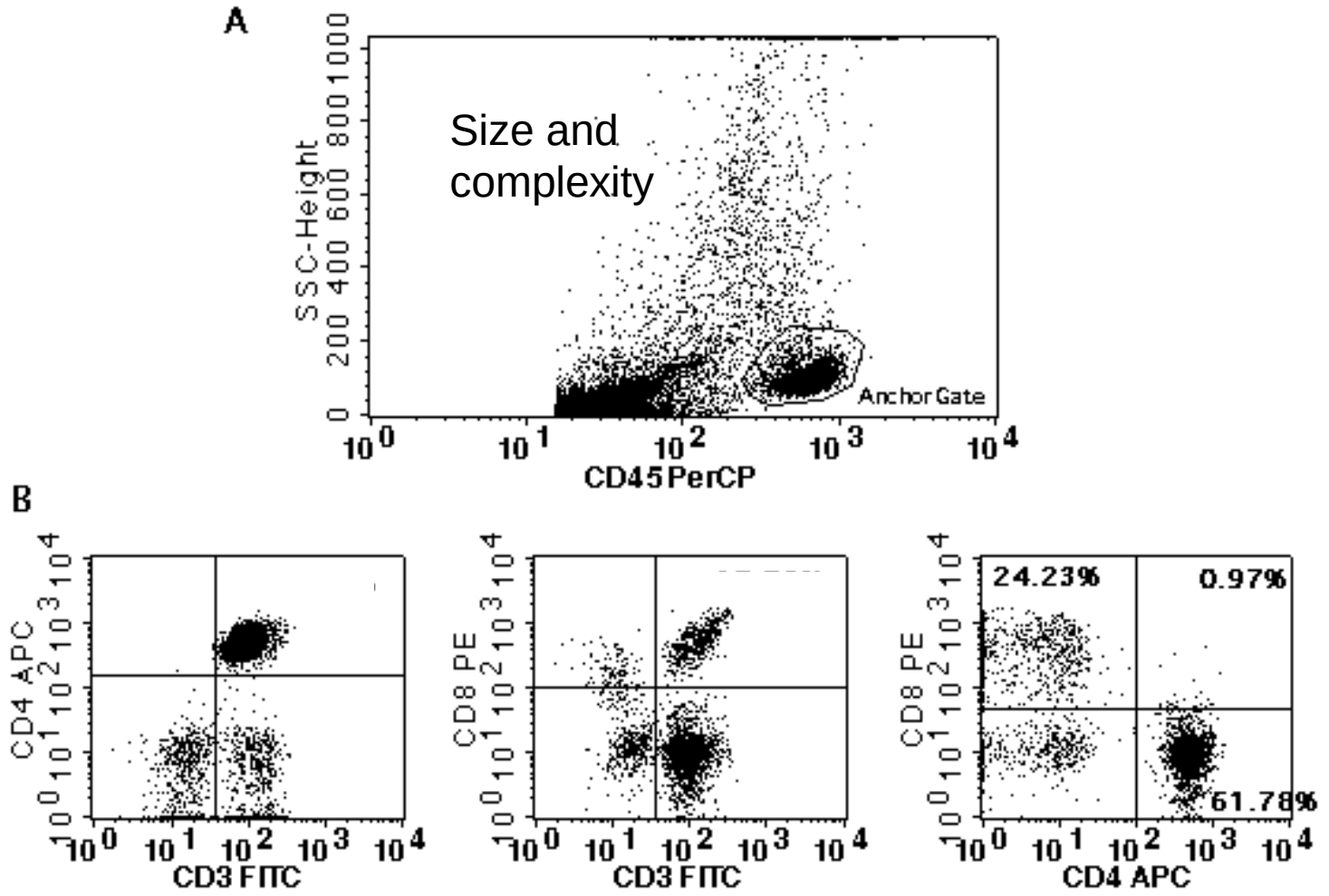
Fingerlin TE. et al. Genetics of Sarcoidosis. Clinics in Chest Medicine. Dec 2015

Immunologic- CD4 T cell mediated disease



BAL research lab

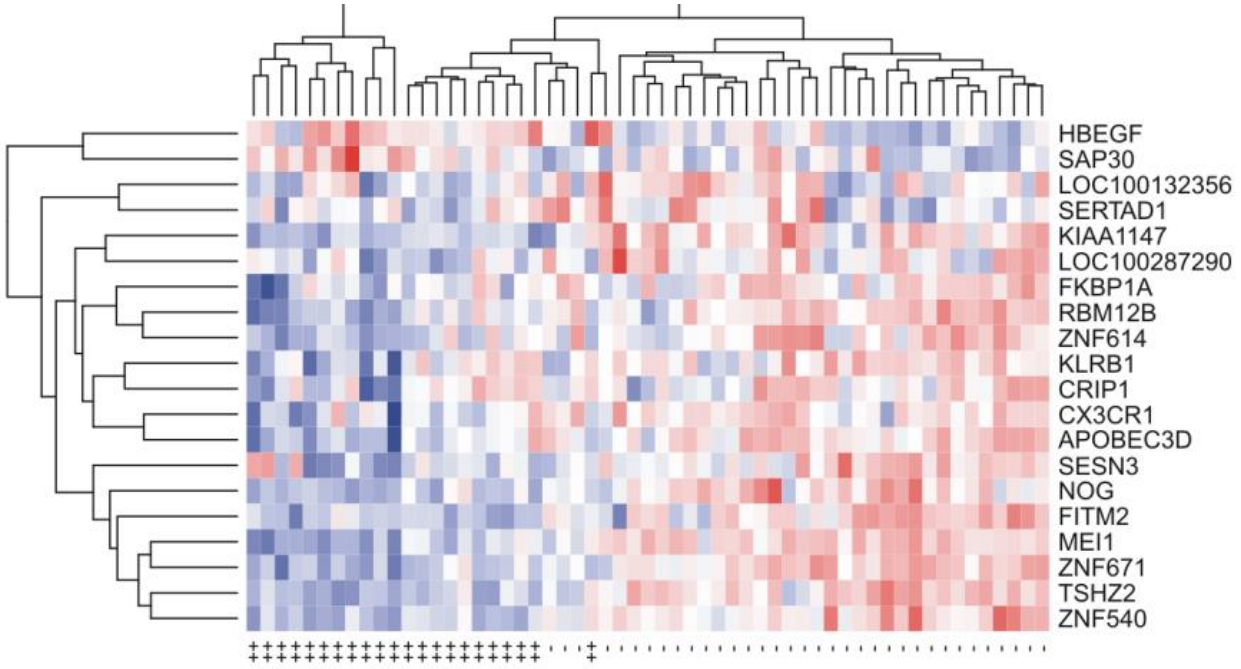




CD4/CD8 ratio = 61.78/24.23 = 2.5 “normal”

Genomic Profiling Produces a Novel Signature and Genomic Biomarker in Sarcoidosis which Predicts Complications

The 20-gene Signature for Complicated** Sarcoidosis



**Cardiac Sarcoid, Neuro Sarcoid, Progressive Lung Sarcoid

Complicated analysis for complicated sarcoidosis ;)

T Zhou et al *PlosOne* 2012

Familial Aggregation of Sarcoidosis

A Case–Control Etiologic Study of Sarcoidosis (ACCESS)

BENJAMIN A. RYBICKI, MICHAEL C. IANNUZZI, MARGARET M. FREDERICK, BRUCE W. THOMPSON, MILTON D. ROSSMAN, EDDY A. BRESNITZ, MICHAEL L. TERRIN, DAVID R. MOLLER, JULIANA BARNARD, ROBERT P. BAUGHMAN, LOUIS DePALO, GARY HUNNINGHAKE, CAROL JOHNS,† MARC A. JUDSON, GENELL L. KNATTERUD, GEOFFREY McLENNAN, LEE S. NEWMAN, DAVID L. RABIN, CECILE ROSE, ALVIN S. TEIRSTEIN, STEVEN E. WEINBERGER, HENRY YEAGER, REUBEN CHERNIACK, and the ACCESS RESEARCH GROUP

Family history = Old school genetics

TABLE 1. SUMMARY OF SARCOIDOSIS FAMILIAL ASSOCIATIONS IN 706 ACCESS CASE–CONTROL PAIRS

	Cases		Controls			
Relative Type	N	Number Affected (%)	N	Number Affected (%)	Odds Ratio (95% Confidence Interval)	p Value
Parents	1,468	18 (1.2)	1,396	4 (0.3)	3.8 (1.2–11.3)	0.019
Sibs	2,722	28 (1.0)	2,587	6 (0.2)	5.8 (2.1–15.9)	0.0007
Children	1,335	5 (0.4)	1,354	3 (0.2)	3.3 (0.3–32.2)	0.298
All first-degree relatives	5,525	51 (0.9)	5,337	13 (0.2)	3.8 (1.9–7.6)	0.0001
Grandparents	2,936	67 (2.3)	2,792	12 (0.4)	5.2 (1.5–18.0)	0.008
Avuncular	5,884	21 (0.4)	5,435	3 (0.1)	5.7 (1.6–20.7)	0.008
All second-degree relatives	8,820	88 (1.0)	8,227	15 (0.2)	5.2 (1.5–18.2)	0.009
All first- and second-degree relatives	14,345	139 (1.0)	13,564	28 (0.2)	4.6 (2.2–9.6)	0.0006
Spouses	702	5 (0.7)	700	7 (1.0)	0.2 (0.04–1.1)	0.058

Am J Respir Crit Care Med Vol 164. pp 2085–2091, 2001

Etiologic agent

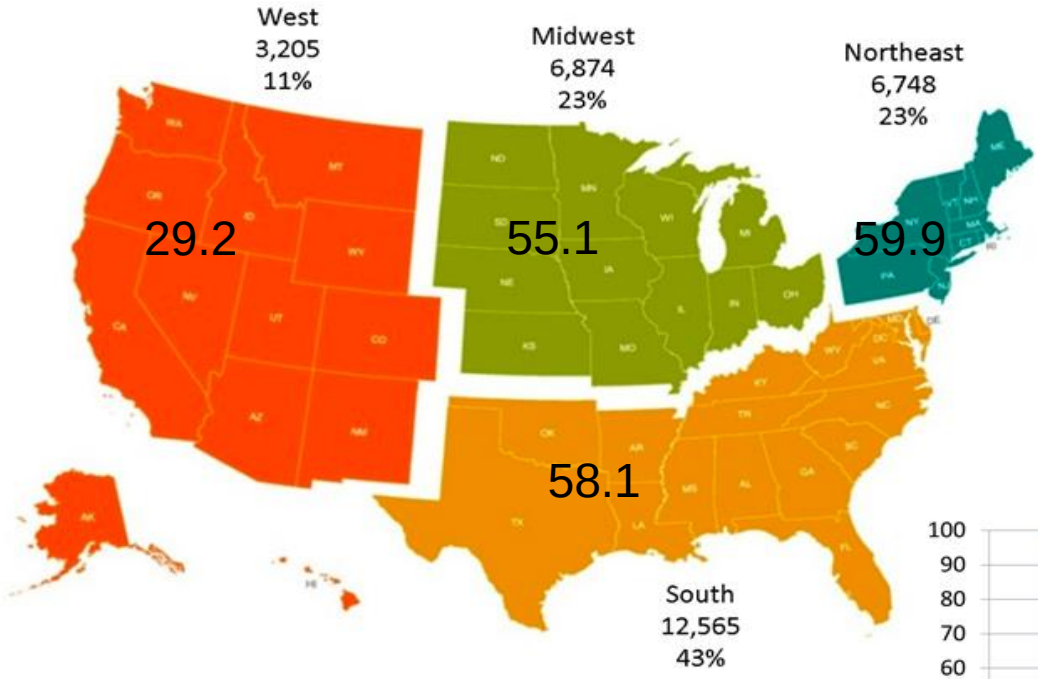
(Environment vs infection)

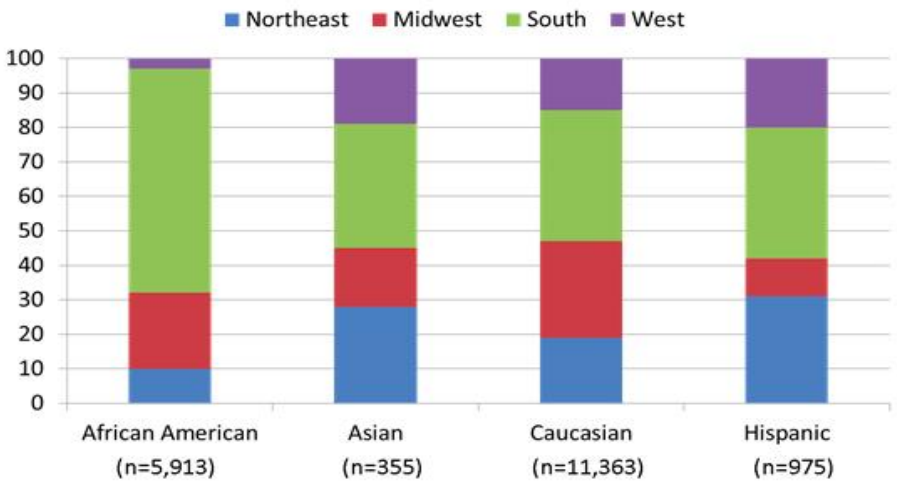
Sarcoidosis = Genetic X Antigen X Immunologic

Environment

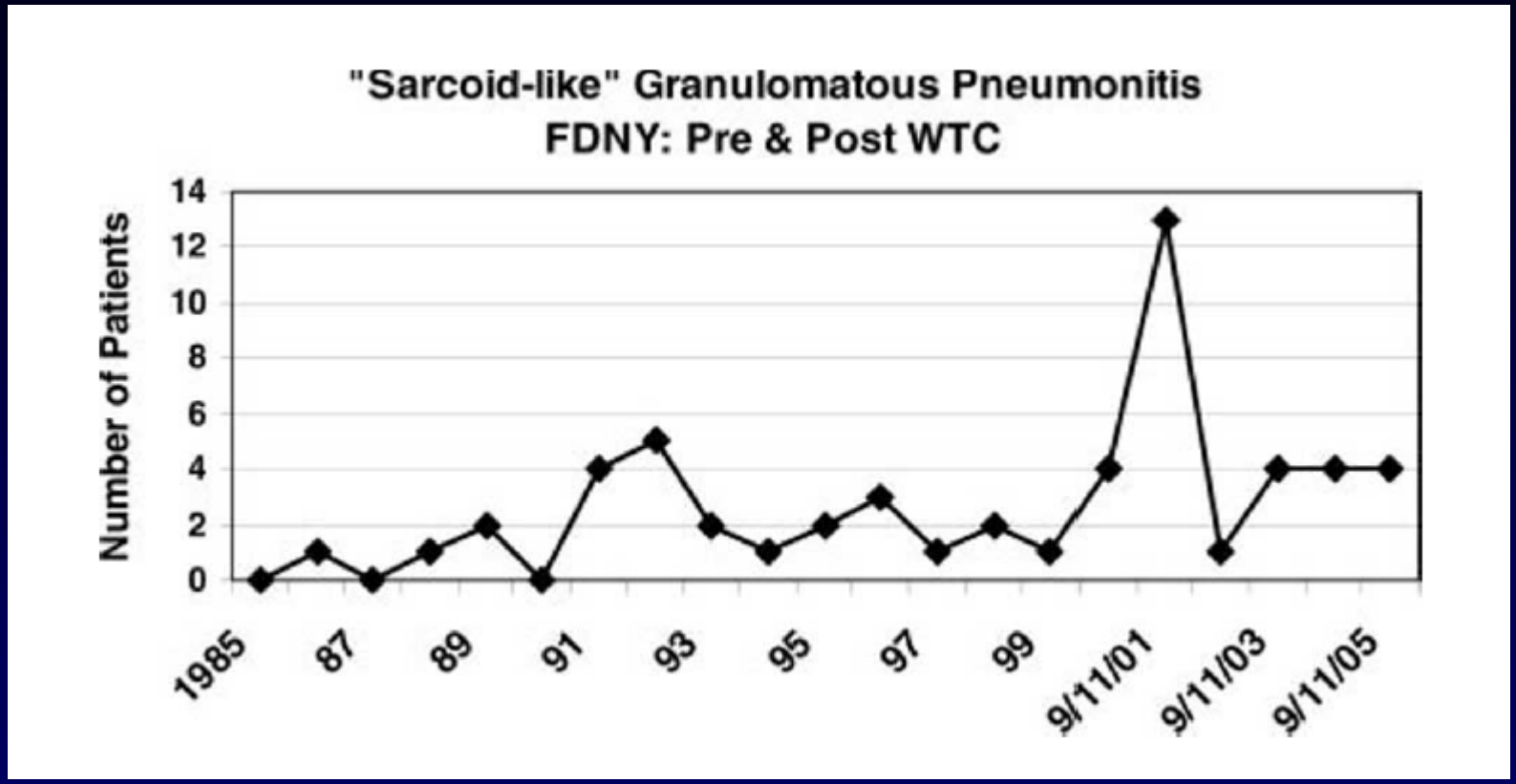
- Beryllium- similar disease
- "Clustering" many reports, (ie: navy)
- Geographical ("farther from the equator")
  - Seasonal "springtime dz"
  - cases reported worldwide.

Prevalence of Sarcoidosis across America per 100,000 population





Baughman RP. Ann Am Thorac Soc 2016



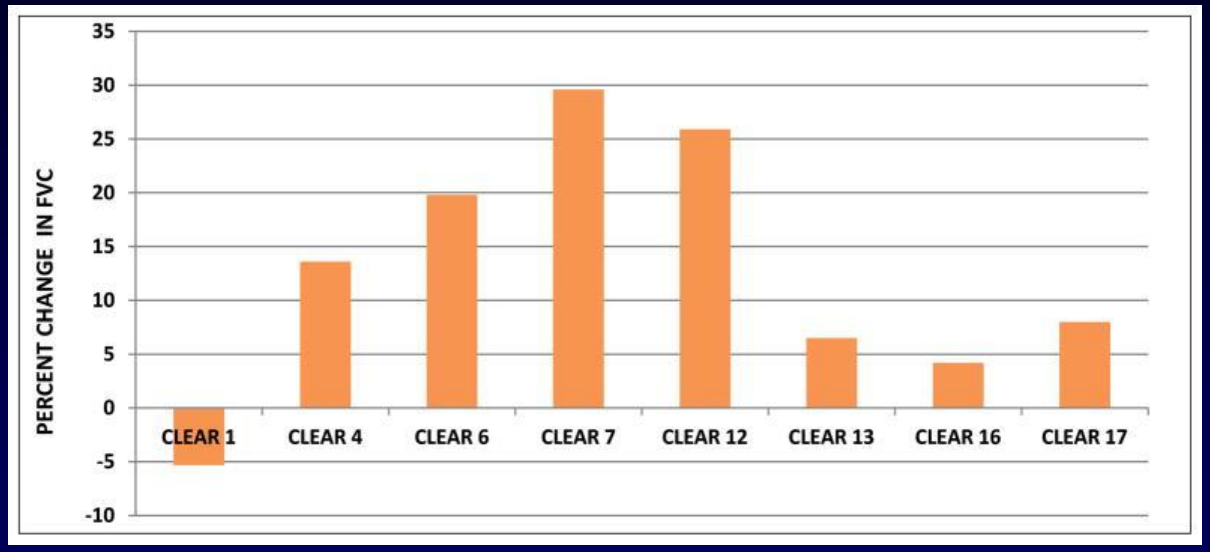
“The sarcoidoses”

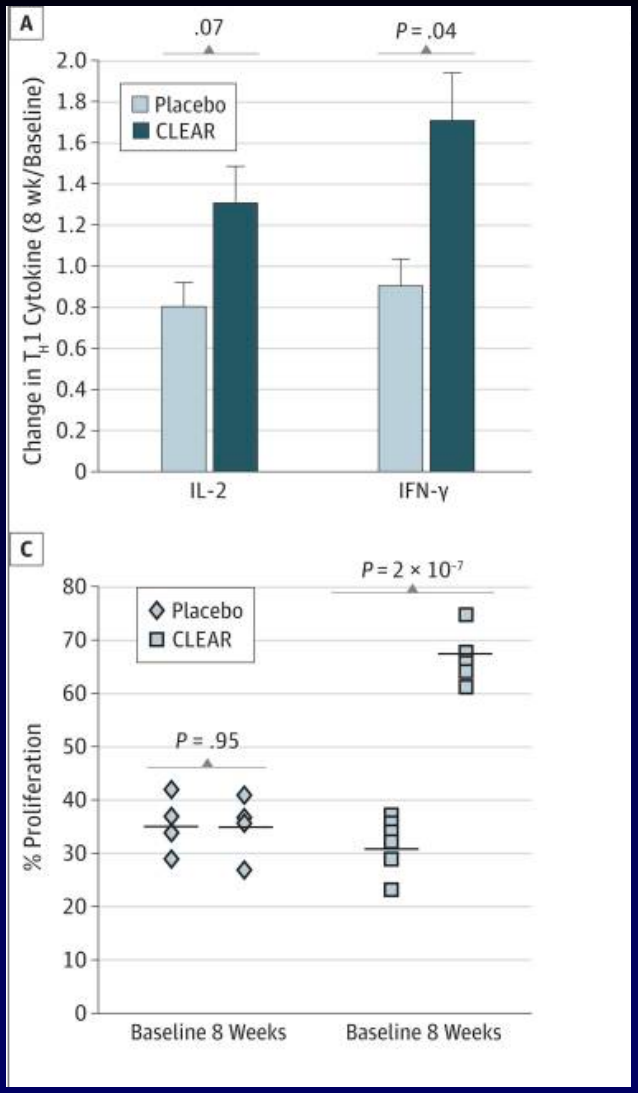
CHEST / 13 1 / 5 / MAY, 2007

Infections that mimic or potential etiology

- Tuberculosis (ESAT-6 and mKat-G)
  - PCR, T cell responses, eluting
- Propionibacteria (Ishigi, Lancet, 1999)
- Histoplasmosis (Indiana experience)
- Coccy (Arizona experience)

CLEAR TRIAL(s): Concomitant Levofloxacin, Ethambutol, Azithromycin, and Rifampin





Drake et al. JAMA Dermatol. 2013 Sep; 149(9): 1040–1049.
Drake et al. Sarcoidosis Vasc Diffuse Lung Dis. 2013 Nov 25; 30(3): 201–211.

Infection Hypothesis

Microbiome (GRADS study)

- Prevotella
- Veillonela
- Streptococcus
- Actinomyces
- Pasteurellaceae

All seen across the sarcoid cohort OW>BAL

Sarcoid reactions

Associated with “Immune-modulating” therapy

- IFN therapy for hepatitis
  - Pietropaoli A et al. Interferon-alpha therapy associated with the development of sarcoidosis. Chest. 1999 Aug;116(2):569-72.
- HIV reconstitution syndrome (IRIS)
  - Foulon et al. Sarcoidosis in HIV-infected patients in the era of highly active antiretroviral therapy. Clin Infect Dis. 2004 Feb 1;38(3):418-25.
- Anti-TNF
- IL-2

Summary

- Inflammatory disorder
- Many genes and cytokines involved
- Cause unknown, but infectious and autoantigens recently defined
- Role of clearance vs antigen persistence
- Cohort matters
- Further study based on clinical phenotype

Epidemiology and ACCESS

Sarcoidosis- epidemiology

Second most common lung disease in young adults (second only to asthma)

- Lifetime risk .85% for US whites
- Lifetime risk 2.4% for US blacks
- Blacks:Whites 3-7:1 in US

Clinical Characteristics of Patients in a Case Control Study of Sarcoidosis

ROBERT P. BAUGHMAN, ALVIN S. TEIRSTEIN, MARC A. JUDSON, MILTON D. ROSSMAN, HENRY YEAGER, JR., EDDY A. BRESNITZ, LOUIS DEPALO, GARY HUNNINGHAKE, MICHAEL C. IANNUZZI, CAROL J. JOHNS, GEOFFREY MCLENNAN, DAVID R. MOLLER, LEE S. NEWMAN, DAVID L. RABIN, CECILE ROSE, BENJAMIN RYBICKI, STEVEN E. WEINBERGER, MICHAEL L. TERRIN, GENELL L. KNATTERUD, REUBEN CHERNIAK, and A CASE CONTROL ETIOLOGIC STUDY OF SARCOIDOSIS (ACCESS) RESEARCH GROUP

TABLE 2. DISTRIBUTION OF CASES BY SEX AND ETHNIC ORIGIN

	White	Black	Other	Percent
Female	223	234	11	63.6
Male	170	91	7	36.4
Percent	53.4	44.2	2.4	

Am J Respir Crit Care Med Vol 164. pp 1885–1889, 2001

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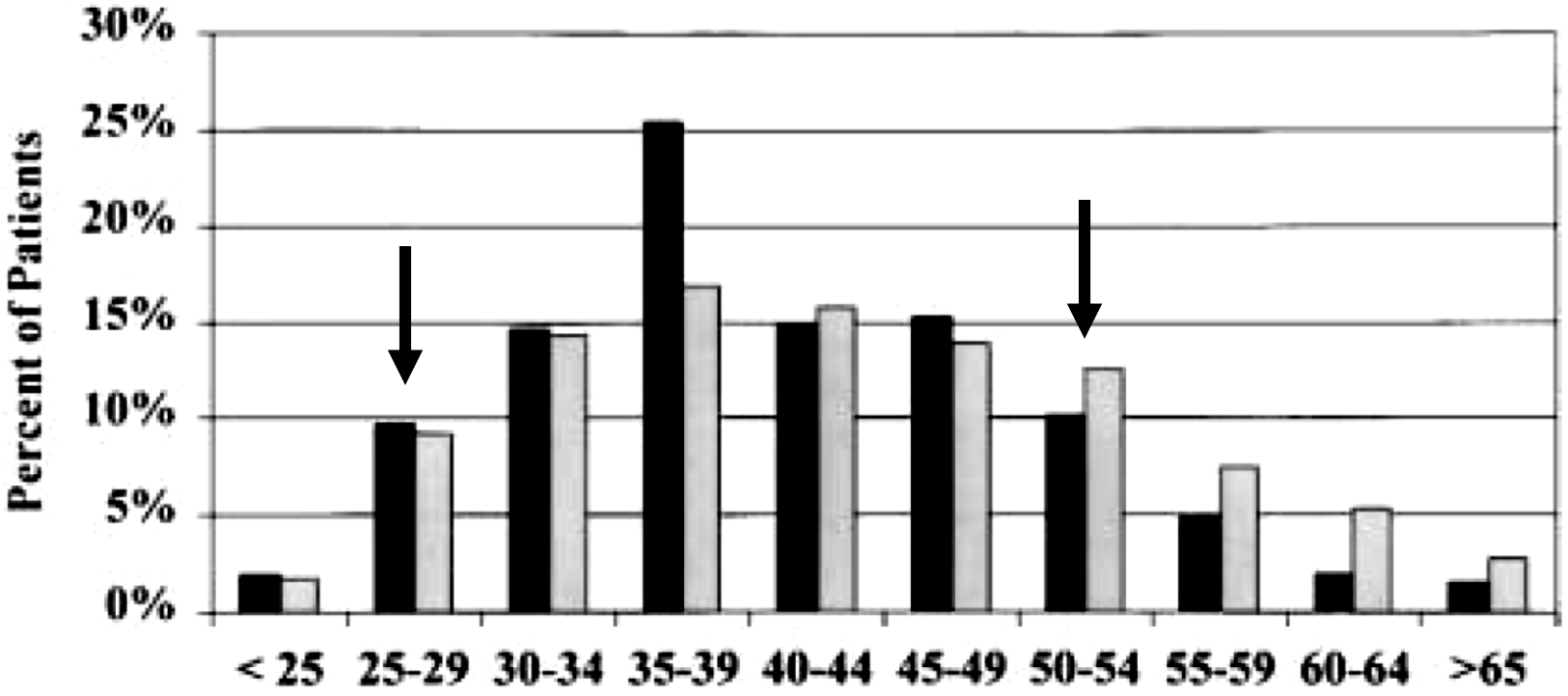


Am J Respir Crit Care Med Vol 164. pp 1885–1889, 2001

A Case Control Etiologic Study of Sarcoidosis

Environmental and Occupational Risk Factors

Lee S. Newman, Cecile S. Rose, Eddy A. Bresnitz, Milton D. Rossman, Juliana Barnard, Margaret Frederick, Michael L. Terrin, Steven E. Weinberger, David R. Moller, Geoffrey McLennan, Gary Hunninghake, Louis DePalo, Robert P. Baughman, Michael C. Iannuzzi, Marc A. Judson, Genell L. Knatterud, Bruce W. Thompson, Alvin S. Teirstein, Henry Yeager, Jr., Carol J. Johns†, David L. Rabin, Benjamin A. Rybicki, Reuben Cherniack, and the ACCESS Research Group*

Am J Respir Crit Care Med Vol 170. pp 1324–1330, 2004

Variable	Odds Ratio	Confidence Inter
Positive Associations with Sarcoidosis		
Exposure to musty odors, occupational	1.62	(1.24-2.11)
Insecticide exposures, occupational	1.61	(1.13-2.28)
Use of air conditioning in home	1.48	(1.10-1.99)
Job as middle or high school teacher	1.80	(1.14-2.83)
Job with radiation exposure †	2.28	(1.17-4.47)
Job in automobile manufacturing	13.38	(1.48-120.9
Job in cotton ginning	4.98	(1.19-20.89
Job raising birds	3.73	(1.10-12.59
Bird exposure, avocational †	1.49	(1.00-2.21)

Am J Respir Crit Care Med Vol 170. pp 1324–1330, 2004

Variable	Odds Ratio	Confidence Inter
Negative Associations with Sarcoidosis		
Ever smoked cigarettes	0.65	(0.51-0.82)
Childcare, unpaid	0.64	(0.50-0.81)
Use of feather/down pillows	0.69	(0.54-0.87)
Cats	0.66	(0.50-0.87)
Hot tub use	0.70	(0.54-0.91)
Job as data processor/typist, programmer	0.70	(0.54-0.91)
Fish (tank >10 gallon)	0.74	(0.58-0.94)
Foam pillow use †	0.73	(0.55-0.95)
Hospital volunteer †	0.60	(0.39-0.93)
Gold exposure, occupational †	0.26	(0.08-0.85)
Exposure to welding †	0.40	(0.16-0.96)

Am J Respir Crit Care Med Vol 170. pp 1324–1330, 2004

Clinical manifestations and Diagnosis

Approach to Diagnosis

- Appropriate Clinical Setting
- Supportive evidence (ie: organ involvement, BAL, PFTs, ACE)
- Find the Granuloma
- Exclude other causes of Granuloma
- “Can never be 100% sure”
    - Diagnosis of exclusion

Diagnostic evaluation

The ATS consensus statement (1999) suggests performing a comprehensive initial evaluation including:

- history (occupational and environmental exposure)
- physical examination
- posteroanterior chest radiography;
- pulmonary function tests (spirometry and DLCO)
- peripheral blood counts, serum chemistries (calcium, liver enzymes, creatinine, blood urea nitrogen);
- urine analysis
- Electrocardiogram
- routine ophthalmologic examination
- tuberculin skin test

Symptoms

- Nonspecific
  - Fever, sweats
  - Weakness,
  - Weight loss
  - Aches and pains
  - Lumps and bumps
- Psychological issues
- Organ specific symptoms

Malignancies Observed in Patients with Sarcoid Reactions

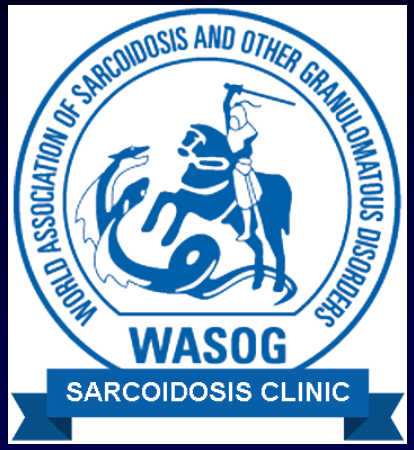
Hematologic Malignancies	Solid Tumors
CLL	Bile Duct
CML	Breast
Hodgkin disease	Esophagus
NHL	Renal
T-Cell Lymphoma	Pancreas
	Rectum
	Stomach
	Lung
	Melanoma
	Ovary/Testicular

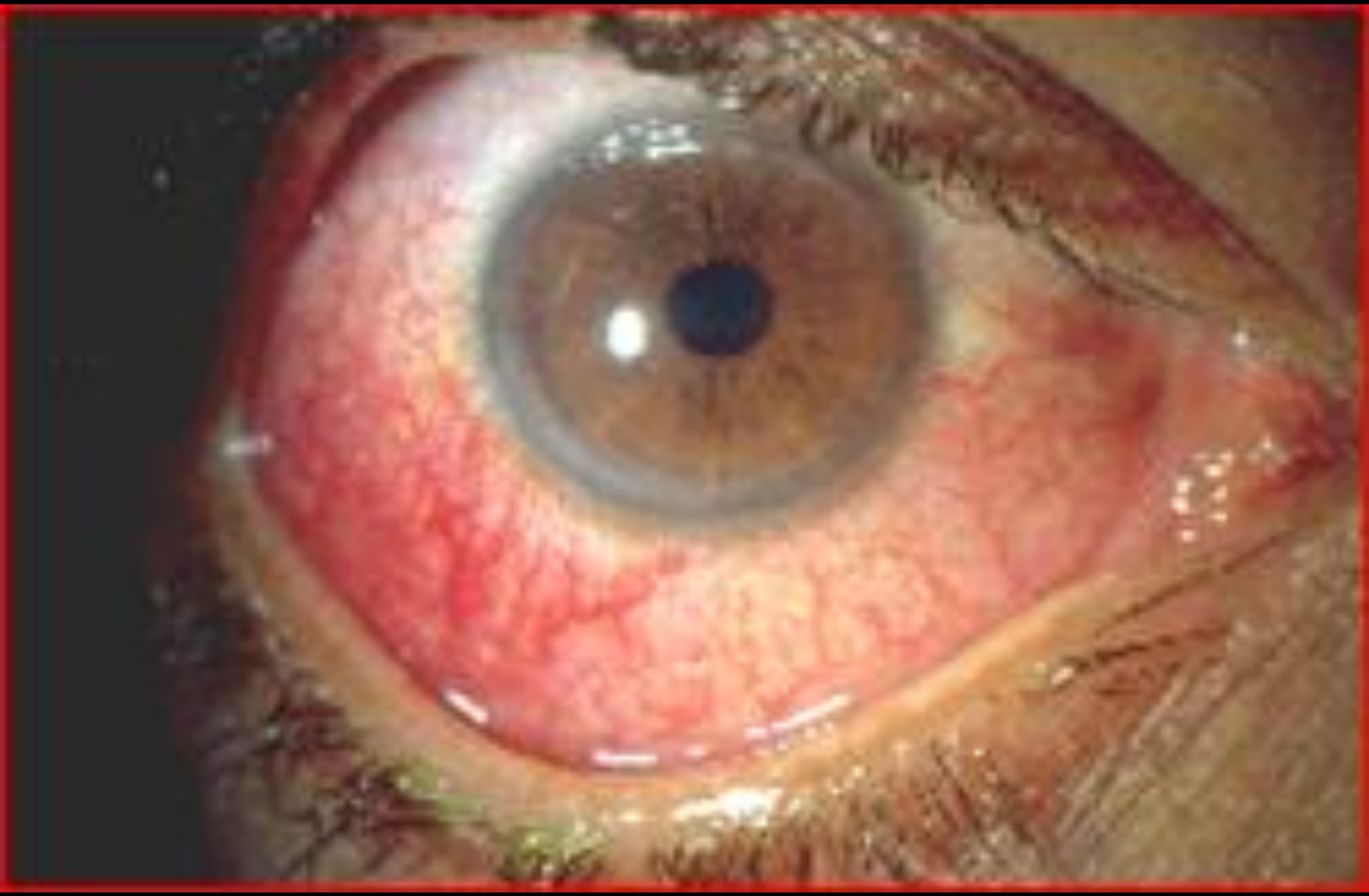
Laboratory Testing

- Routine bloodwork
  - Blood counts (CBC)
    - Lymphopenia (45%); leukopenia (30%)
    - Anemia up to 20%; low platelets < 2%
  - Hepatic profile
    - Isolated Alk phos
    - Transaminitis
  - ACE level
    - Gaucher disease, leprosy, untreated hyperthyroidism, psoriasis, infants with ARDS, amyloidosis, and histoplasmosis
    - Polymorphisms, ACE inhibitors

More Directed Testing

- Sarcoid clinic:
  - ACE, lysozyme, ESR, CRP
  - RF, CCP, ANA
  - Immunoglobulins, Vit D, Ca++
  - CK, aldolase
  - histoplasma, coccy studies
  - Soluble IL-2r and KL-6, some centers
  - Biopsy affected site
  - BAL, biopsy lung





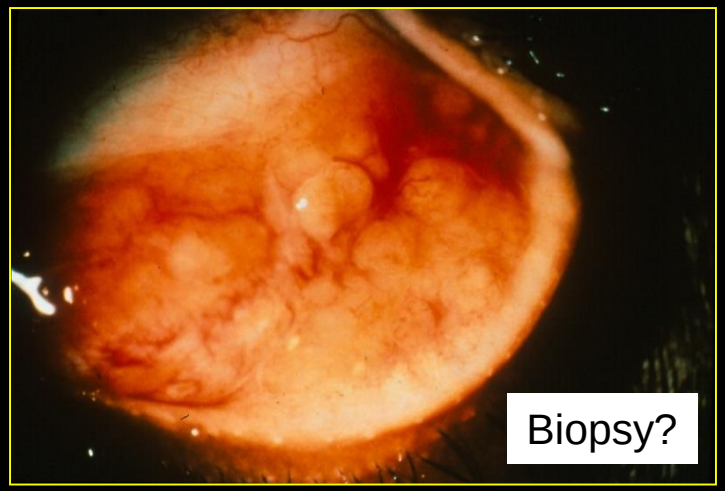
Diagnosis- Ocular

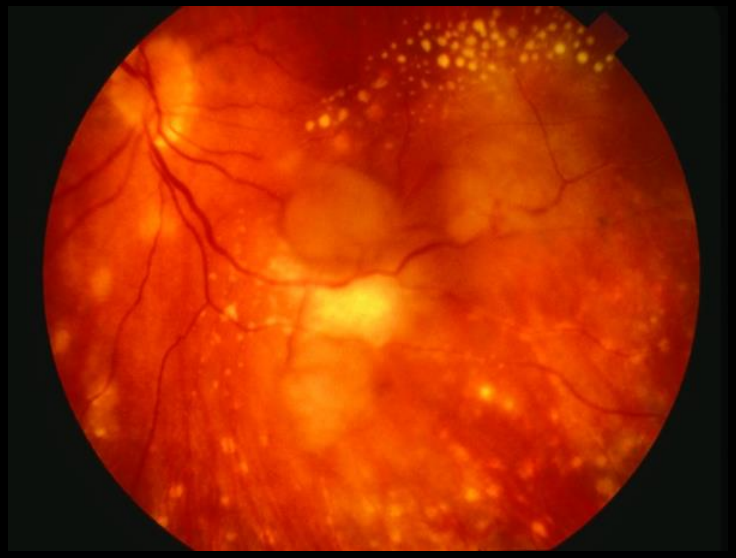
- Eye: anterior or posterior uveitis, mass
- Testing: Slit-lamp eye exam, MRI
- Diagnosis: can biopsy lid if small lesions
  - Reluctant if no visible lesion (yield < 20-50%)

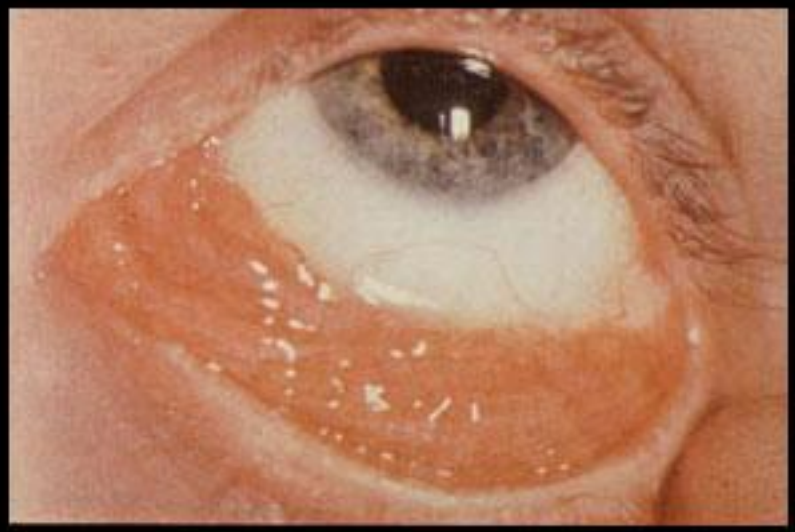
25% of patients

Eye

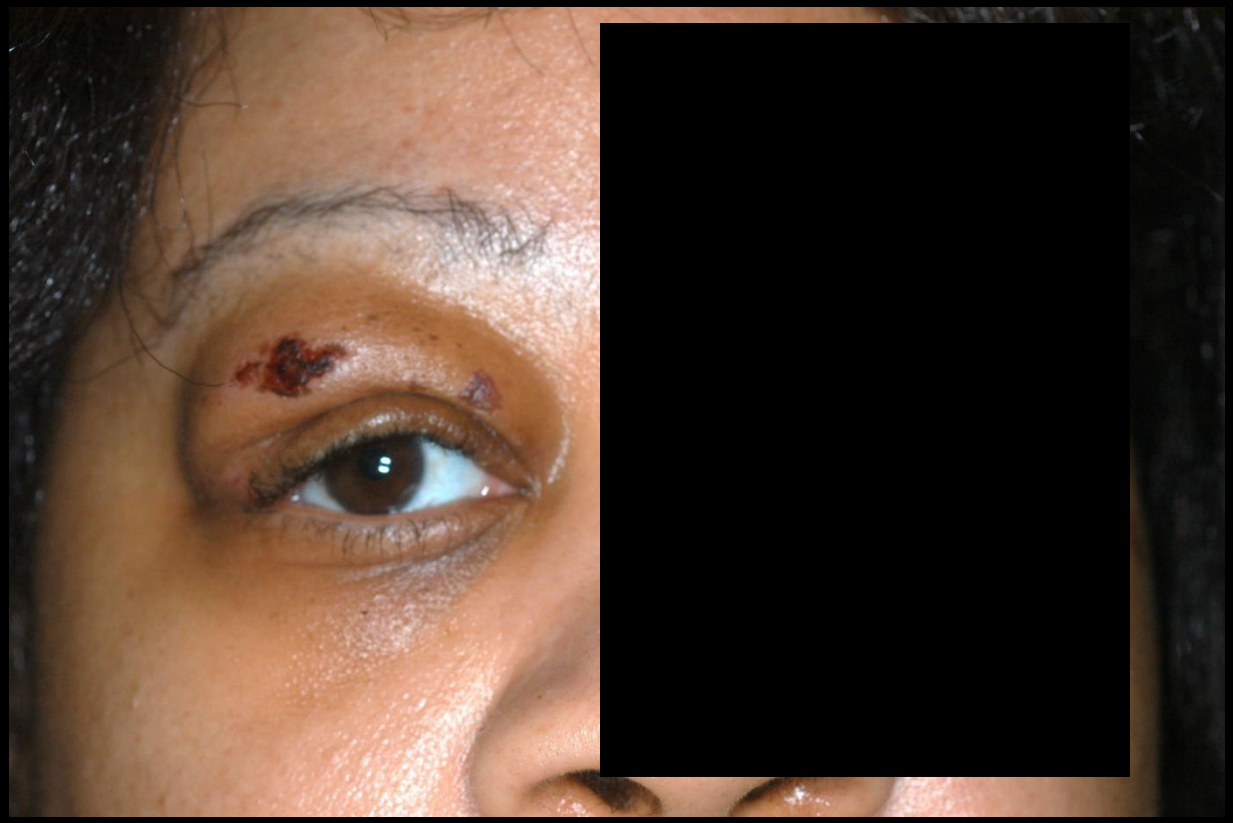
Courtesy: Ramana Moorthy







Eye

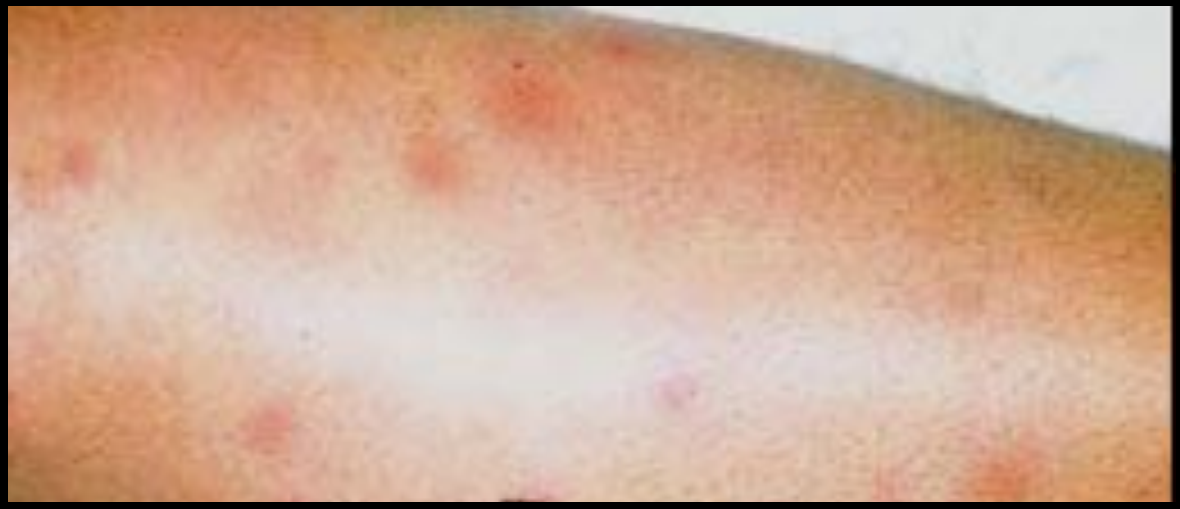


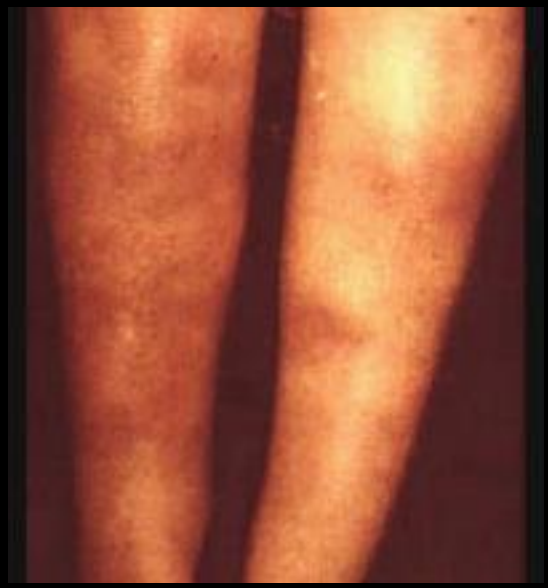
Diagnosis and Derm

- Skin: many rashes
  - Lupus pernio (biopsy)
  - Nodules, flat patches (biopsy)
  - Erythema Nodosum (biopsy non-specific)
- Diagnosis: Appearance can be classic, biopsy to support

20% of patients

Skin

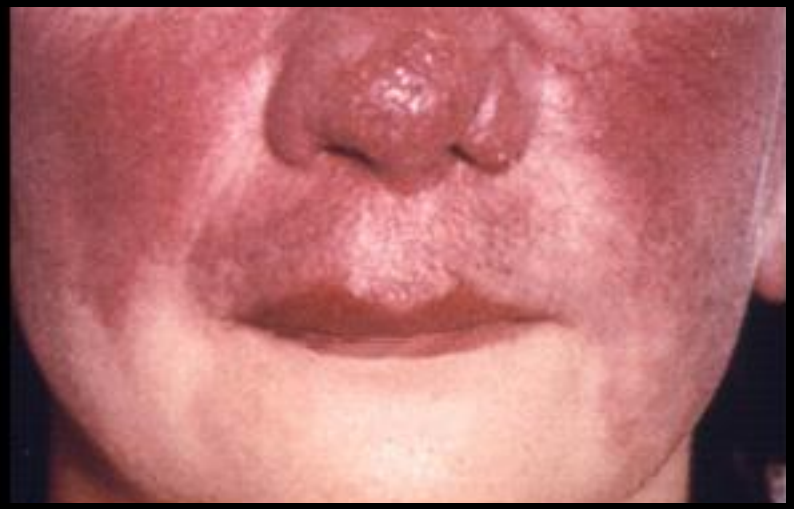




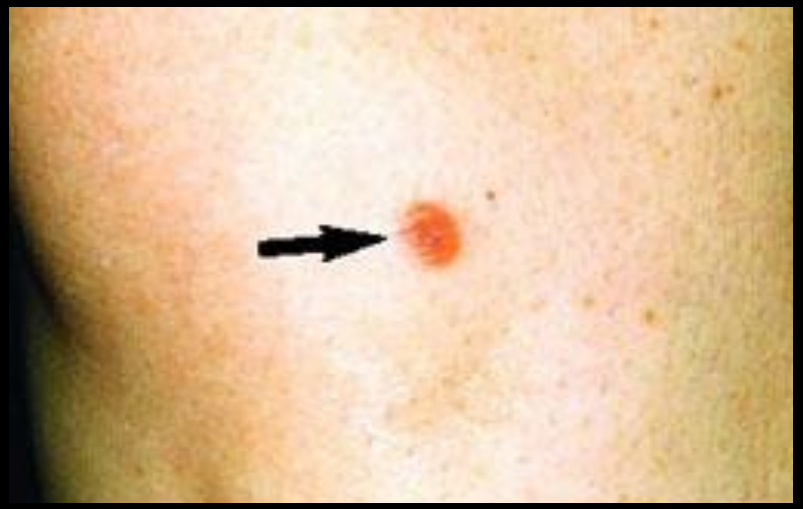
Erythema nodosum

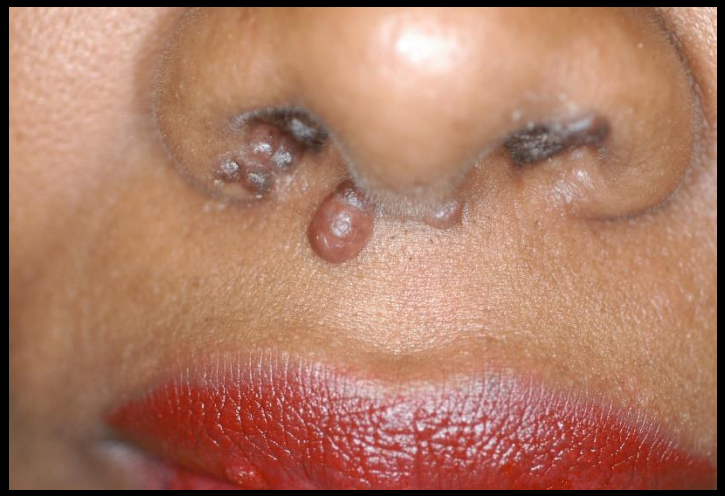
Skin

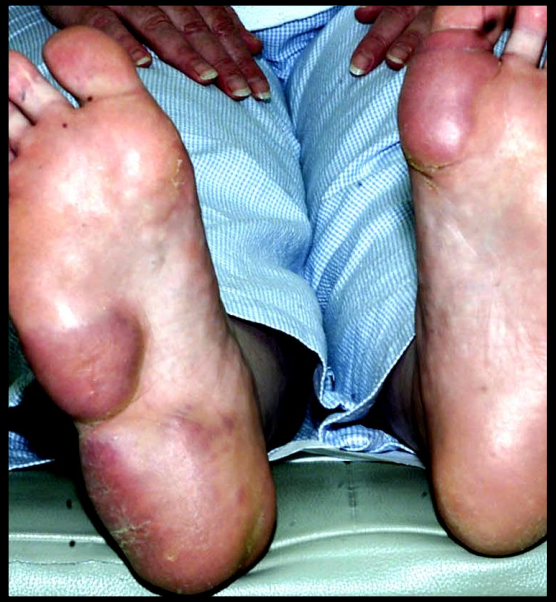
Terrence DEMOS [tdemos@lumc.edu], with permission

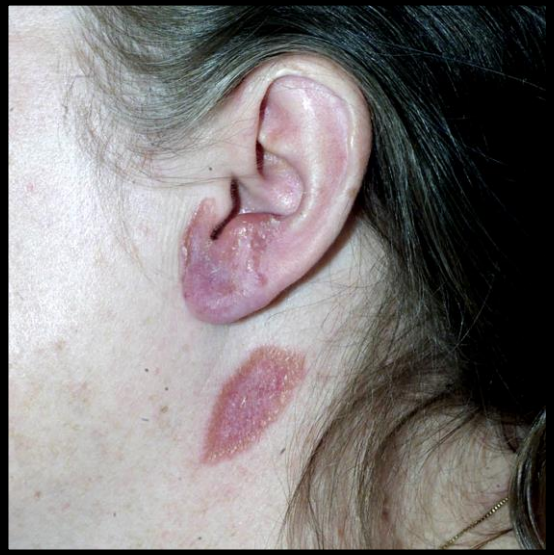


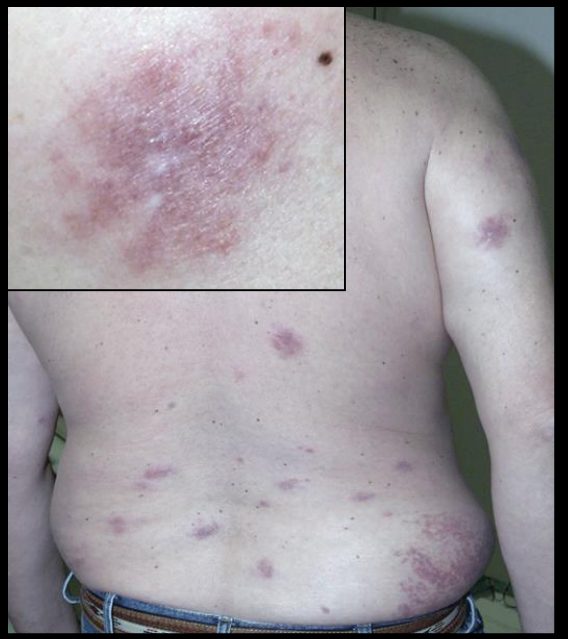
Lupus pernio

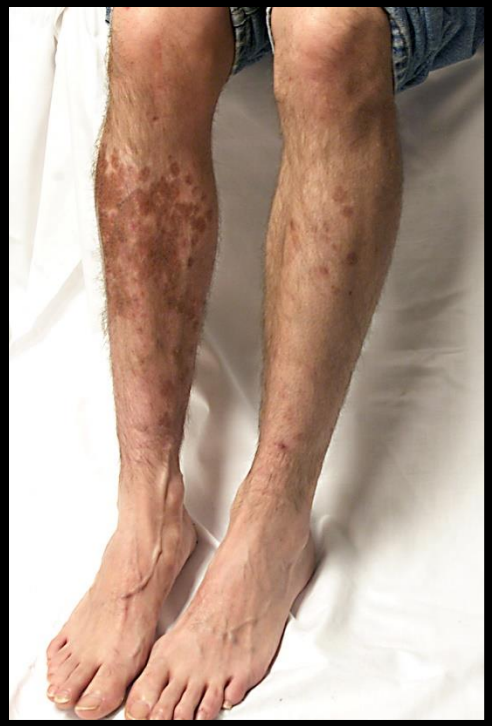


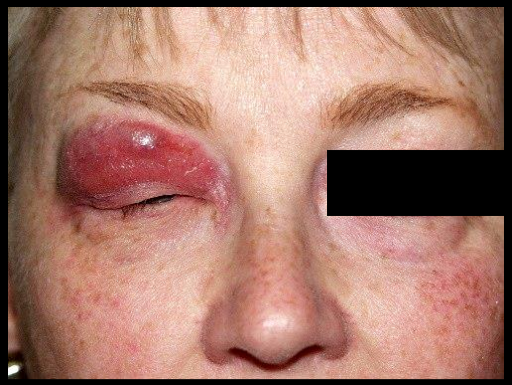


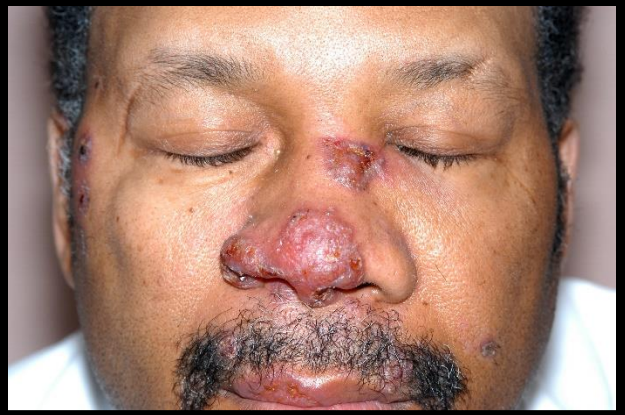


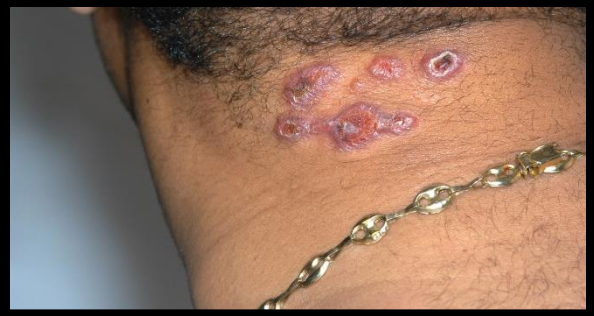


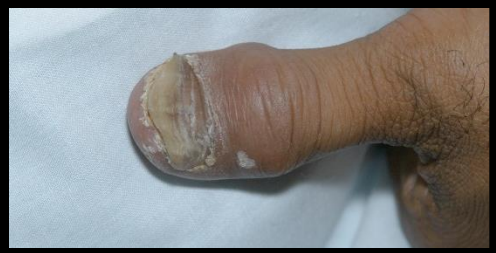








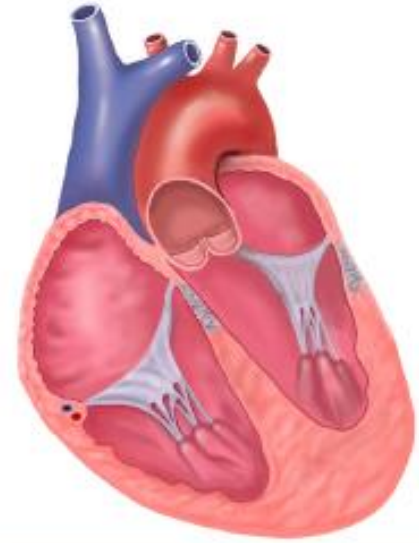




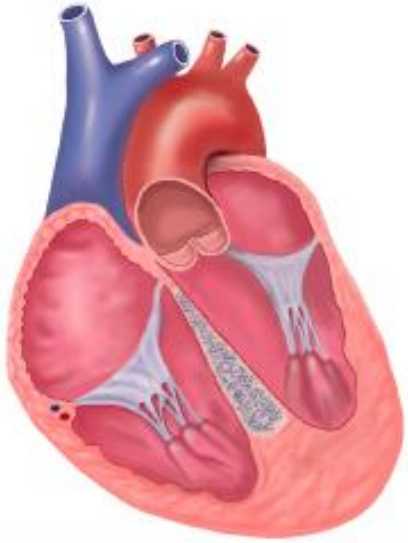
Diagnosis- cardiac

- Heart: dysrhythmia, pericardial, pulm htn if severe, causing reduced LV function
- Testing: EKG, echo, Holter,
  - MRI, PET, EPS → ?AICD
- Diagnosis:
  - Can biopsy heart, but not typical
  - Presumed if sarcoidosis affecting other organs

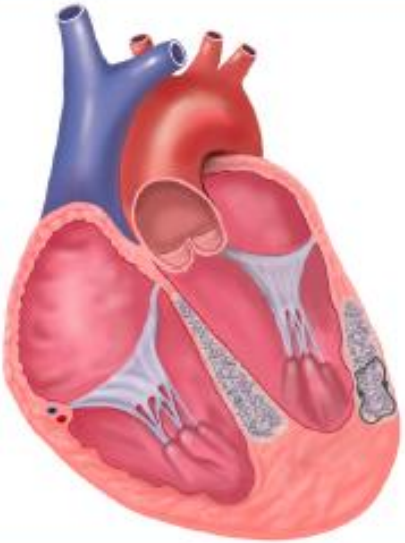
5% symptomatic, 30% incidental, Japanese



Small patches of basal involvement, usually clinically silent



Large area of septal involvement, often clinically manifest as heart block

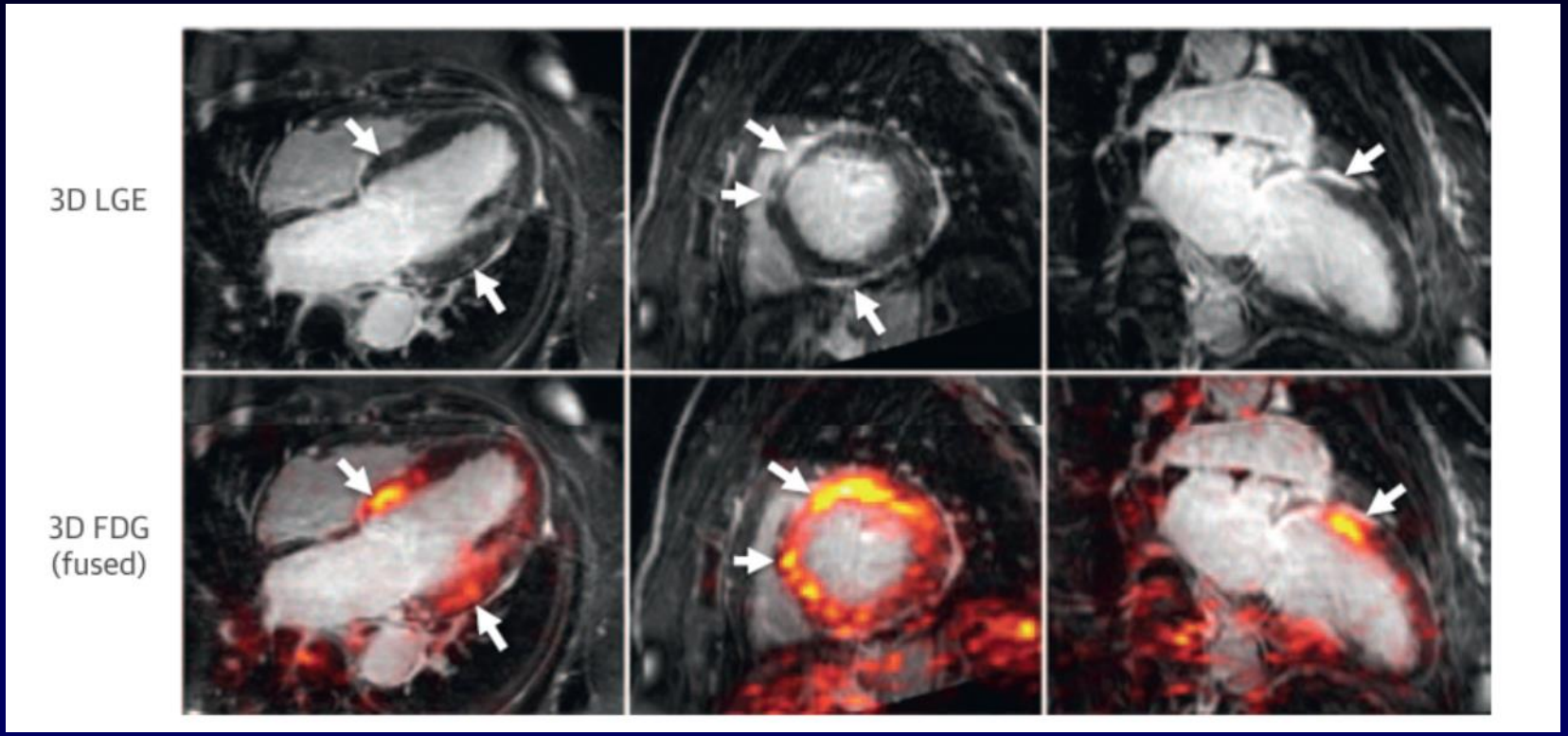


Re-entrant circuit involving area of granuloma/fibrosis leading to VT

Extensive areas of LV and RV involvement, often clinically manifest as heart failure +/- heart block +/- VT

Birnie, D.H. et al. J Am Coll Cardiol. 2016;68(4):411–21.

Heart



Birnie, D.H. et al. J Am Coll Cardiol. 2016;68(4):411–21

Therapy	Medication	Mechanism	Potential benefit	Potential harm
Medical immunosupressive therapy	Prednisone (level of evidence C)	Anti-inflammatory, start 40–60 mg per day	No RCT data. An observational study of 23 cardiac sarcoid subjects suggests that ^{18}F-FDG PET may guide steroid therapy (LVEF of 3.8% per reduction in SUV volume of 100 cm^3 above a threshold value, P=0.022) (18)	Diabetes, weight gain, hypertension, insomnia, depression and irritability, fractures, infection
	Methotrexate (level of evidence C)	Anti-metabolite and immune-modulator	Steroid-sparing. No RCT data. In a three year open-label study comparing 7 *vs.* 10 CS subjects treated with steroid or steroid + MTX, respectively, steroid + MTX had improved LVEF (44.5%±13.8% *vs.* 60.7%±14.3%, P=0.04) (19)	Thrombocytopenia, anemia, immunosuppression, pulmonary and liver toxicity, neurologic toxicity, infection
	Other immune-modulators (level of evidence C)	Varied	Steroid-sparing. Case reports only have included Infliximab, Azathioprine, Cyclosporine, Anti-malarials, Pentoxifylline, Azathioprine, Thalidomide	Anemia, immunosuppression, other specific toxicities
Medical therapy for heart failure	ACE/ARB (level of evidence A)	Improves adverse cardiac remodeling	Class I to reduce mortality and morbidity of HFrEF. Class IIa for structural heart disease without impaired LVEF or symptoms (20)	Renal impairment, electrolyte abnormality, allergy, angioedema, cough
	Beta-blockers (level of evidence C)	Negative inotrope, delays AV conduction	Class I to reduce mortality and morbidity for HFrEF (20)	Fatigue, cardiac conduction block, mood effects, erectile dysfunction
	Diuretics and restricted dietary sodium (level of evidence C)	Fluid and sodium excretion	Class I for HFrEF and symptoms (20)	Renal impairment, electrolyte abnormality, orthostasis

Hulten et al. Cardiac sarcoidosis. *Cardiovasc Diagn Ther* 2016;6(1):50-63

	Intervention	Mechanism	Potential benefit	Potential harm
Device therapy	ICD, secondary prevention (level of evidence C) (7)	Defibrillation of potential recurrent VT/VF	Class I recommendation to reduced mortality in patients with structural heart disease and syncope, VT/VF, or sustained VT/VF inducible by EP study. Class III if life-expectancy <1 year (7)	Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock
	ICD, primary prevention (level of evidence C) (7)	Defibrillation of potential VT/VF	Class I recommendation to reduce mortality in patients with structural heart disease and EF <30–35% despite medical therapy. Class IIa for those needing pacemaker, unexplained syncope, or sustained VT/VF inducible by EP study. LGE on CMR may be used to consider EP study. Class IIb for LVEF 36–49% or RVEF <40% despite medical therapy. Class III if life-expectancy <1 year (7)	Pain, infection, cost, lead fracture, need for re-implantation, inappropriate shock
	Pacemaker (level of evidence C) (7)	Prevention of immediately fatal arrhythmia	Class I recommendation to reduce mortality and symptoms from complete heart block and bradyarrhythmia (7,21)	Pain, infection, cost, lead fracture, re-implantation, device removal complex if heart block resolves
Surgical	Heart and lung transplantation (level of evidence C)	Surgical transplant	Surgically replace organs affected by sarcoidosis with donor organs when end-stage organ dysfunction that may include refractory cardiogenic shock, IV inotrope dependence, peak VO_2 <10 mL/kg per min with achievement of anaerobic metabolism, refractory VT/VF (20)	Infection, need for chronic immunosuppression, risk of surgery, acute and chronic rejection, chance of recurrence (17)

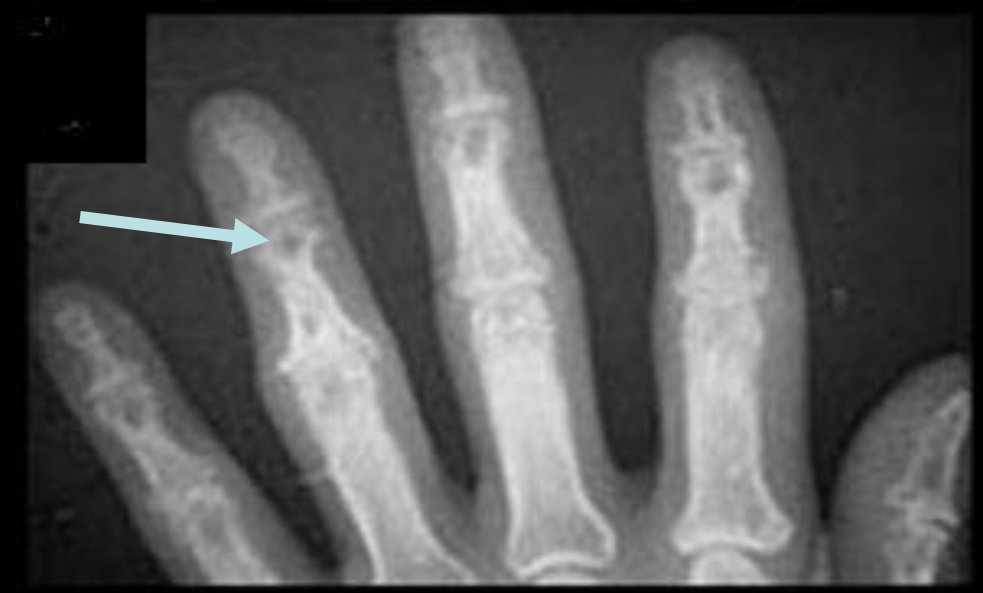
Hulten et al. Cardiac sarcoidosis. *Cardiovasc Diagn Ther* 2016;6(1):50-63

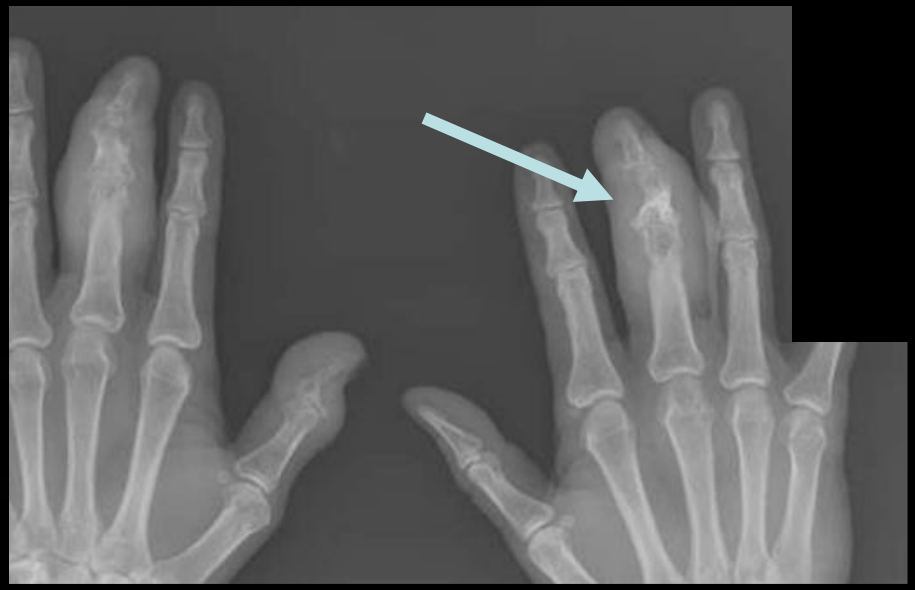
Diagnosis- musculoskeletal

- Bone: pain, arthritis
- Testing: X-ray
- Diagnosis:
  - Can have classic features

< 5% have bone involvement; less than 1% have chronic muscle involvement

Bone



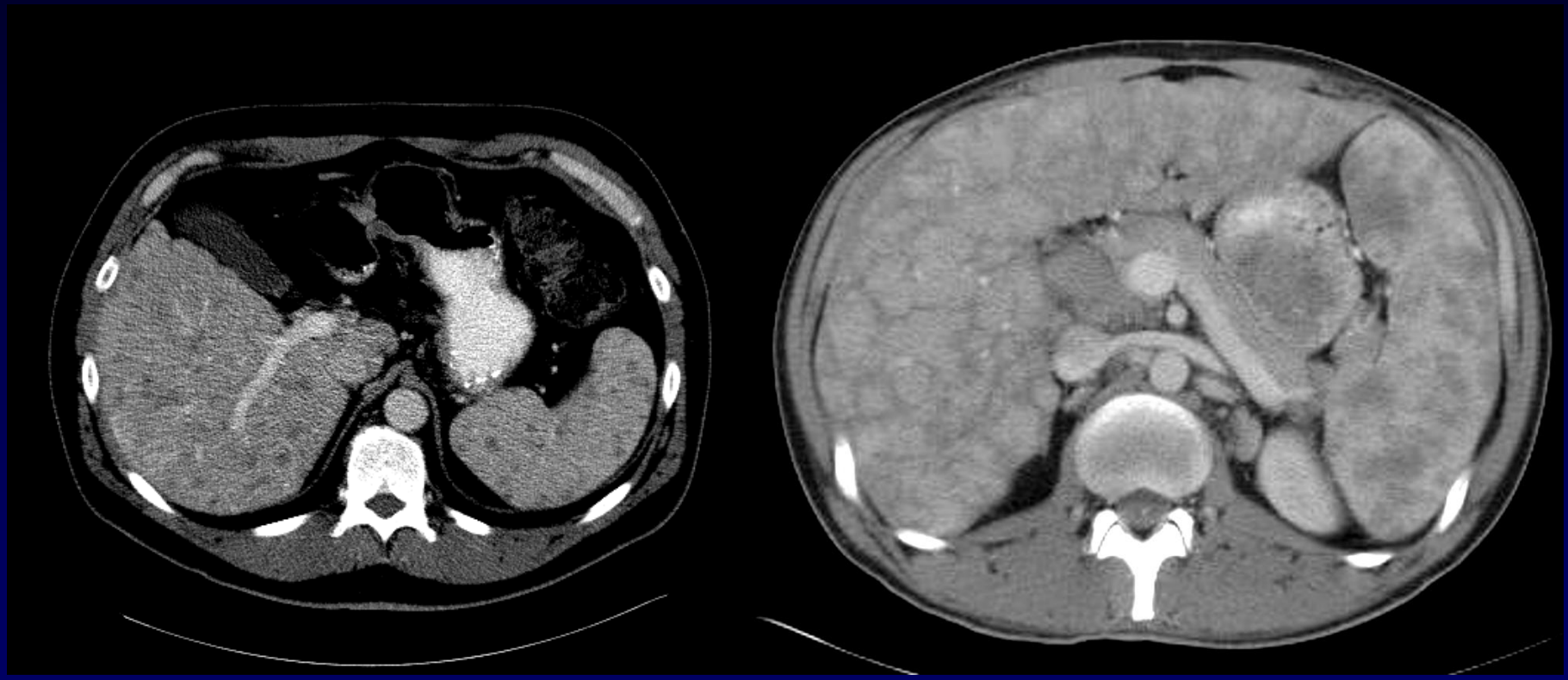


Diagnosis- liver/spleen

- Liver/spleen: abd pain, satiety
- Testing: CT scan, US, liver Biopsy, cytopenias
- Diagnosis:
  - Can see granulomas on biopsy, cirrhosis

Male, more common, involvement in 90%

Liver/Spleen

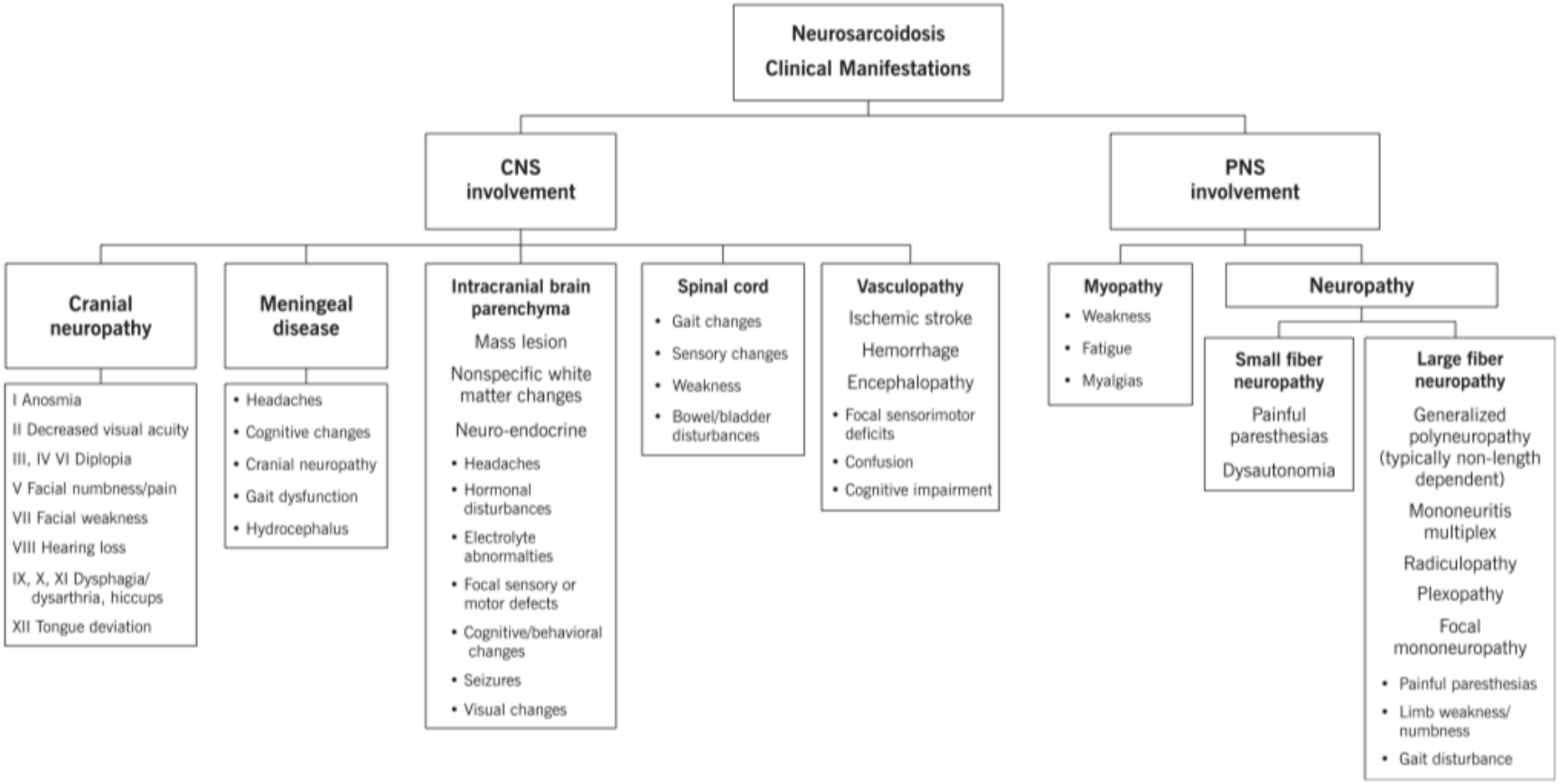


Diagnosis of Neurosarcoidosis

CNS: headache, memory loss, palsy, weakness, dizziness, visual, stroke

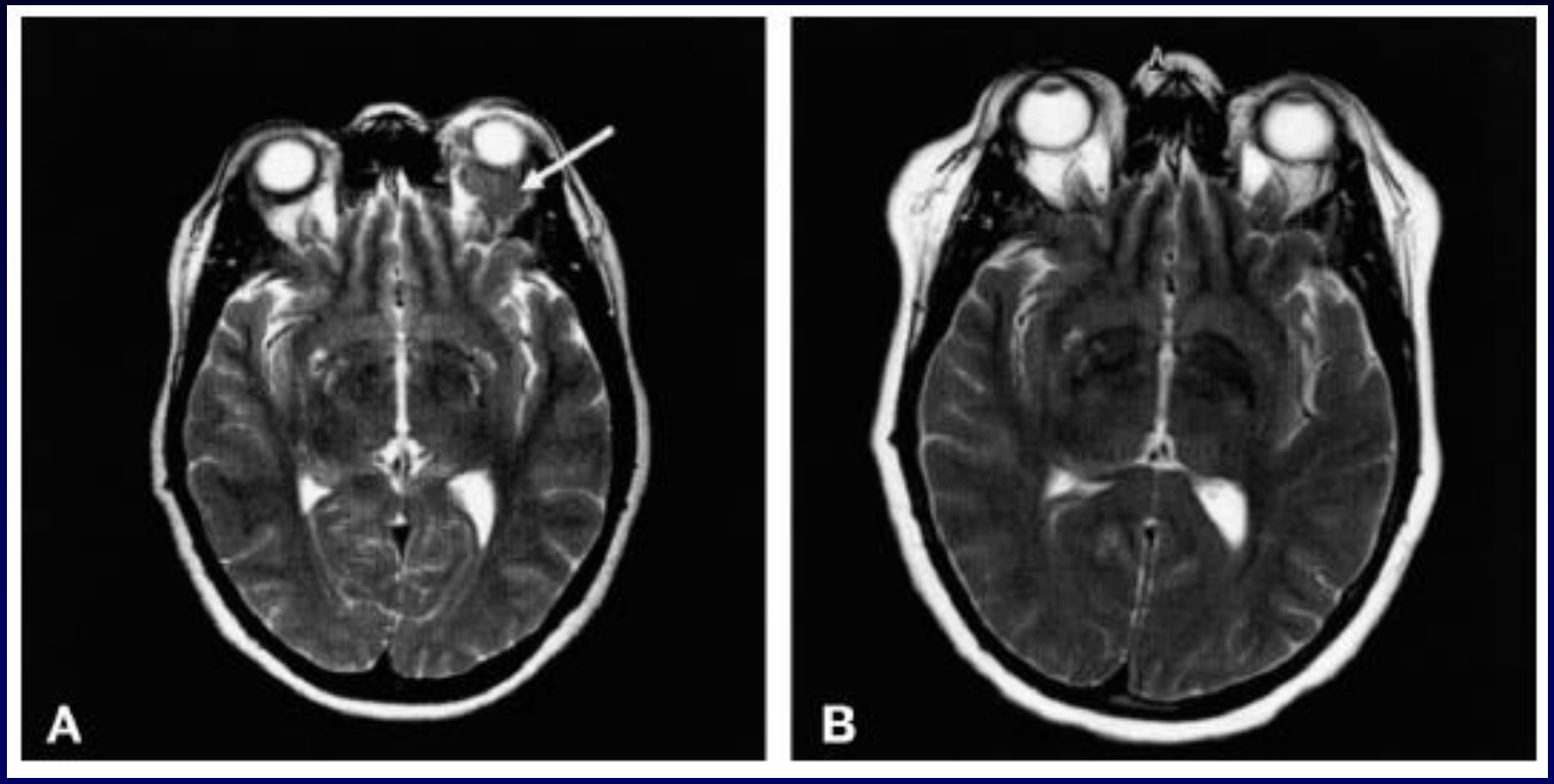
- Testing: EEG and EMG, muscle/nerve biopsy, MRI brain and spinal cord, CSF ACE
- Features: can be presenting sign, can occur during course of Rx, spontaneous remission
- Diagnosis: biopsy CNS or other. Clinical…

5% symptomatic, 15% overall

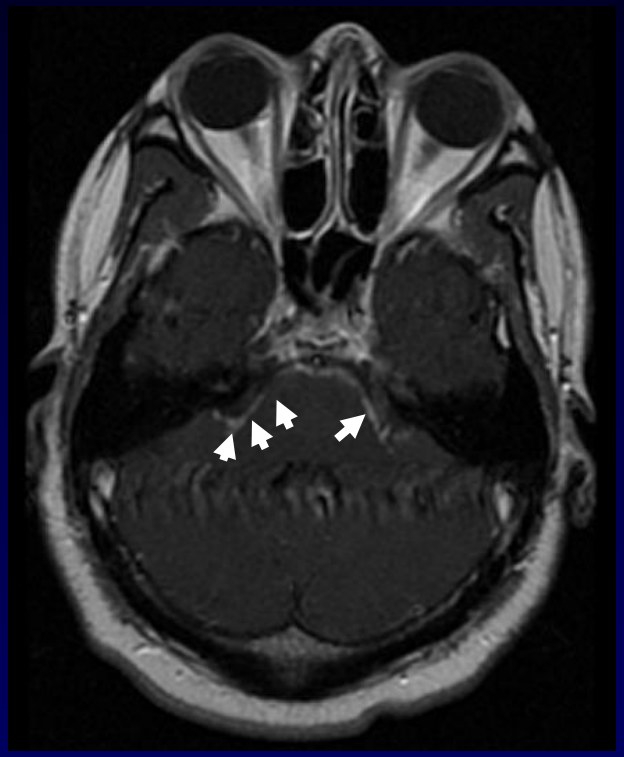


Tavee et al, Clinics Chest Med 2015

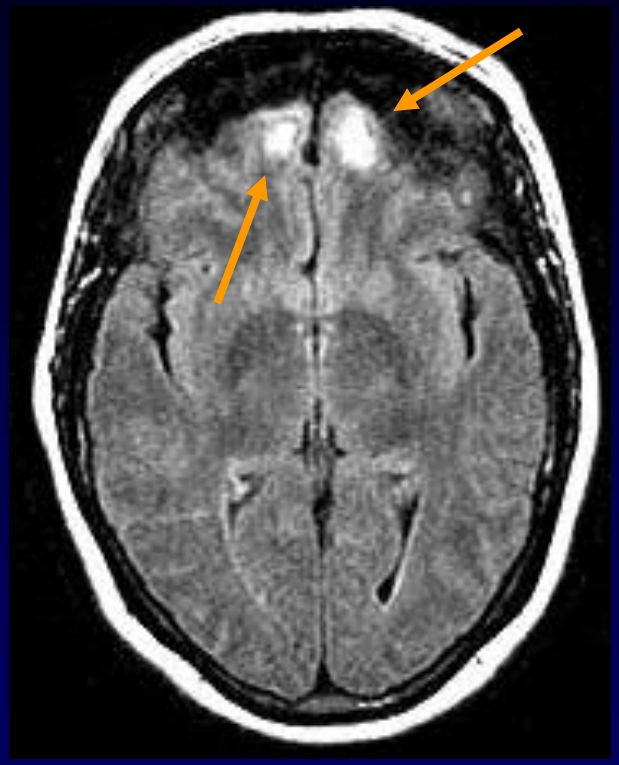
Neurologic/ophthalmic



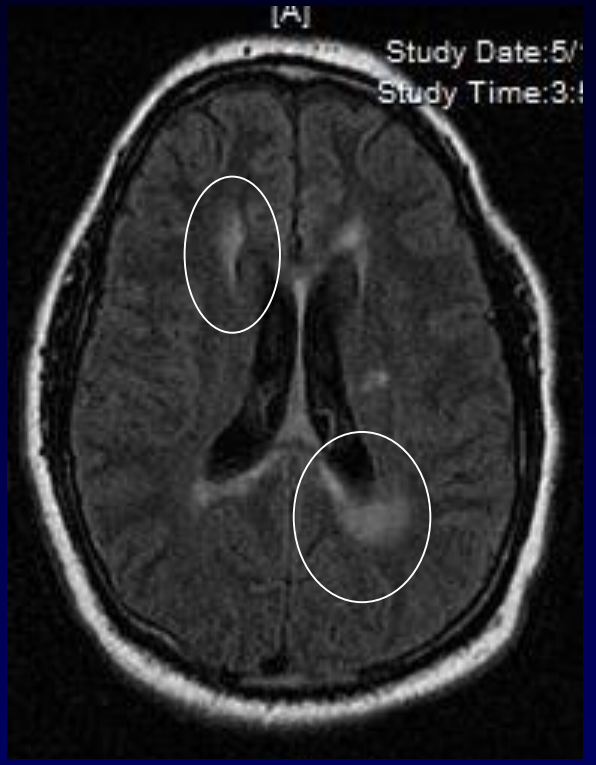
Neurosarcoid



35 year old AA male patient with neurosarcoidosis and chronic headaches



44 year old WF with visual changes, personality changes and chronic headache



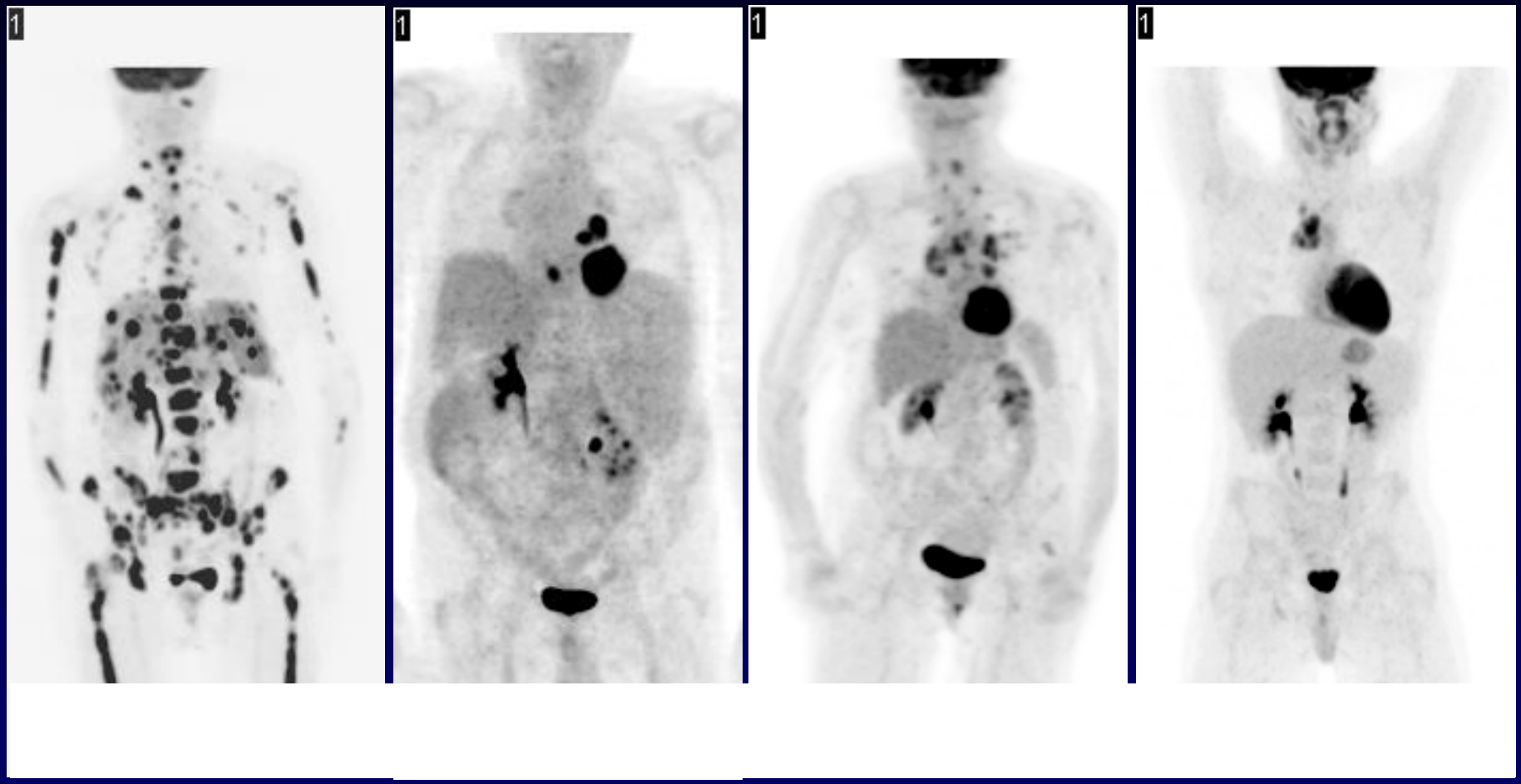
36 year old male patient with history of “stroke”- slurred speech and right sided weakness.

Pulmonary Diagnosis of Sarcoid

Lung: cough, short of breath, chest pain

- Testing: PFTs, chest x-ray and CT scan
- Diagnosis: often requires biopsy
  - to exclude other things that look like sarcoid
  - to support the diagnosis of sarcoid
  - Bronchoscopy (BAL, Biopsy), Mediastinoscopy

54 y/o female with spot on lung



Lung

PFTs

- Restrictive pattern most common
  - Diffusing capacity first, then TLC
- Can have obstruction (asthma-like)
  - ACCESS >13%
- Low Oxygen levels at rest, with exercise or sleep, but not prominent

Lung

Staging disease by Chest X-ray:

Stage 0 Normal (5%, ACCESS 8%)

Stage 1 Large chest lymph nodes only (50%,40%)

Stage 2 Chest nodes and lung infiltrate (25%,37%)

Stage 3 Lung infiltrates only (15%, 10%)

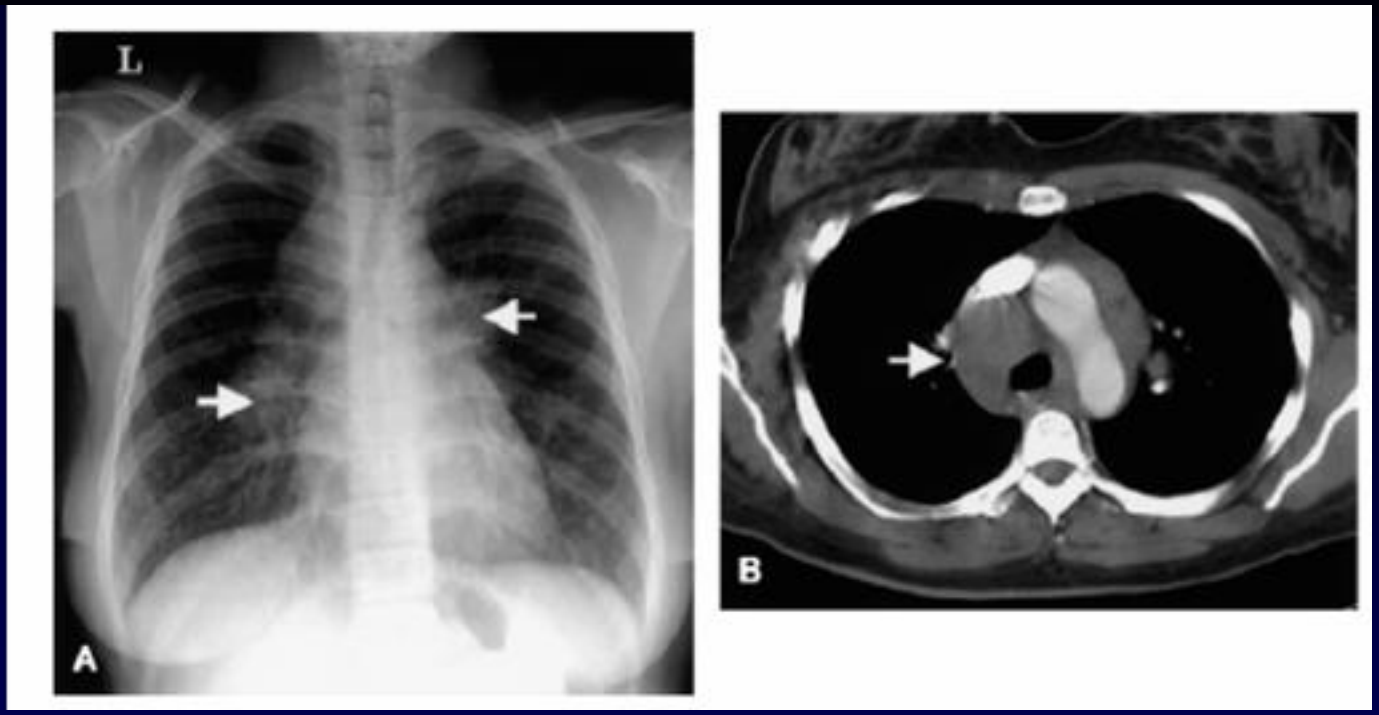
Stage 4 Fibrosis (5%, 5%)

Prognostic factors

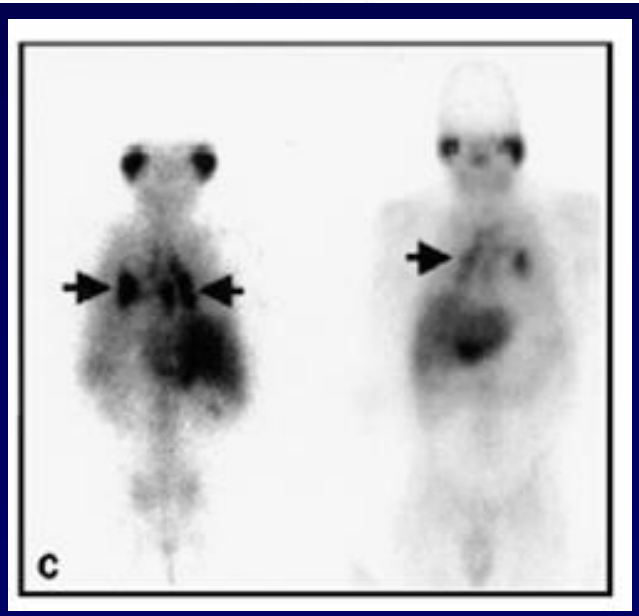
By Chest X-ray (not CT):

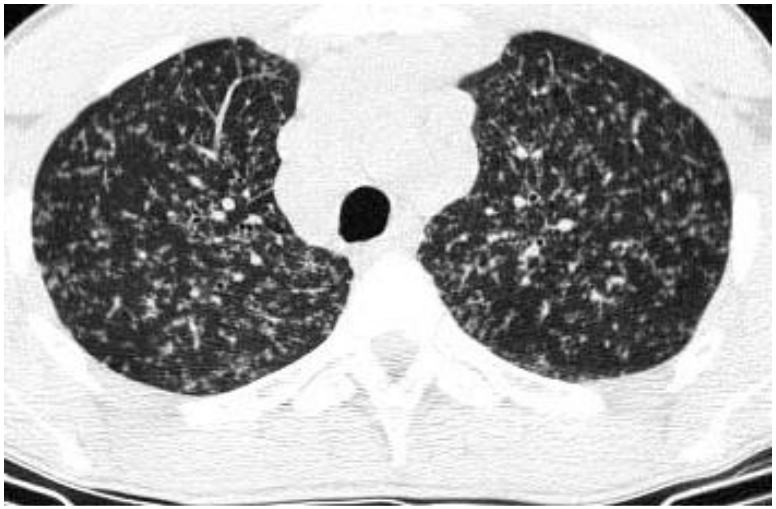
- Stage 1 Very good 80% improve
- Stage 2 Good 50% improve
- Stage 3 Fair 20% improve
- Stage 4 Poor (Scar), high mortality
- Stage 0 = Normal (up to 8%)

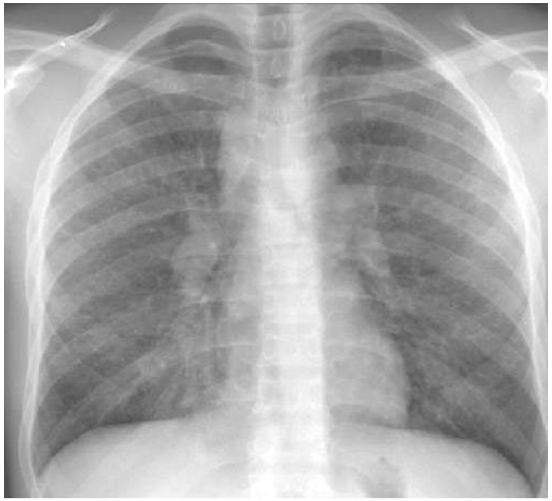
* Means nothing if extrapulmonary involvement



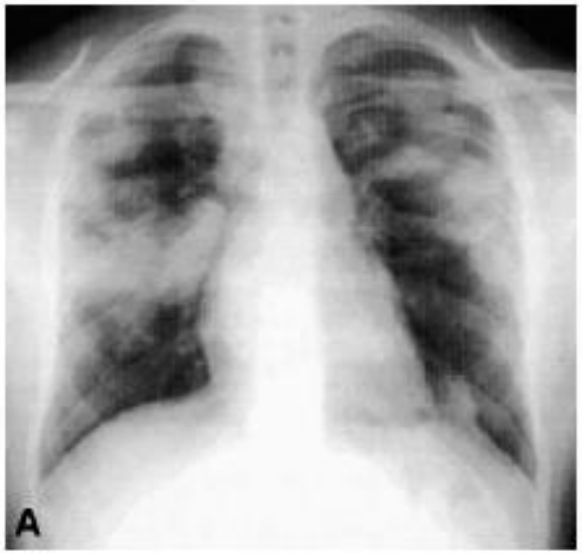
Stage 1

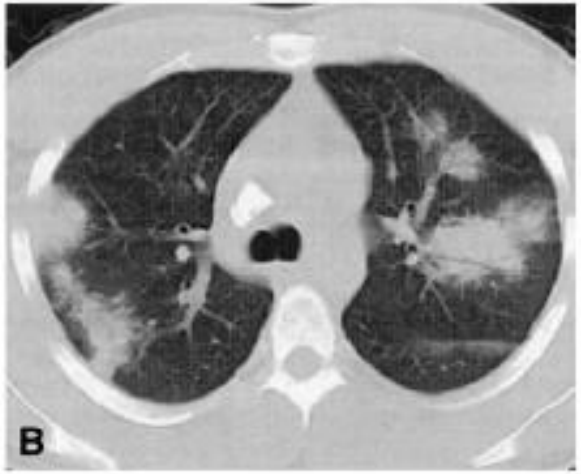


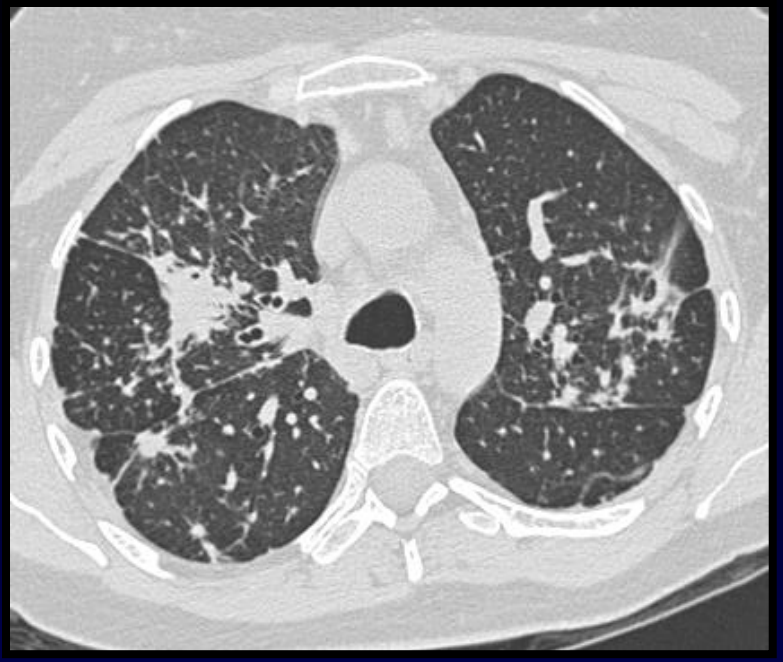


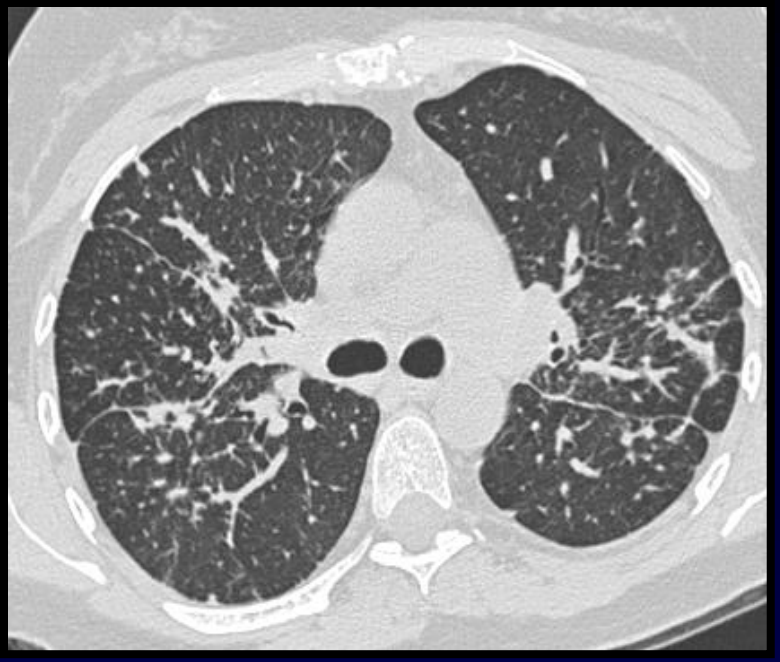


Stage 2

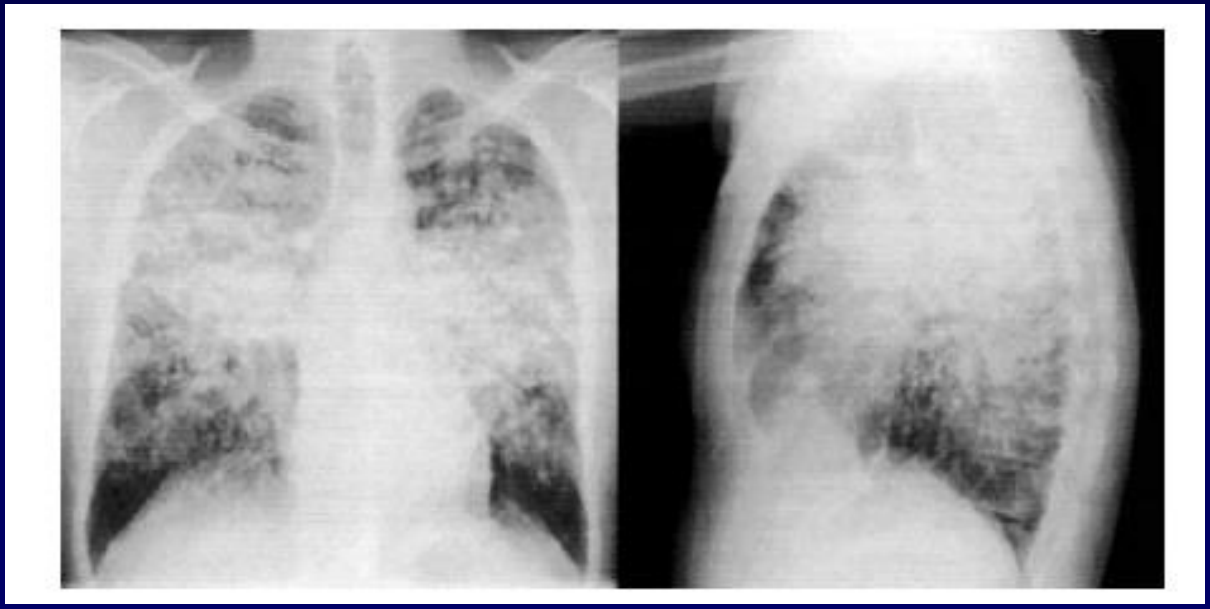


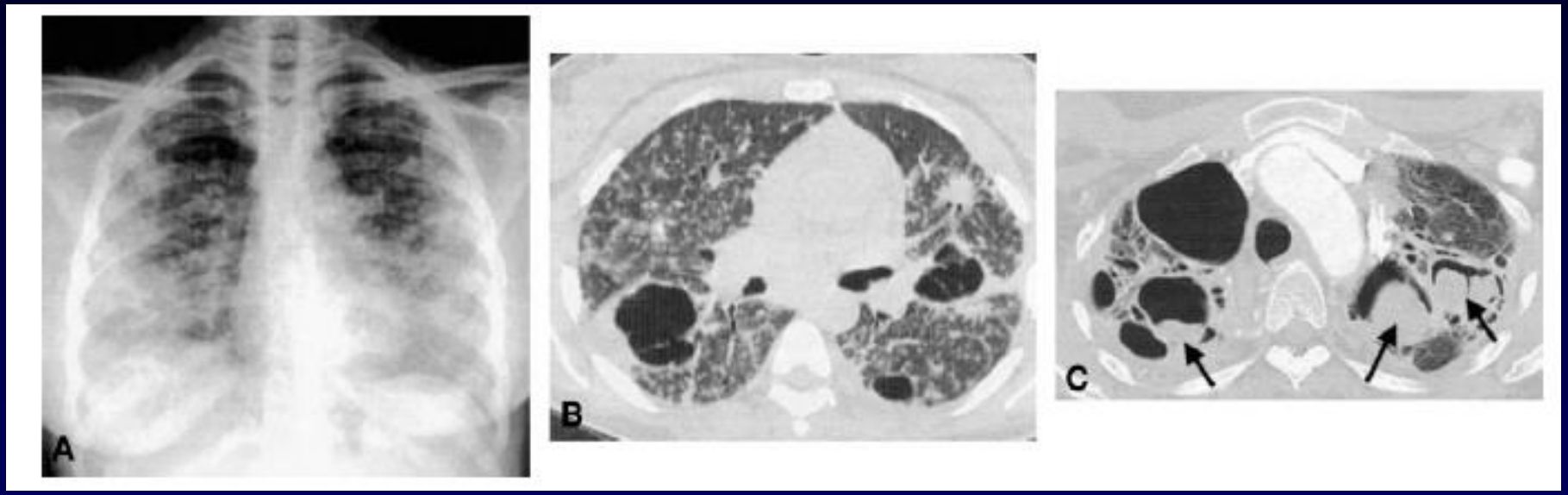




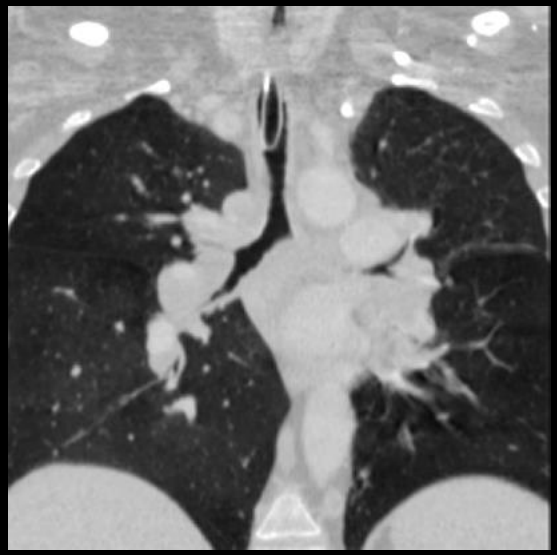
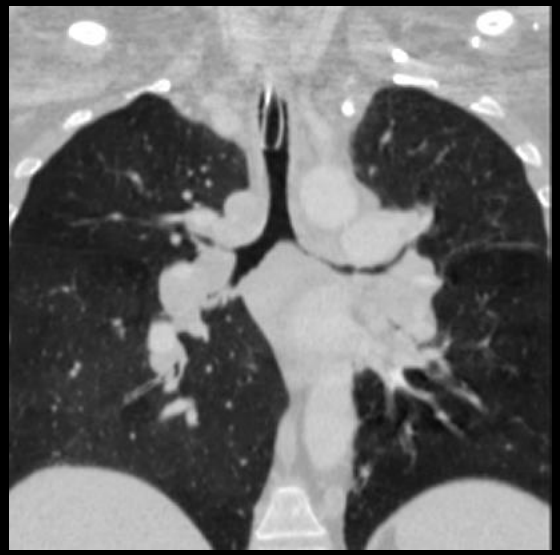
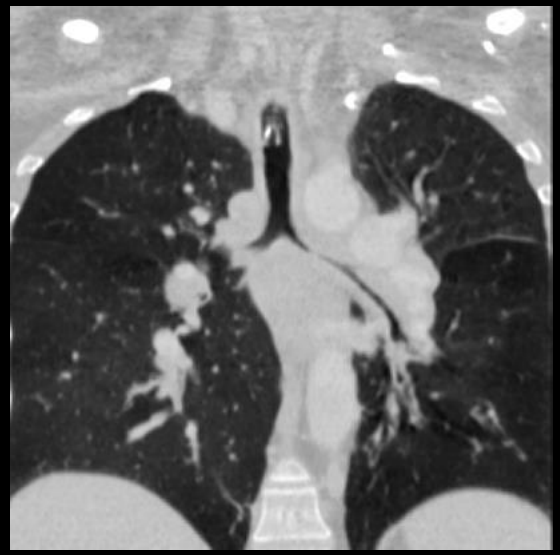
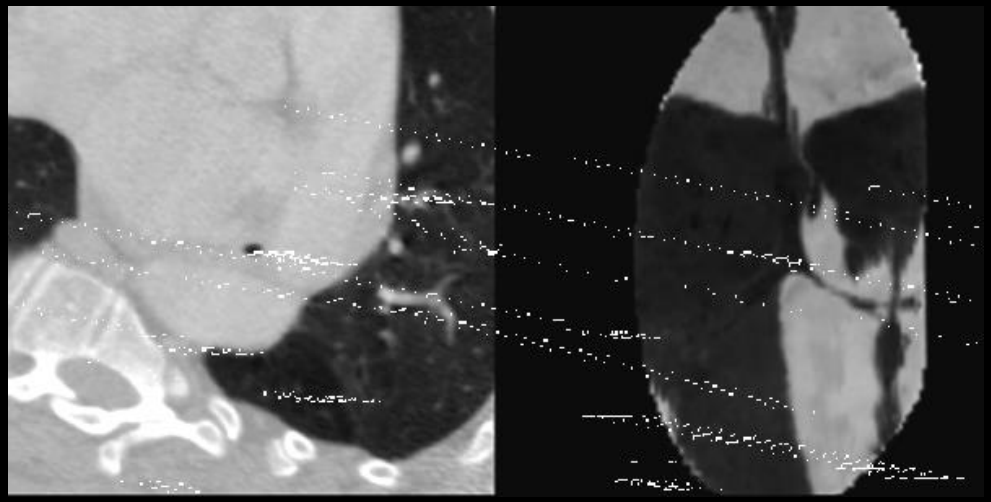
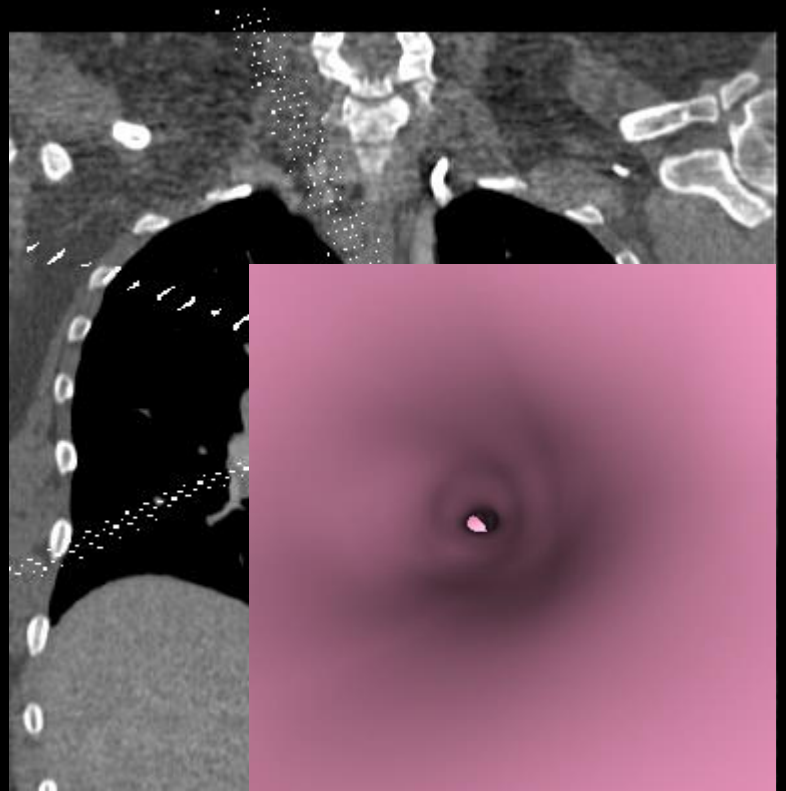


Stage 3
-Perilymphatic
-Peribronchovascular



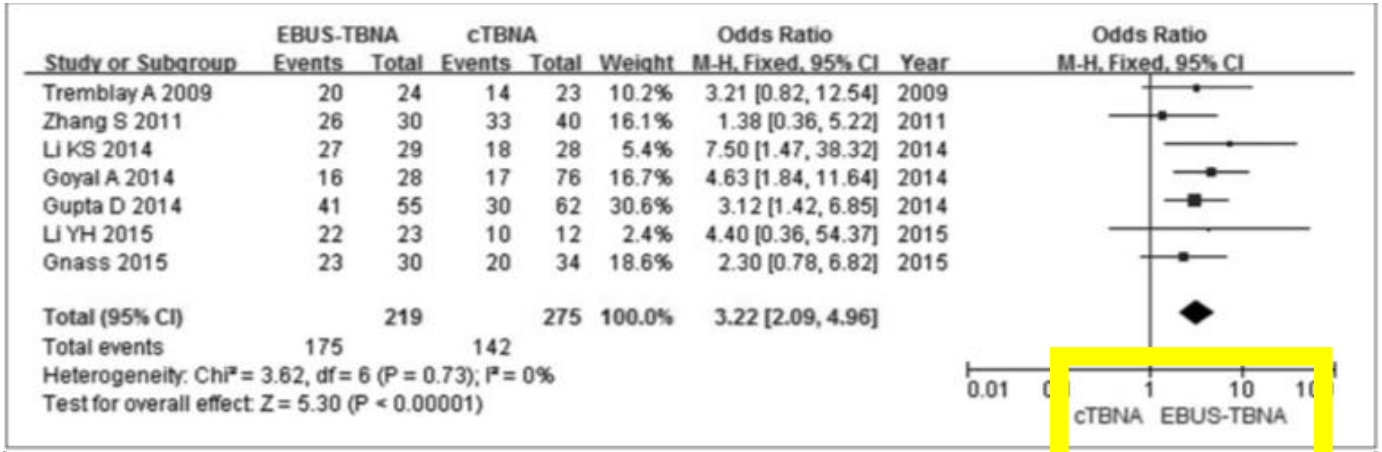


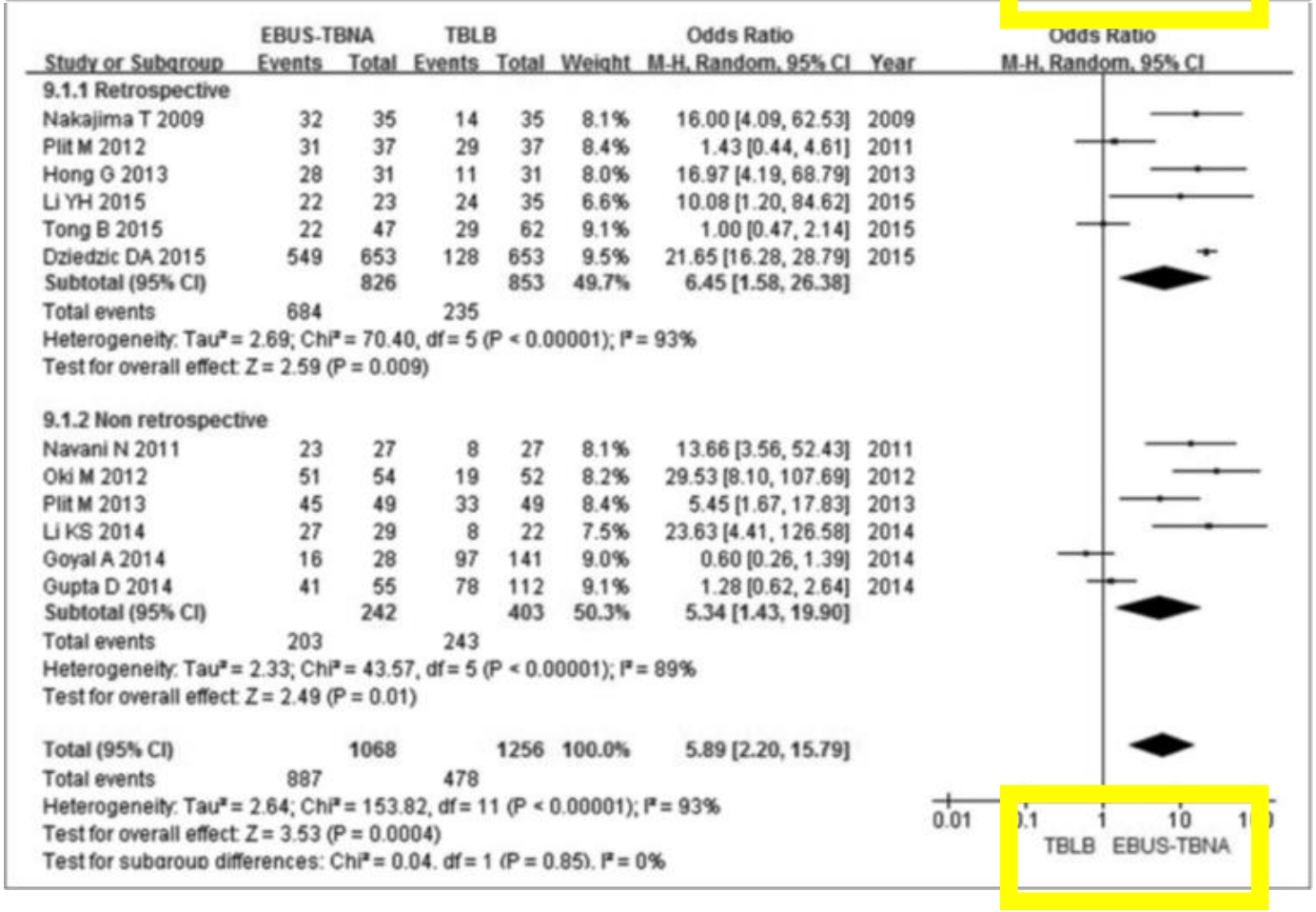
Stage 4

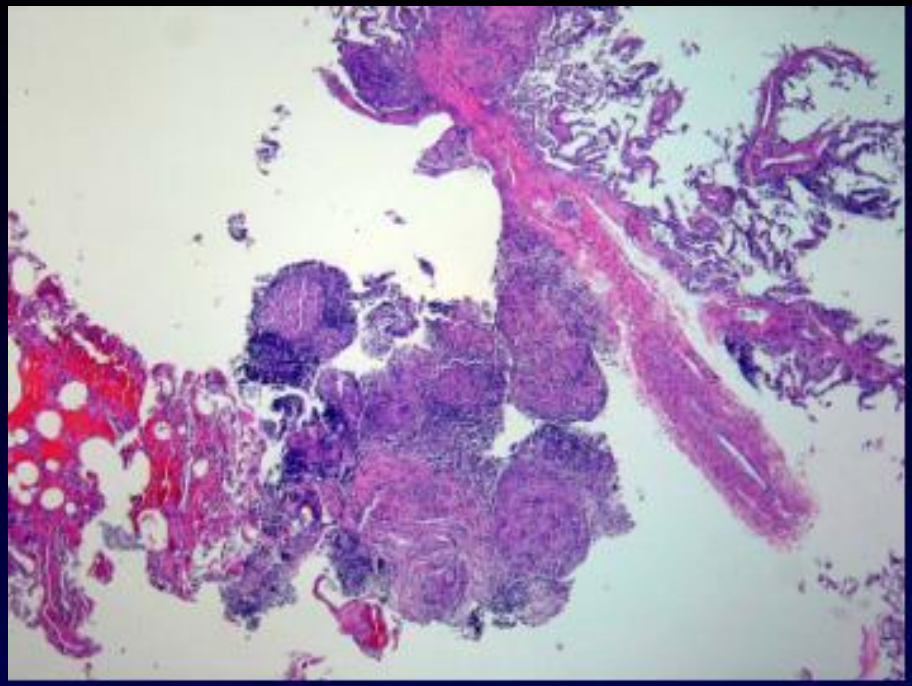
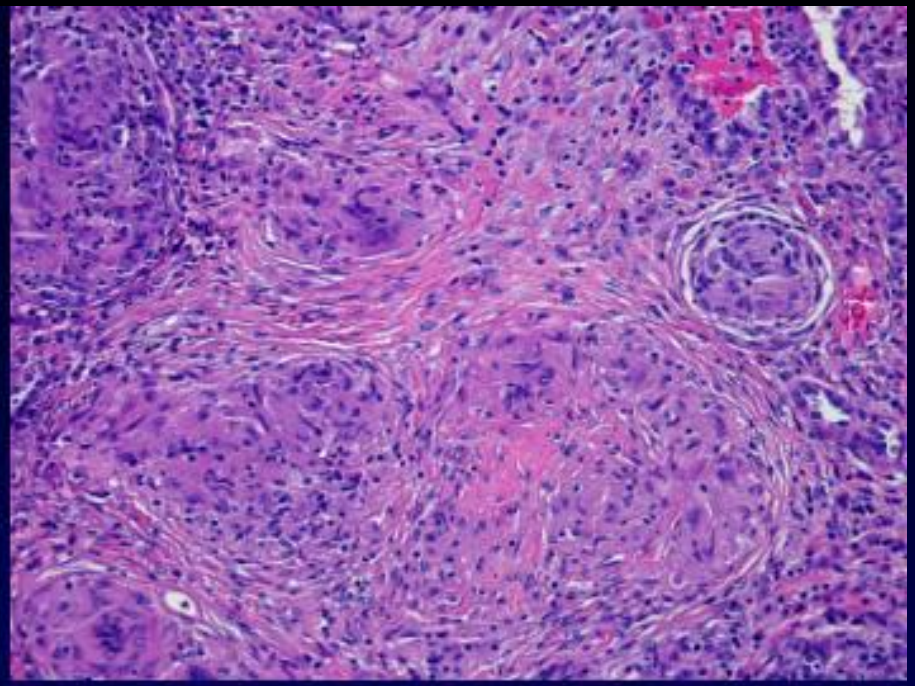
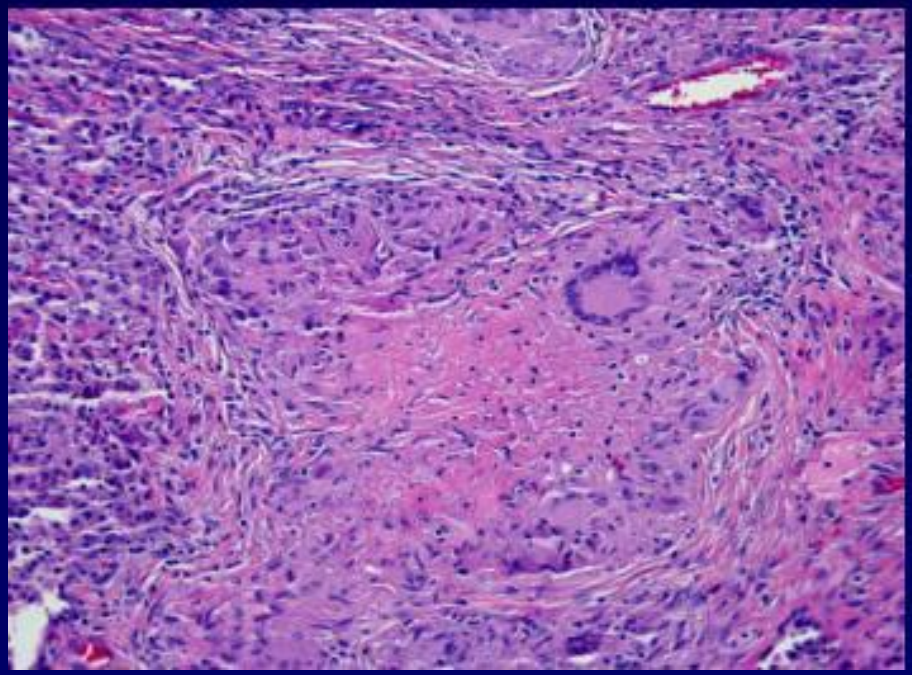
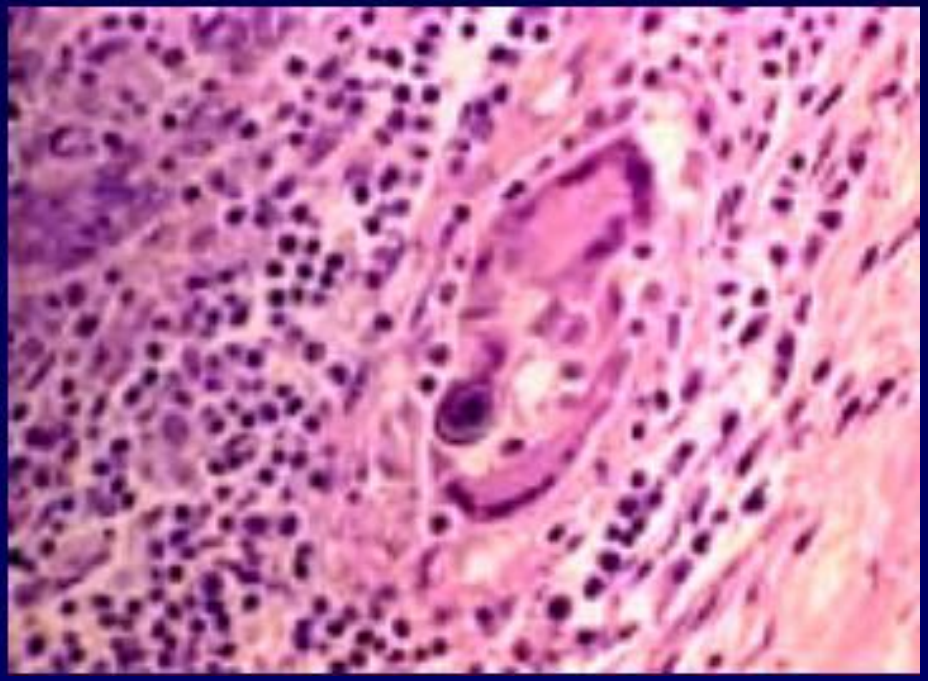






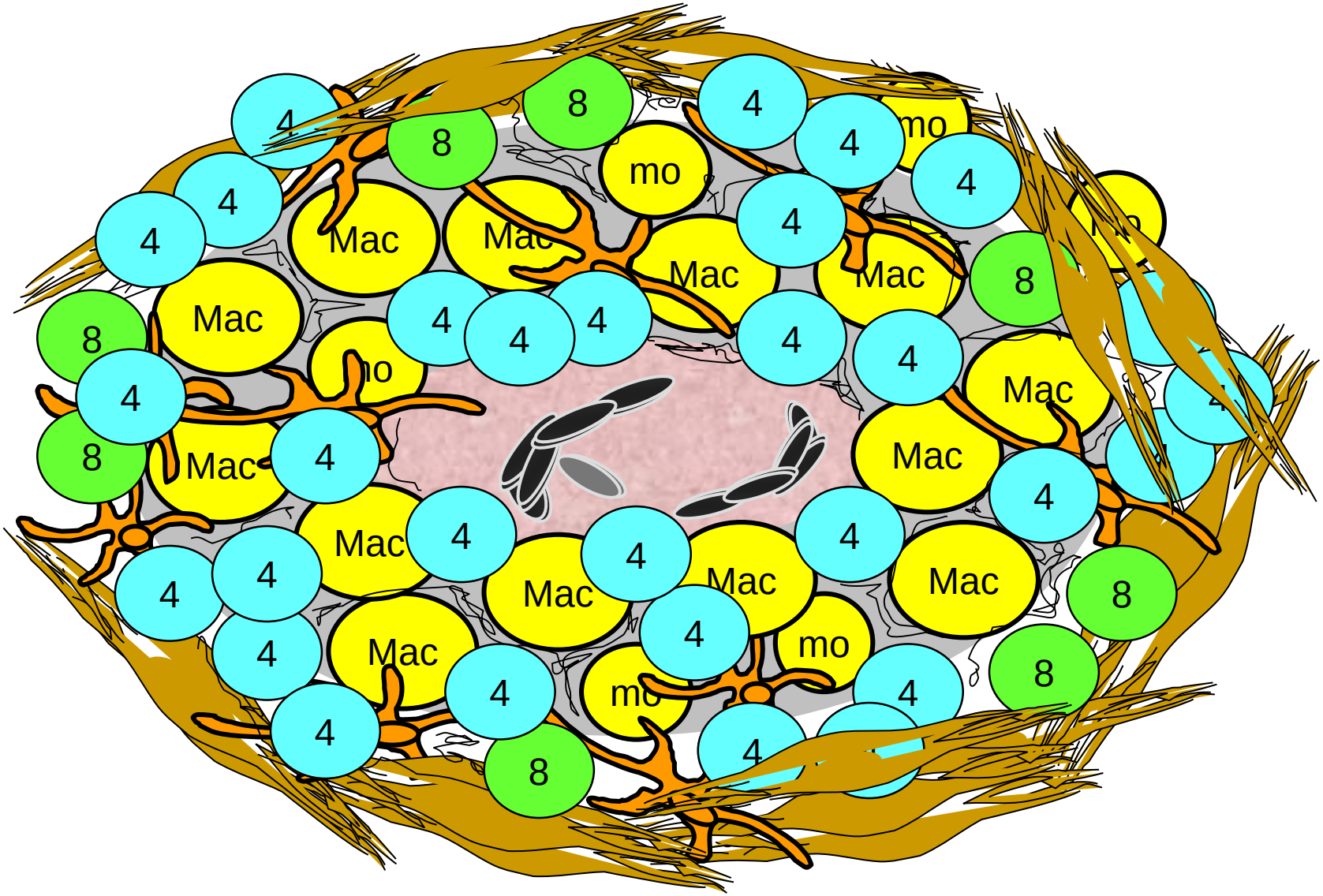
Sarcoid Granuloma

Hu LX, Chen RX, Huang H, Shao C, Wang P, Liu YZ, Xu ZJ. Endobronchial Ultrasound-guided Transbronchial Needle Aspiration versus Standard Bronchoscopic Modalities for Diagnosis of Sarcoidosis: A Meta-analysis. Chin Med J 2016;129:1607-15.







Fibronectin, Collagen Matrix
Epitheloid macrophages
Multinucleated giant cell

Perimeter of fibroblasts
Surrounding lymphocytes

Treatment

Clinical phenotypes

Sarcoidosis vs Sarcoidoses

- Do we lump or split the phenotypes?
  - Lofgren syndrome and others
    - European, good prognosis
  - Lung only
    - Inflammatory vs fibrotic
    - African American, poor prognosis
  - Skin or other organ only
  - Lymphopenic Phenotype (Crouser ED, Chest 2010)
    - “The CD4+ lymphopenic sarcoidosis phenotype is highly responsive to anti-tumor necrosis factor-{alpha} therapy”

Sarcoidosis

- Difficult to tell who will progress
  - 50% improve without therapy
    - some slowly, some very quickly
  - 20-30% stabilize with and after therapy
  - 20-30% get worse even with aggressive therapy
  - Greater than 5% die
- Not all sarcoid is created equal…

Treatment Philosophy

- Don’t over treat
- Manage symptoms
- Manage Expectations
- Two things that can go wrong:
  - too much Prednisone
  - not recognizing poor prognosis/debilitating manifestations

When to treat ?

Traditionally difficult to treat (need long-term therapy possibly with many agents)

- Lung stage III, vocal cord/upper airway obstruction
- Eye (posterior uveitis) and vision loss
- Central nervous system (seizure, mass)
- Cardiac (syncope, rhythm problem, failure)
- Skin (disfiguring, lupus pernio)
- Misc: Calcium, stones, portal, liver, fatigue, arthritis

Treatment options- first line

CONSIDER NOT TREATING

- Can wait up to 6 months to see if spontaneous remission occurs (especially pulmonary)
- Side effects- weight gain, glucose, cataracts, bone loss, insomnia, infection, ulcer, adrenal
- Old dogma- early treatment alters natural course of disease unfavorably…
- If treat, not committed to long term therapy. Bursts and alternate dosing en vogue

Treatment options- first line

Topical steroids as primary therapy

MILD DISEASE

- Eyedrops
- Creams/ointments
- Intralesional
- Inhaled
  - Alone
  - After oral therapy for maintenance

Treatment options- first line

Steroids are the mainstay of treatment

- Start 20 mg prednisone a day, need to follow closely.
- May need more or intravenous if severe, difficulty expected, or acute disease
- May be able to taper over first 1-3 months to a lower dose or every other day dosing
- Retrospective study suggests 21 day course 20mg/d can treat exacerbation

McKinzie BP et al. Efficacy of short-course, low-dose corticosteroid therapy for acute pulmonary sarcoidosis exacerbations.Am J Med Sci. 2010 Jan;339(1):1-4.

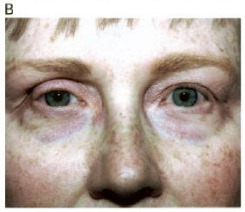
Drug	Dosage	Toxicity	Monitoring
Prednisone	5 - 40 mg/day	DM, HTN, Weight gain, Cataracts, Glaucoma	BP, weight, BG, bone density
Hydroxychloroquine	200 – 400 mg/day	Ocular, Hepatic, Cutaneous	Eye exam 6-12 months
Methotrexate	5 – 20 mg / weekly	Hematologic, Pulmonary, Hepatotoxic	CBC, CMP 1-3 months
Azathioprine	5 - 200 mg/daily	Hematologic, GI	CBC, CMP 1-3 months
Leflunomide	10 – 20 mg/day	Hematologic, Hepatotoxic	CBC, CMP 1-3 months
Mycophenolate	500 – 2000 mg/day	Hematologic, GI	CBC, CMP 1-3 months
Infliximab	3-5 mg/kg load/2 week every 4-8 weeks;	Infusion rxn, Infections, HF, ?malignancy	PPD prior Hold drug for infections
Adalimumab	40 – 80 mg every 1-2 weeks	Infusion rxn, Infections, HF, ?malignancy	PPD prior Hold drug for infections
Rituximab	1000 mg load, repeat at 2 weeks, 24 weeks	Infusion rxn, Infections, HF, ?malignancy	PPD prior Hold drug for infections

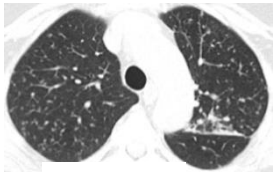
Treatment “options”

Web-based medicine

- www.gethealthyagain.com
- www.ivillagehealth.com
- Chelation
- Marshall plan
- Supplements??
  - Melatonin, Lancet 1995
  - Fish oil??
  - Antioxidants??
  - “Enzyme therapy”

- *Carcinosin*
  - *Euphrasia*
  - *Graphites*
  - *Leuticum (Syphilinum)*
  - *Bacillinum*
  - *Sepia*
  - *Phosphorus*
  - *Arsenicum album*





63 yo
Cough
Fatigue

Pred (30)

Pred (60)
MTX (15)

Pred (40)
AZA (50)

Pred (20)
io steroid
AZA (50)

Pred (20)
io steroid
AZA (75)

Pred pulse 1gm IV QD x3d
Amiodarone for 6 months
AICD placed

Pred (30)
io steroid
AZA (100)
Thalidomide

Inflix started
Pred (10)
io steroid
AZA (75)

Inflix dose 4
Pred (10)
AZA (50)

Infusion reaction
Inflix stopped

12/96 — **1997** — **1999** — **2000** — **11/02** — **01/03**

Diagnosed by transbronchial biopsy
FEV1 1.44 (63%)

FEV1 1.84 (81%)
DLCO 62%
Uveitis: 3+

Uveitis: 3+

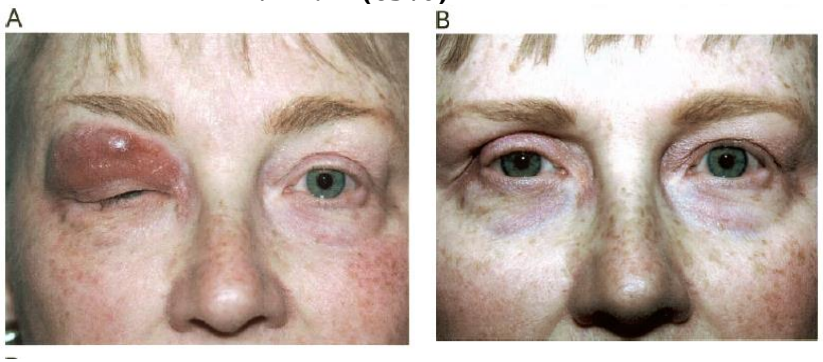
Cardiac arrest

Surgery of eye and reconstruction for ptosis

Mass recurred (Fig 2A)
Uveitis: 1+

Fig 2B

FEV1 2.07 (97%)
DLCO 64%
Uveitis: None



Roberts SD, Wilkes DS, Burgett RA, Knox KS. Chest. 2003 Nov;124(5):2028-31.

Conclusion

- Sarcoid is a systemic disease
- Diagnosis of exclusion
- Most people do well with with/without modest therapy
- Overtreatment has consequences
- Some people will have a complicated course and need aggressive therapy
- It takes a village
- Sarcoid specialists exist

Questions?