SARCOIDOSIS

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Definition

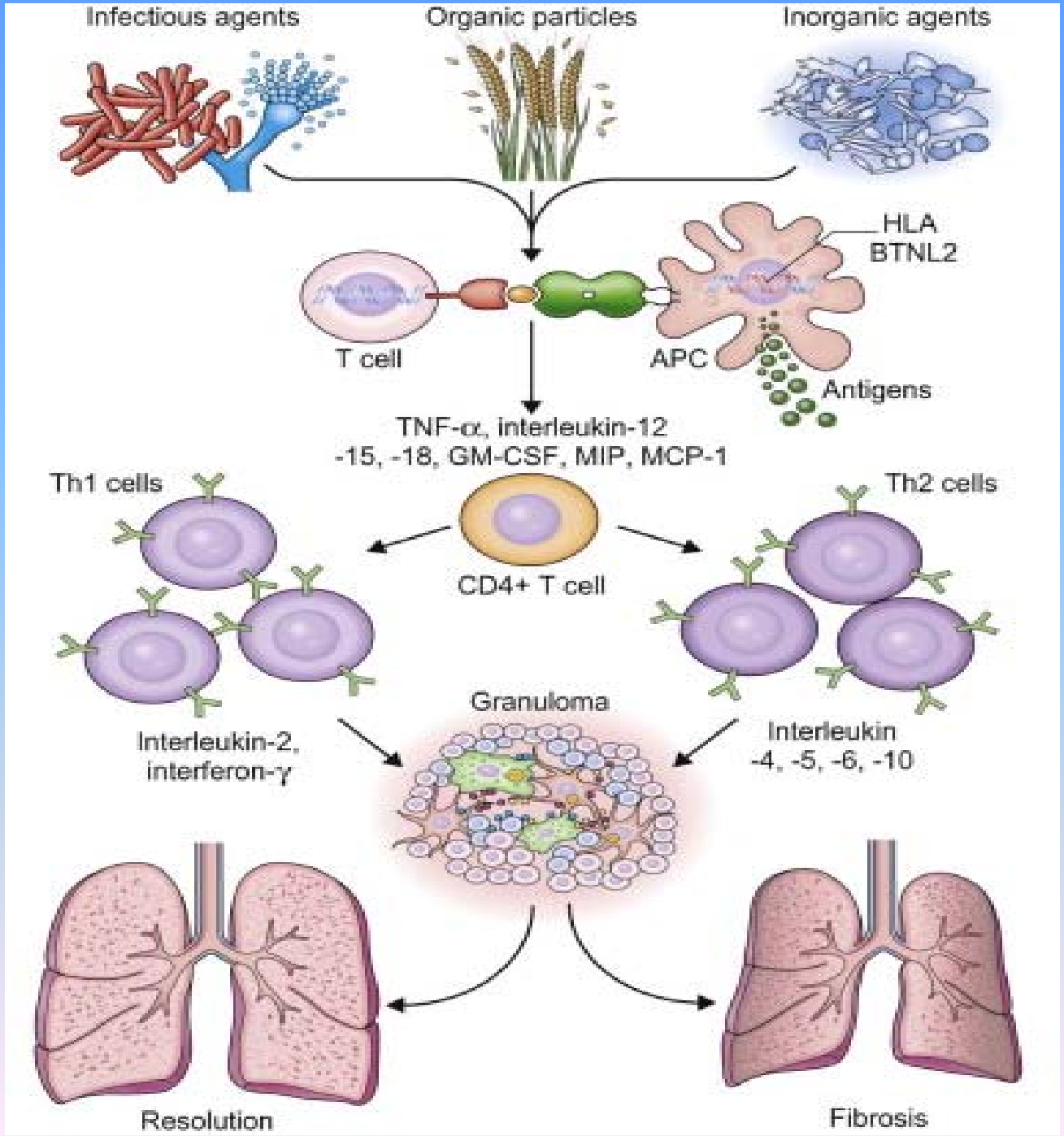
- Sarcoidosis is a multisystem disorder of unknown etiology characterized by noncaseating granulomas in more than one organ or tissue.
- Occurs world-wide with high prevalence in Scandinavia, the United States, and Japan

Epidemiology

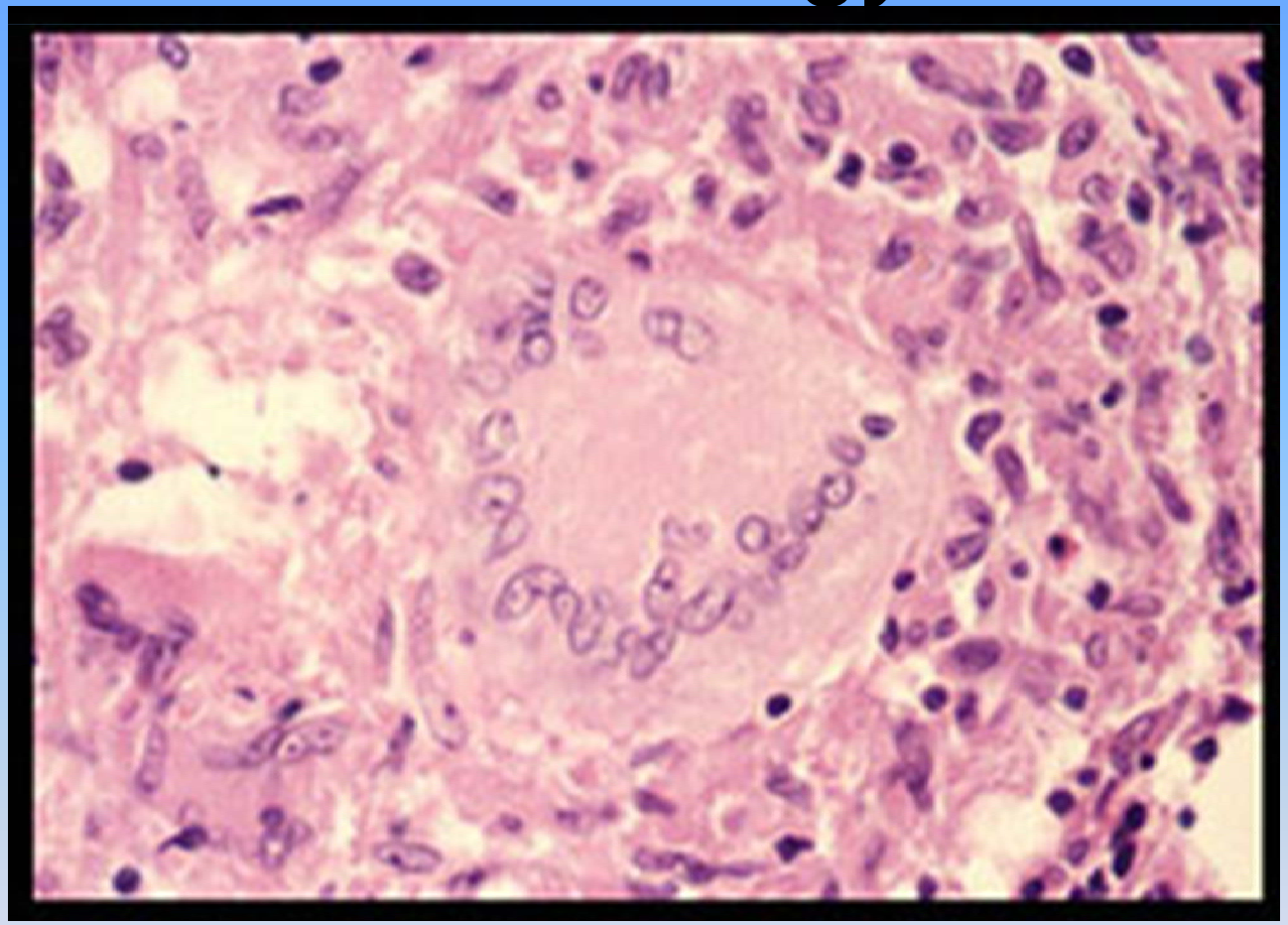
- **Race-** More common in blacks (40 per 100,000 blacks vs. 5 per 100,000 whites in U.S.
- **Age**- Usually manifest between ages of 20 to 40 years; rarely in children or the elderly
- **Sex-** Females equal to males worldwide

Etiology- Theories

1. A defect in the immune system
2. An unidentified toxic substance
3. An unknown environmental cause
4. An inherited or genetic cause
5. A viral or bacterial infection

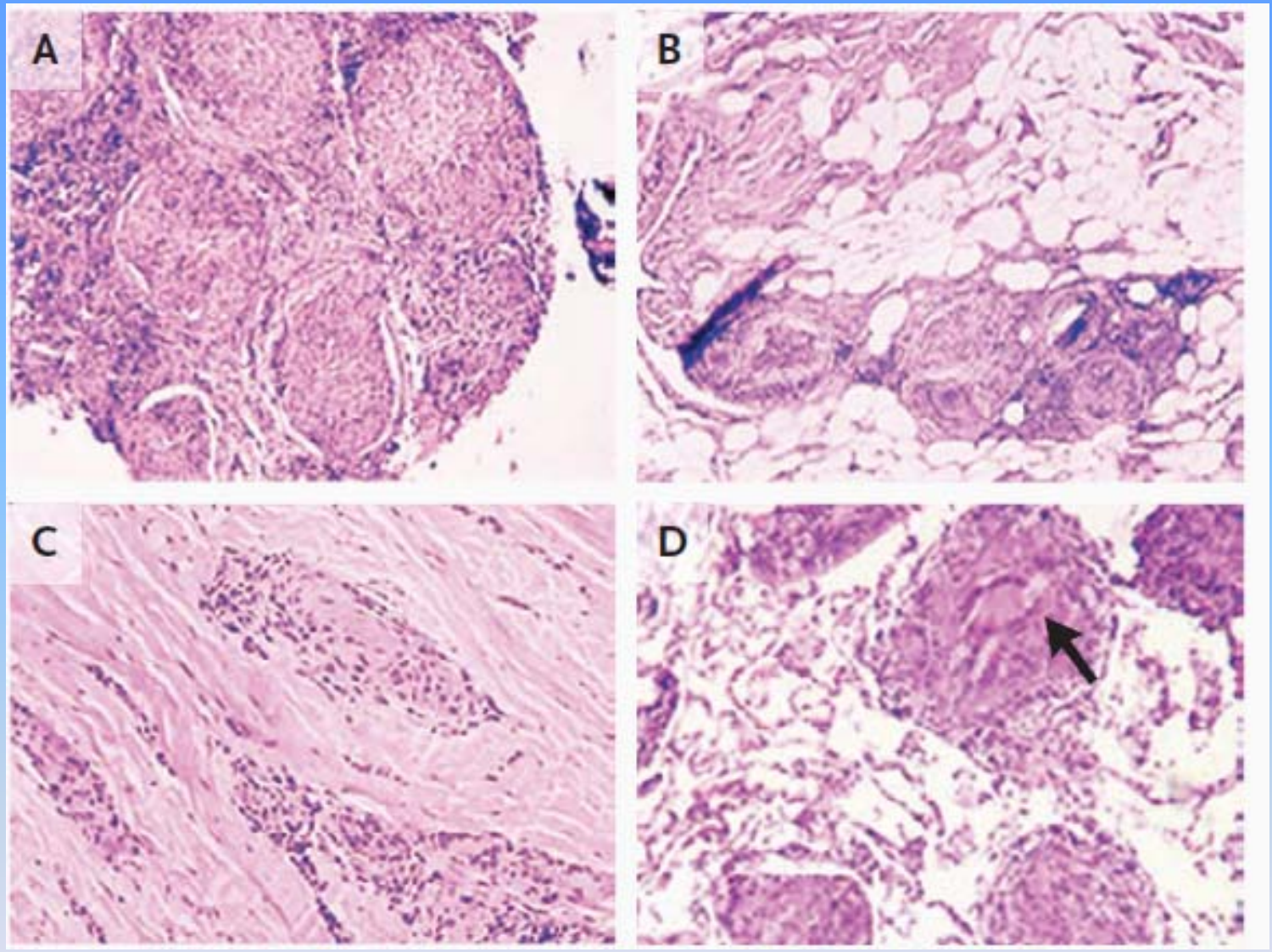

Infectious agents
Organic particles
Inorganic agents
HLA
BTNL2
T cell
APC
Antigens
TNF-α, interleukin-12
-15, -18, GM-CSF, MIP, MCP-1
Th1 cells
CD4+ T cell
Th2 cells
Granuloma
Interleukin-2,
interferon-γ
Interleukin
-4, -5, -6, -10
Resolution
Fibrosis

Pathology



Characteristic lesion is the sarcoid GRANULOMA

Sarcoid granulomas are of noncaseating type, containing macrophages, epithelioid cells (modified macrophages), multinucleated giant cells, and lymphocytes

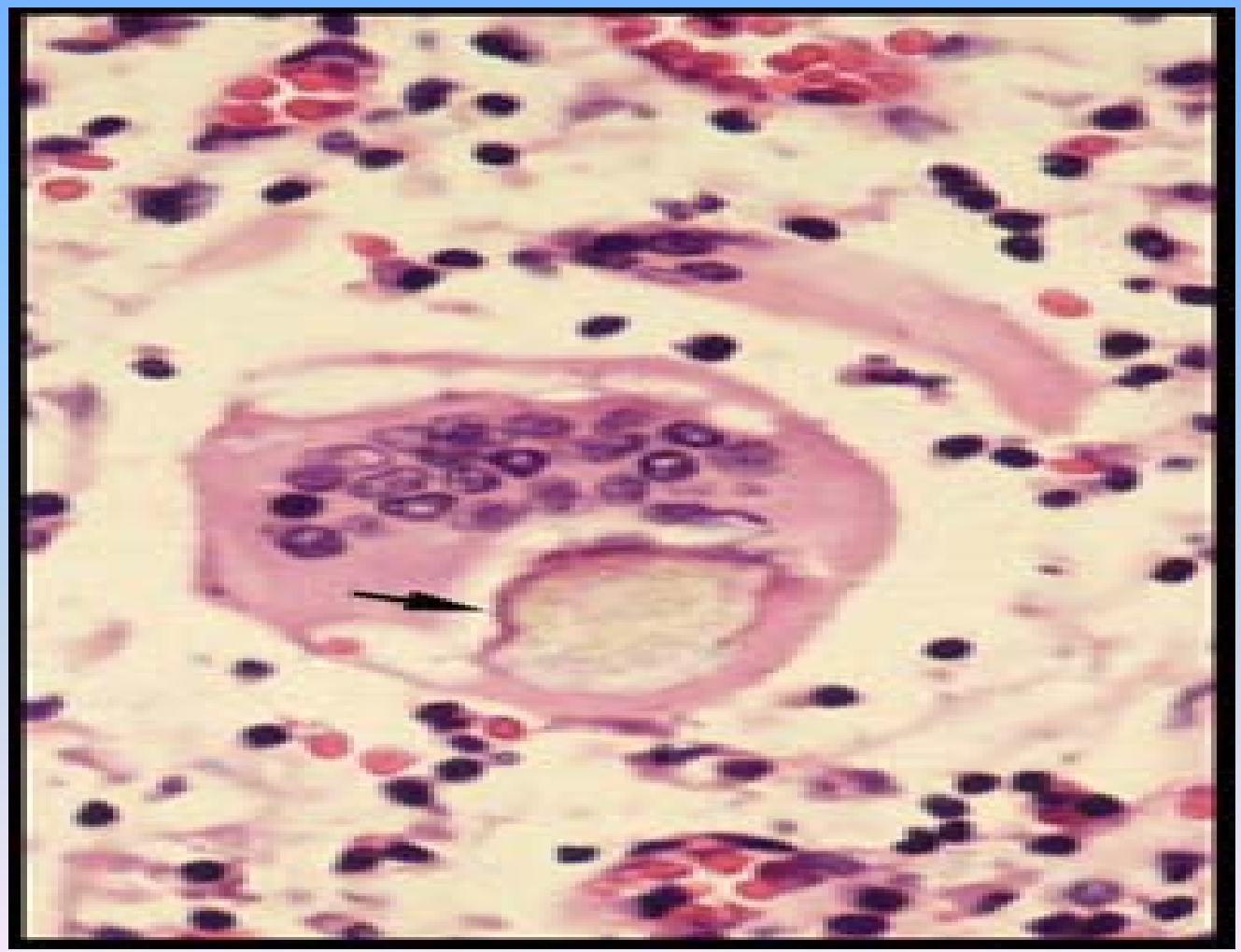


Granulomas are shown in nasal mucosal tissue (Panel A), synovial tissue (Panel B), a scar on the skin (Panel C), the lung (Panel D, arrow points to

- Giant cells in the central part of the granuloma
- The central epithelioid and giant cells are surrounded by a rim of lymphocytes, mostly T-helper cells
- T-cell lymphocytes are increased in areas of active granulomas
- Histologic studies of pulmonary sarcoidosis suggest a sequential course from alveolitis and granuloma formation to fibrosis

CYTOPLASMIC INCLUSION BODY

Schaumann body (arrow) is common in sarcoidosis but is nonspecific.



Organ Involvement

Sarcoid granulomas can be found anywhere in the body.

Autopsy series indicate the following distribution:

Lungs	**90%**
Lymph nodes	**50-78%**
Spleen	**54%**
Liver	**33-50%**
Skin	**13-20%**
Bone Marrow	**10%**
Heart	**5-25%**

These percentages do not necessarily mean organ dysfunction

Natural history of the sarcoid granuloma

Most resolve spontaneously

If they do not resolve, they are converted into avascular, acellular connective tissue

Granulomas persisting longer than a year or 2 show fibrosis

In late stages, this fibrosis extends beyond the granuloma into the surrounding tissue

It is the fibrosis associated with non-resolving granulomas that causes organ dysfunction in sarcoidosis

Clinical Presentation

3 types of clinical presentation:

1. CXR or lab abnormalities in asymptomatic patient (40-50% of all recognized cases)
2. Pulmonary symptoms
3. Systemic symptoms or extrapulmonary disease

Symptoms (Specific/Non-specific)

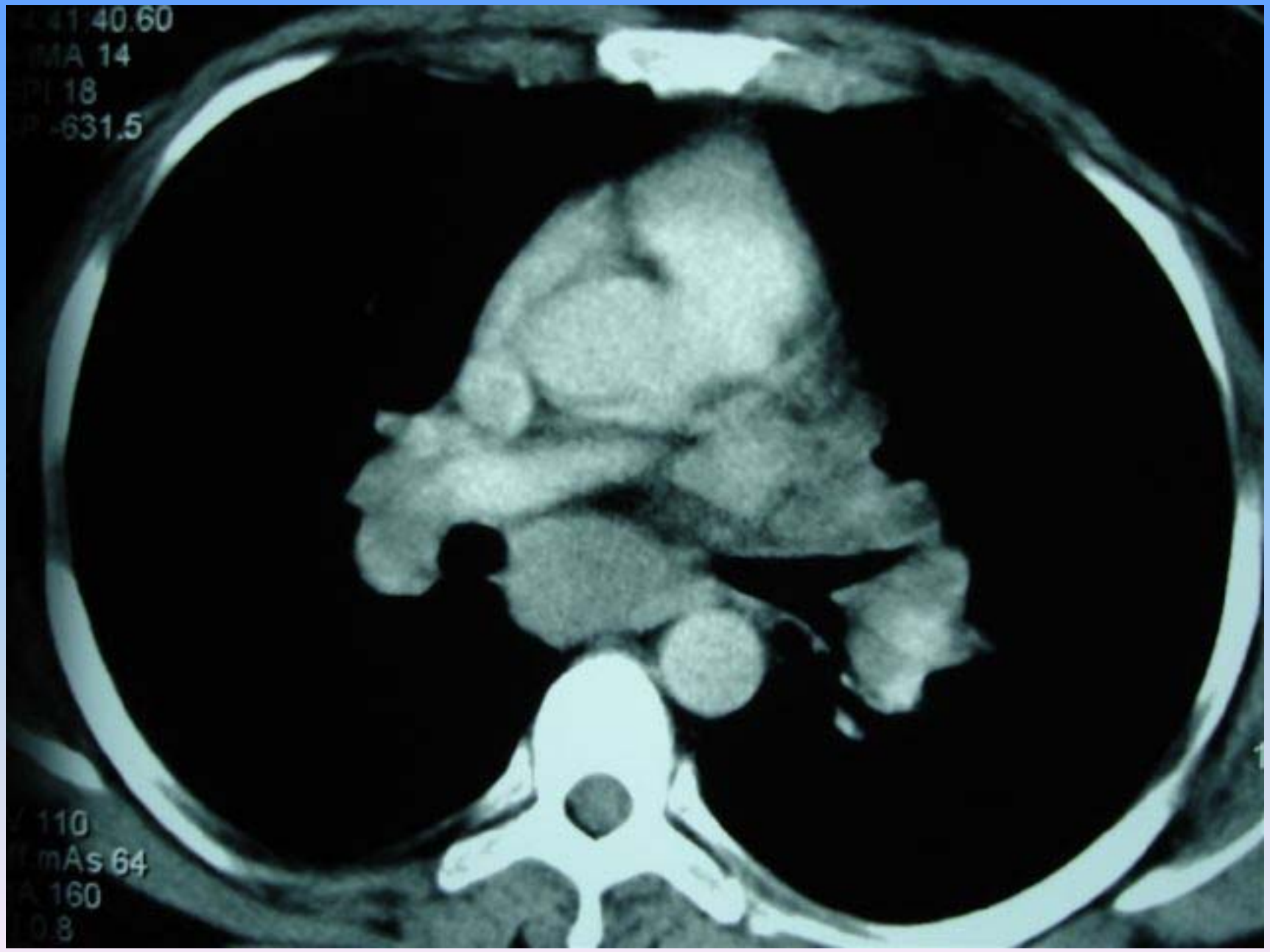
- **Nonspecific**
  - Fever, sweating
  - Weakness,
  - Weight loss
  - Aches and pains
- **Organ specific symptoms**

Sarcoidosis in thorax

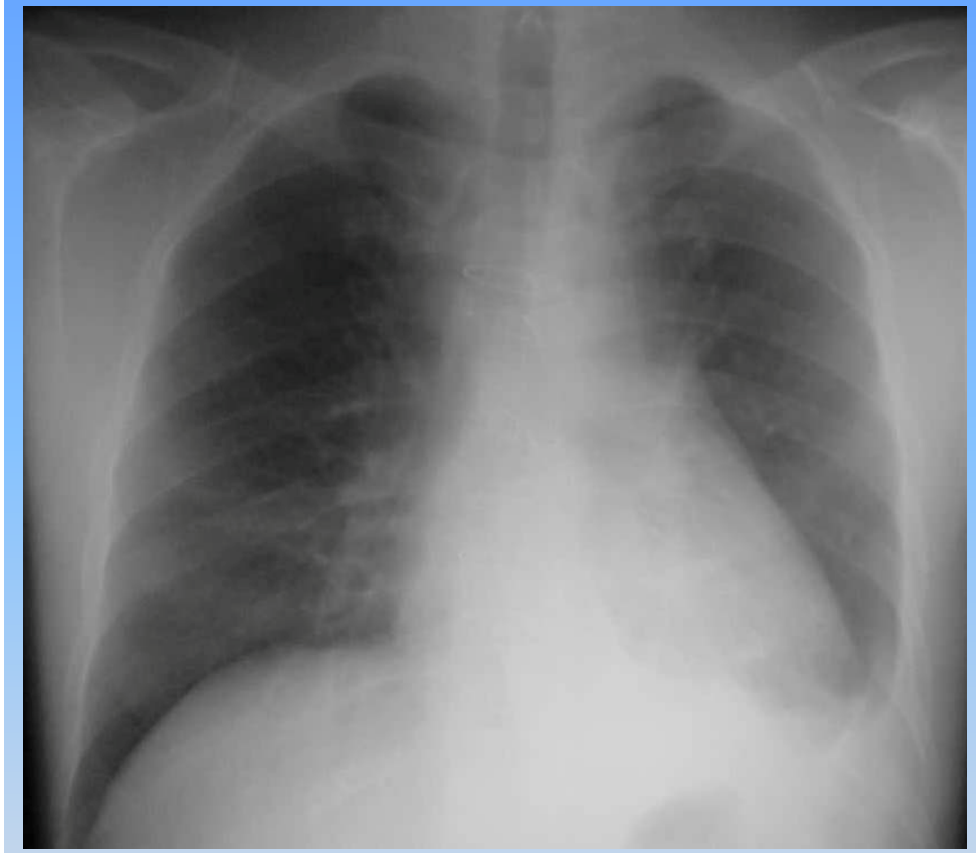
- Lymph nodes
- Pulmonary (parenchymal, interstitial)
- Endo-bronchial
- Pleural effusion, thickening, nodule
- Pneumothorax
- Necrotizing sarcoid granulomatosis

Pulmonary manifestations

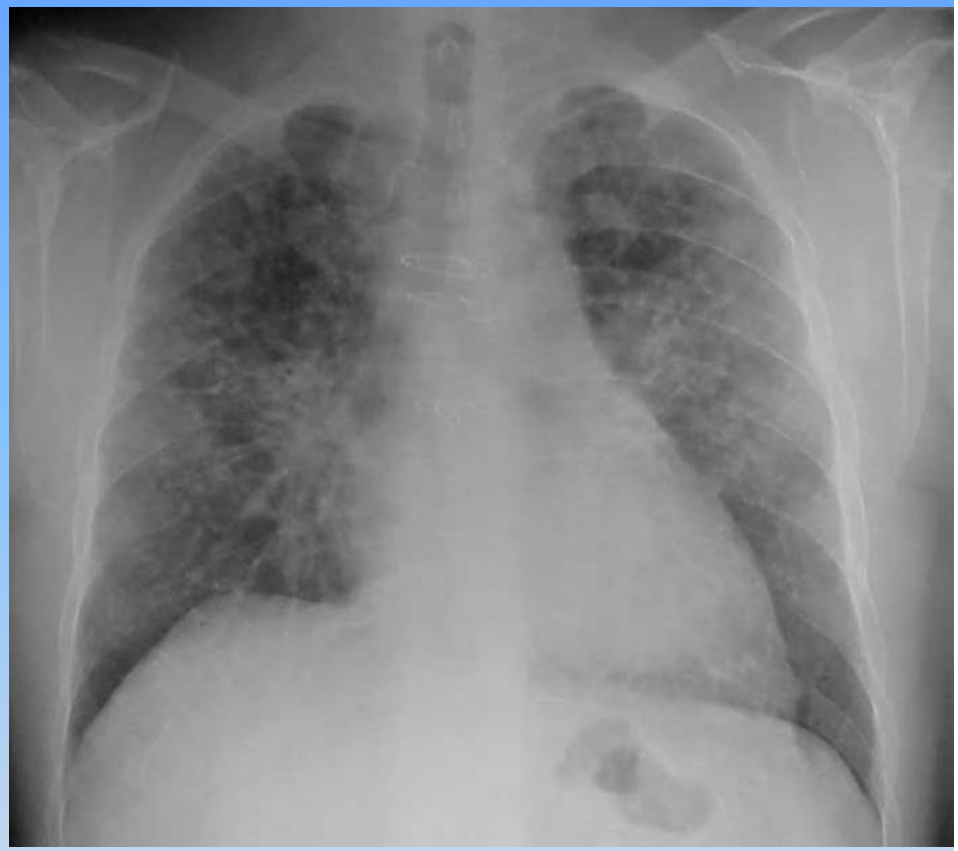
- Normal
- Mediastinal and hilar lymphadenopathy (paratracheal, hilar, aorto-pulmonary window)
- Reticular, nodular, ground glass involvement of upper and middle lung zones
- **Perilymphatic nodules (2-10mm)**around the broncho-vascular bundles, pleural and fissures


40.60
14
18
631.5
110
mAs 64
160

CXR



May 1997



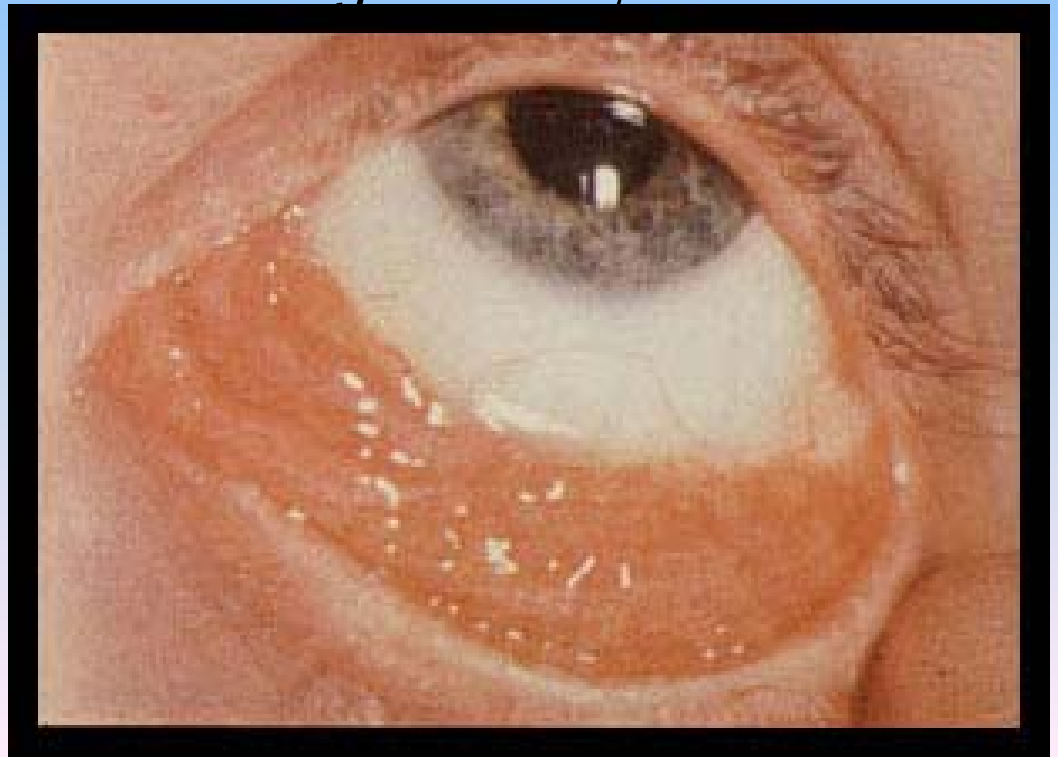
October 2003

Interval development of multiple, bilateral pulmonary nodules throughout both lung fields + a fullness in the hila bilaterally.

- Asymptomatic
- Cough, shortness of breath, fever, weight loss
- Spontaneous resolution
- Imaging, PFT, TBLB (yields diagnosis in 40-90%)

Ocular presentation- 25%

- Eye: Anterior or posterior uveitis, mass
- Blurred vision, pain, photophobia and dry eyes
- Keratoconjunctivitis sicca, Papilledema
- Testing: Slit-lamp eye exam, MRI, biopsy
- Chronic uveitis leads to glaucoma, cataracts and blindness

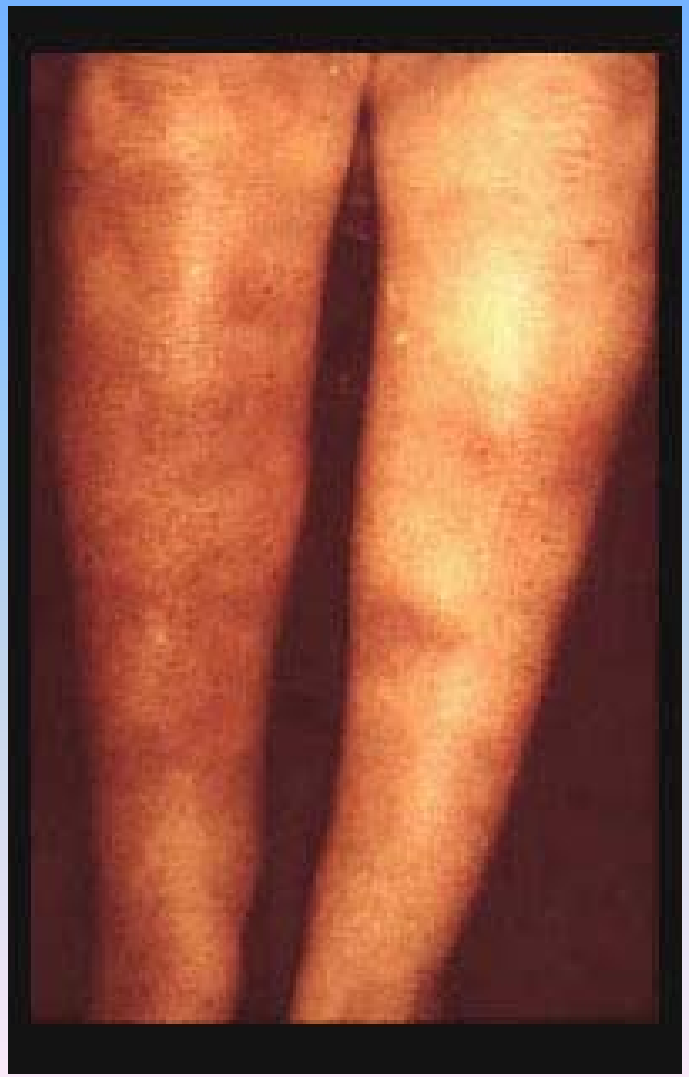


Skin involvement- 20%

- Erythema Nodosum (biopsy non-specific)
- Lupus pernio (biopsy)
- Nodules, flat patches (biopsy)
- Cutaneous anergy is common.
- **LOFGREN'S SYNDROME; acute triad of erythema nodosum, joint pains, and bilateral hilar adenopathy**
- Diagnosis: Appearance can be classic, biopsy to support

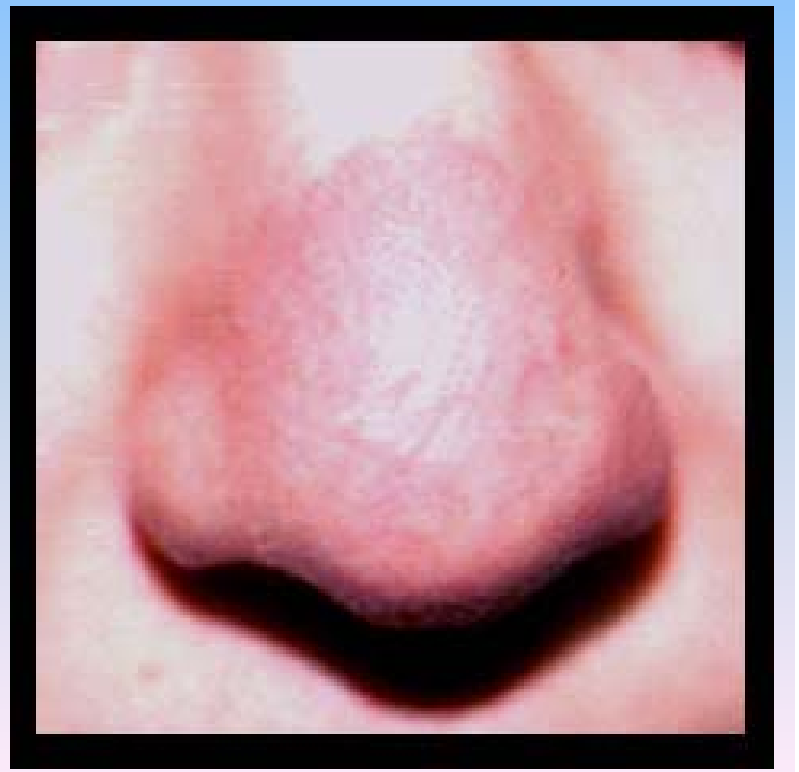
ERYTHEMA NODOSUM

These reddish raised lesions.



Lupus pernio

- Indurated blue purple swollen shiny lesions on nose, cheeks, lips, ears, fingers, rarely buttocks.
- Papules, nodules, and plaques
- Psoriatic like lesions
- Lesions in scars and tattoos



RAISED PLAQUES

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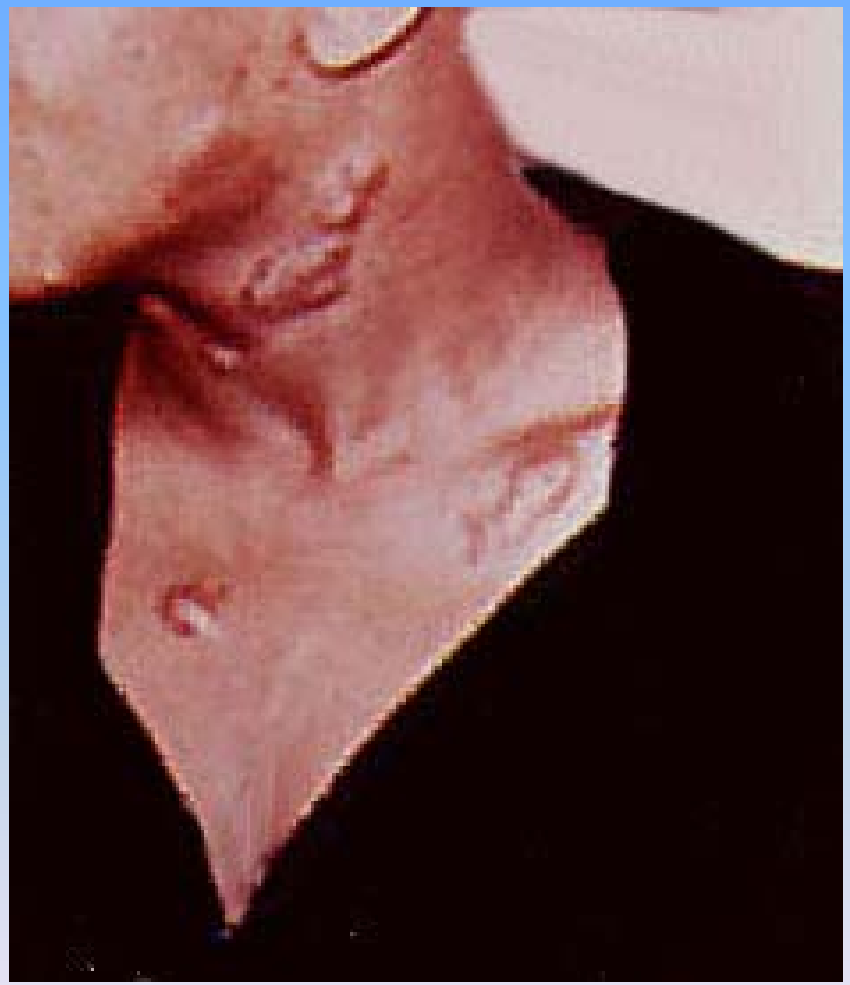


These raised plaques are the result of coalescence of nodules

Liver involvement

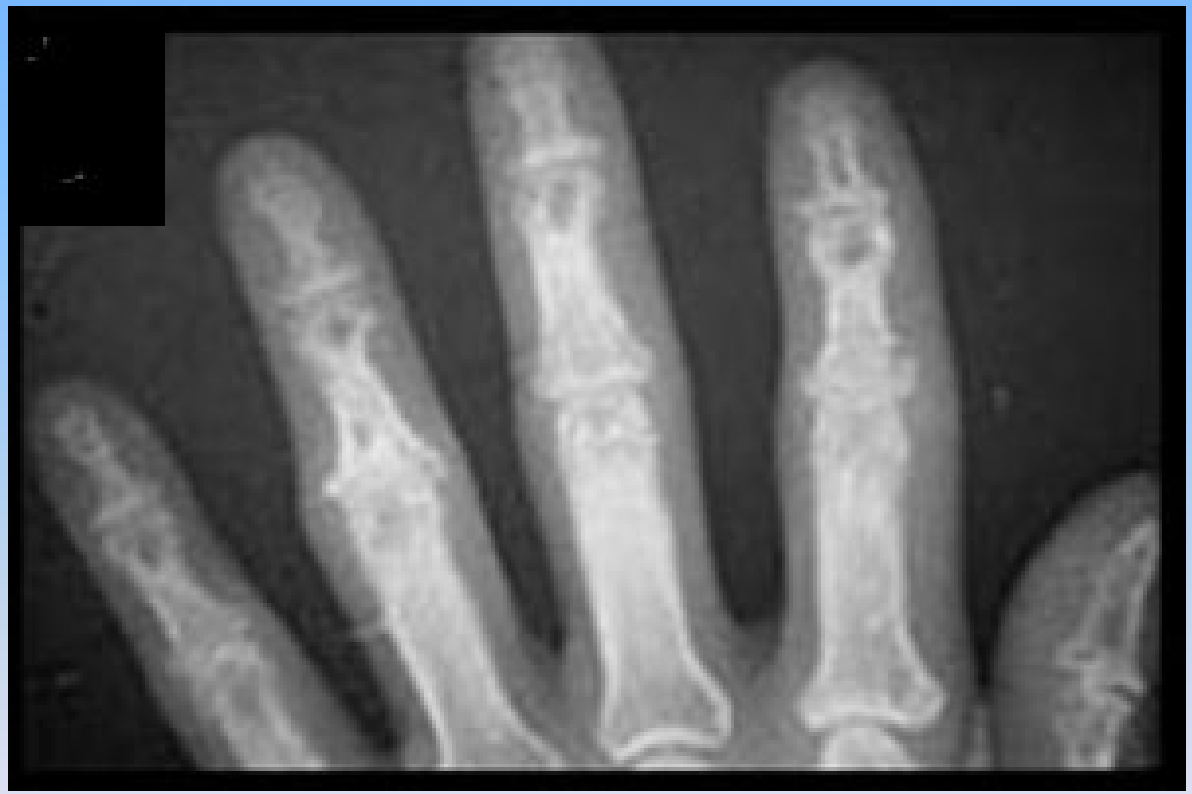
- 33% have hepatomegaly or biochemical evidence of disease
- Symptoms usually absent, jaundice may occur
- Cholestasis, fibrosis, cirrhosis, portal hypertension, and the Budd-Chiari syndrome have been seen

Muscluloskeletal

- Acute polyarthritis
- Fever, Pain, joint swelling
- Usually self limited
- Chronic destructive bone disease with deformity is rare
- Polymyositis and chronic myopathy

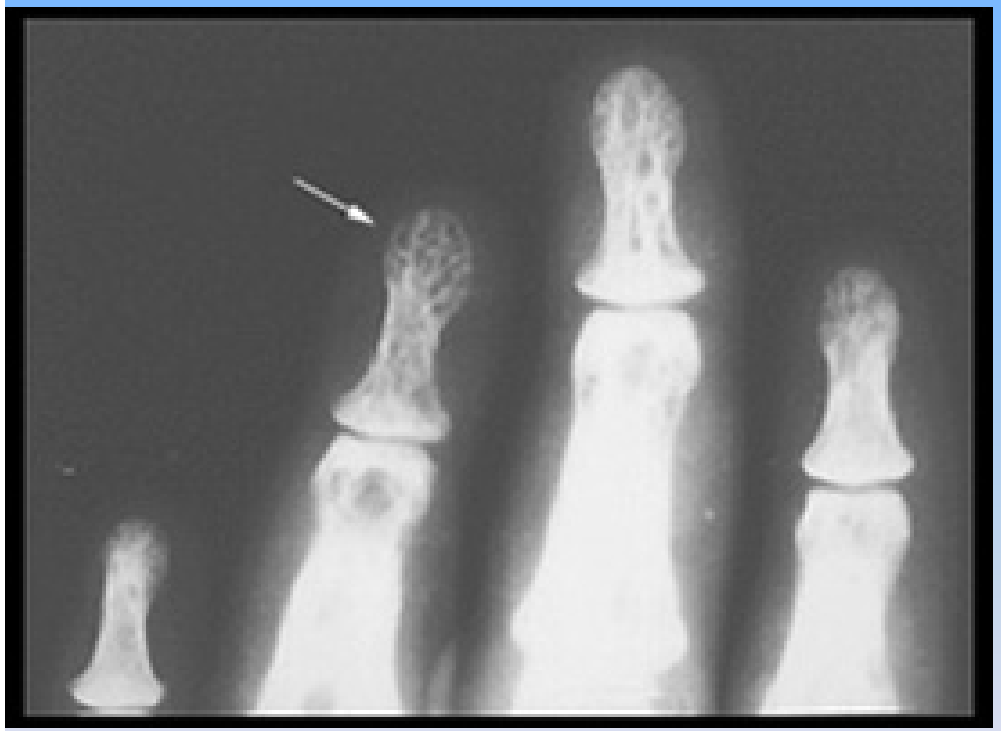
PUNCHED OUT LYTIC LESIONS

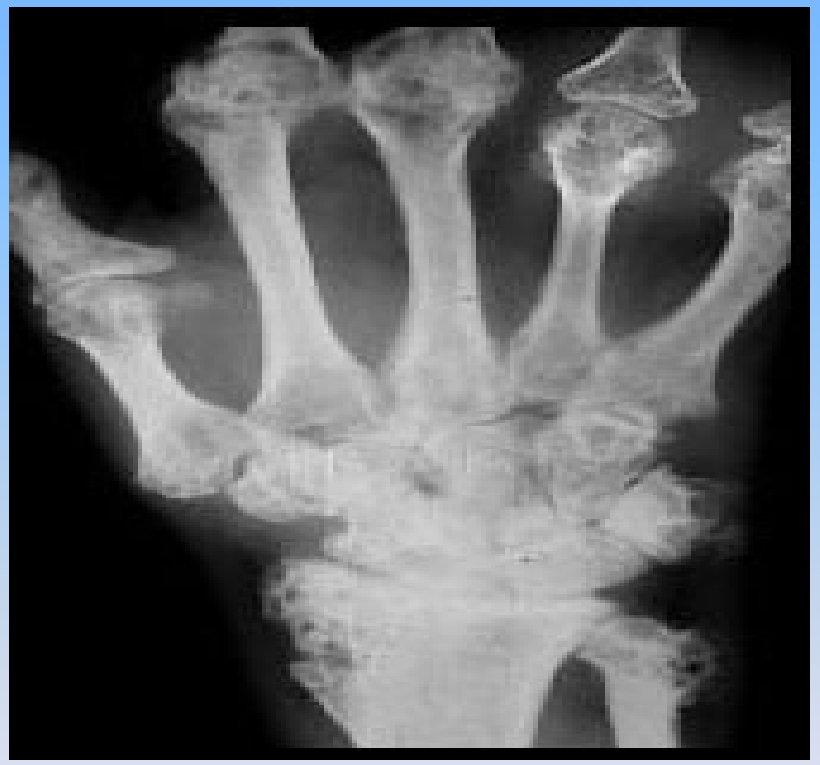
Focal osteolytic lesions in the fingers are most common abnormality.



LACY TRABECULAR PATTERN

Osteolysis has left a lacy trabecular pattern in this phalanx (arrow)





Cardiac manifestations

- Dysrhythmia,
- Pericardial involvement
- Pulmonary hypertension
- breathlessness
- Testing: EKG, echo, MRI with Gadolinium
- Can biopsy heart, but not typical
- **Presumed if sarcoidosis affecting other organs**

5% symptomatic, 30% incidental

Nervous System

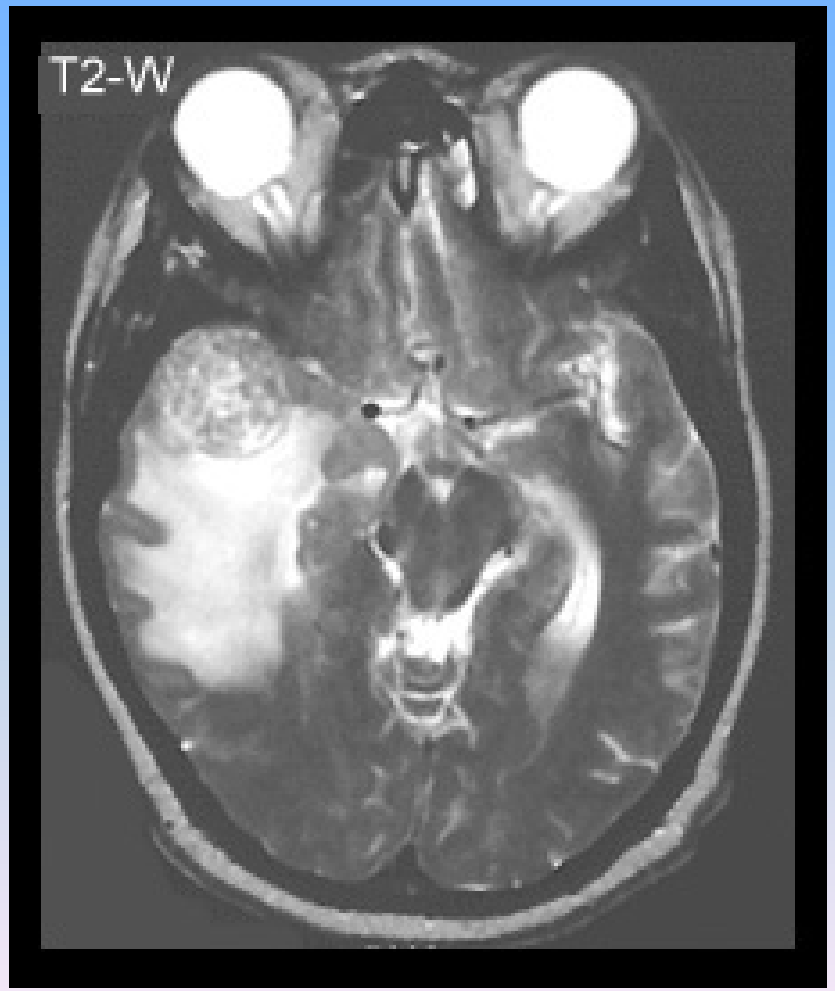
- Cranial nerves, and peripheral nerves can be involved
- 7th nerve facial palsy is most common
- Acute, transient, and can be unilateral or bilateral
- **HEREFORDT'S SYNDROME**; facial palsy accompanied by fever, uveitis, and enlargement of the parotid gland

Nervous system

- Optic nerve dysfunction
- Papilledema
- Palate dysfunction
- Hearing abnormalities
- Paresthesias
- Meningeal granulomas
- Encephalopathy

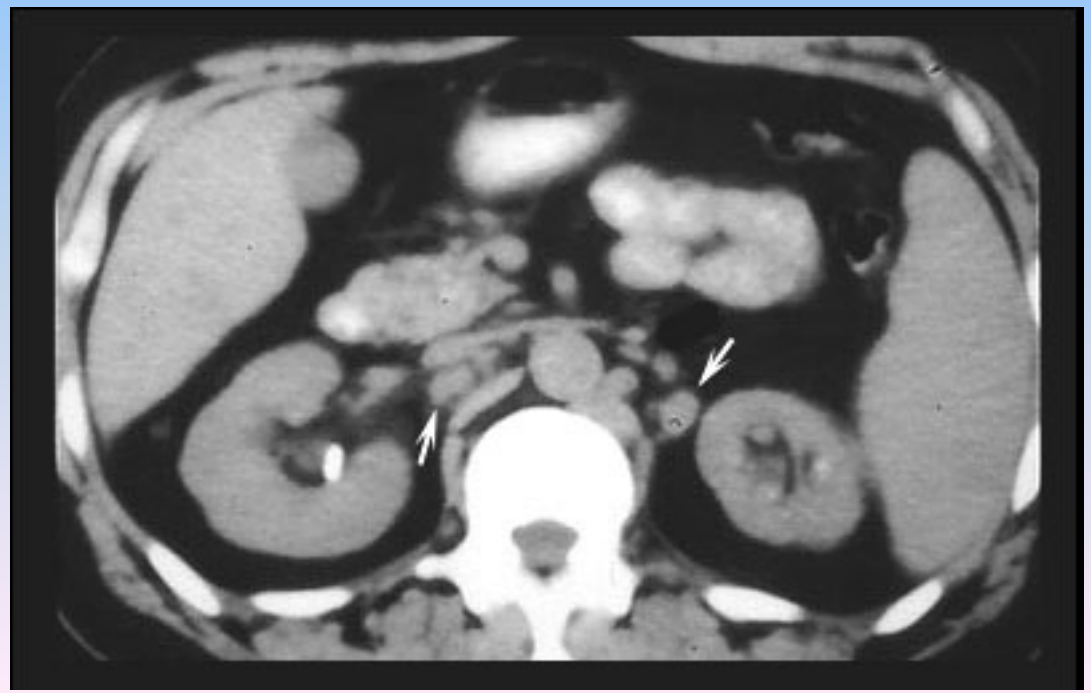
T2-W MR IMAGE

High signal intensity edema surrounding biopsy proven sarcoid lesion.



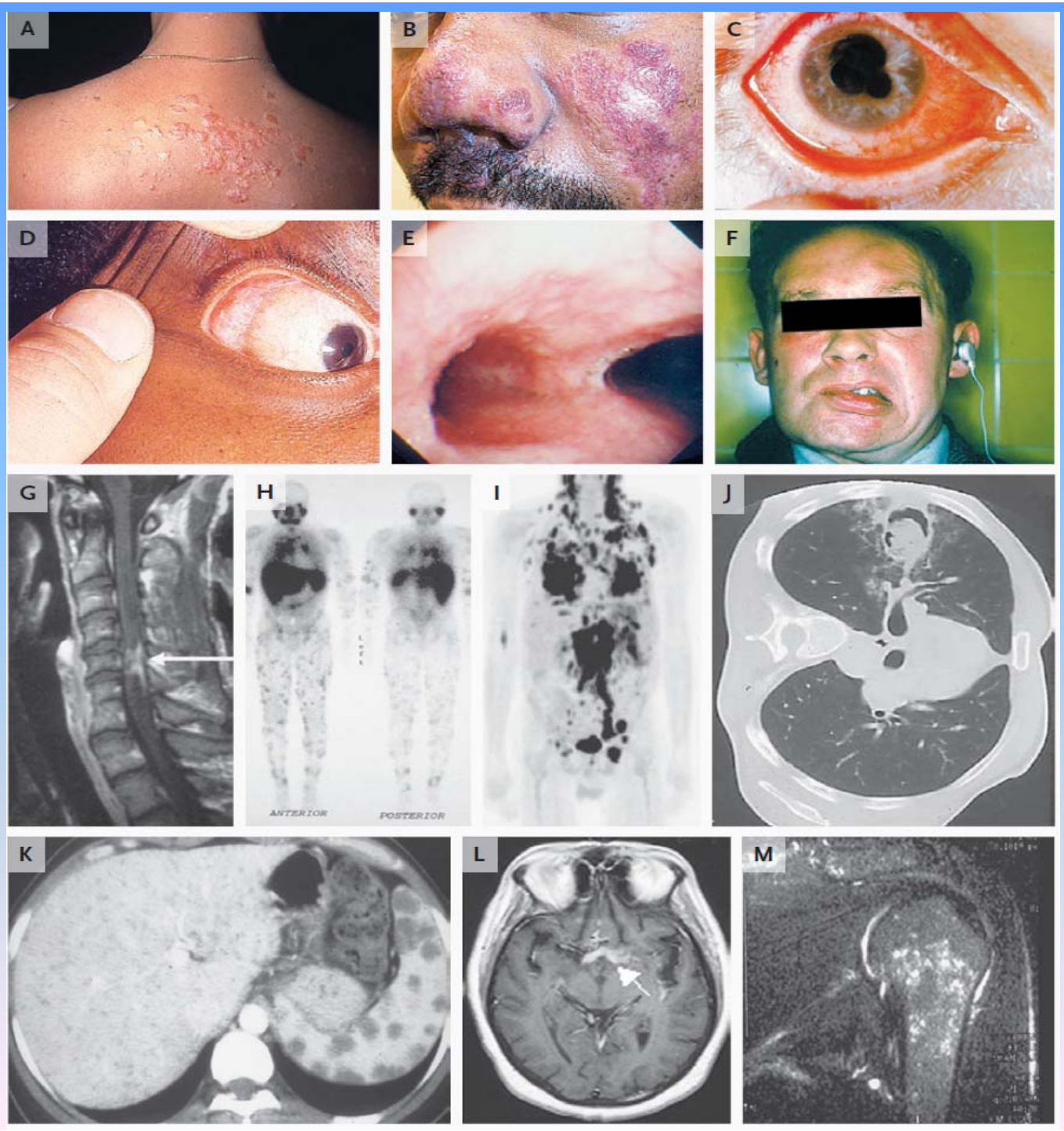
Kidney

- **Granulomatous interstitial nephritis produces renal failure**
- Develops over a period of weeks to months
- Rapid response to steroid therapy
- Kidney stones (nephrolithiasis) and nephrocalcinosis are very unusual secondary to hypercalcemia and hypercalciuria



Lymph nodes

- Lymphadenopathy
- Intrathoracic nodes enlarged in 75-90% patients including hilar nodes and paratracheal nodes.
- Peripheral lymphadenopathy, cervical, axiallary
- Abdominal lymphadenopathy


A
B
C
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ANTERIOR
POSTERIOR
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L
M

Differential diagnosis

Tuberculosis

Lymphoma

Hodgkin's disease

Metastases

Pneumoconioses

Enlarged pulmonary arteries

Infectious mononucleosis

Lymphangitic carcinomatosis

Idiopathic hemosiderosis

Alveolar cell carcinoma

Pulmonary eosinophilia

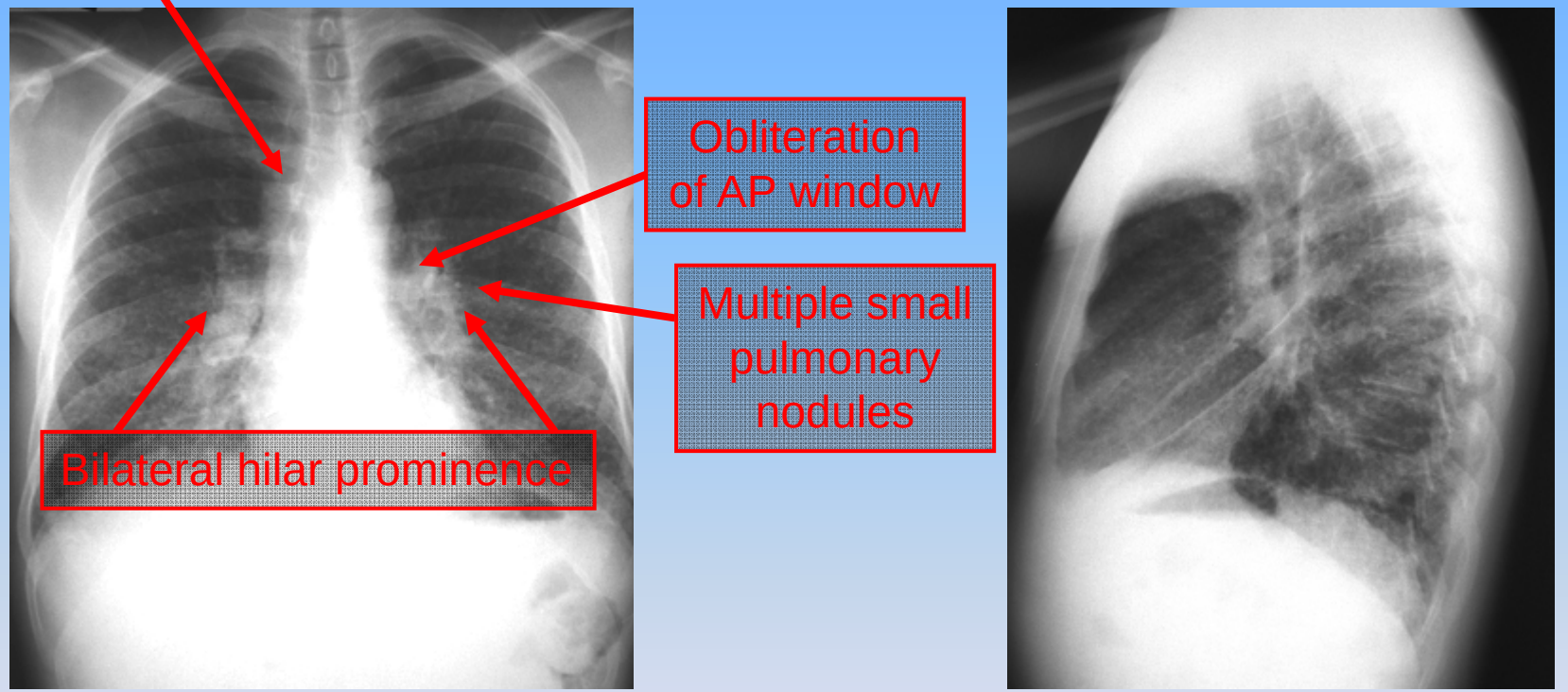
Hypersensitivity pneumonitis

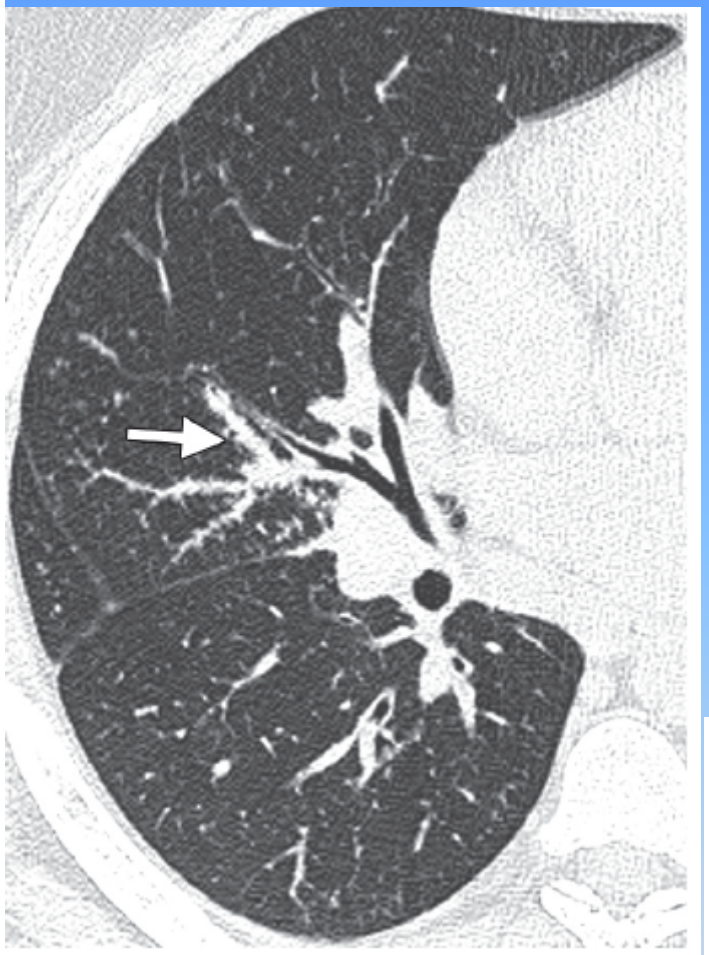
Fibrosing alveolitis

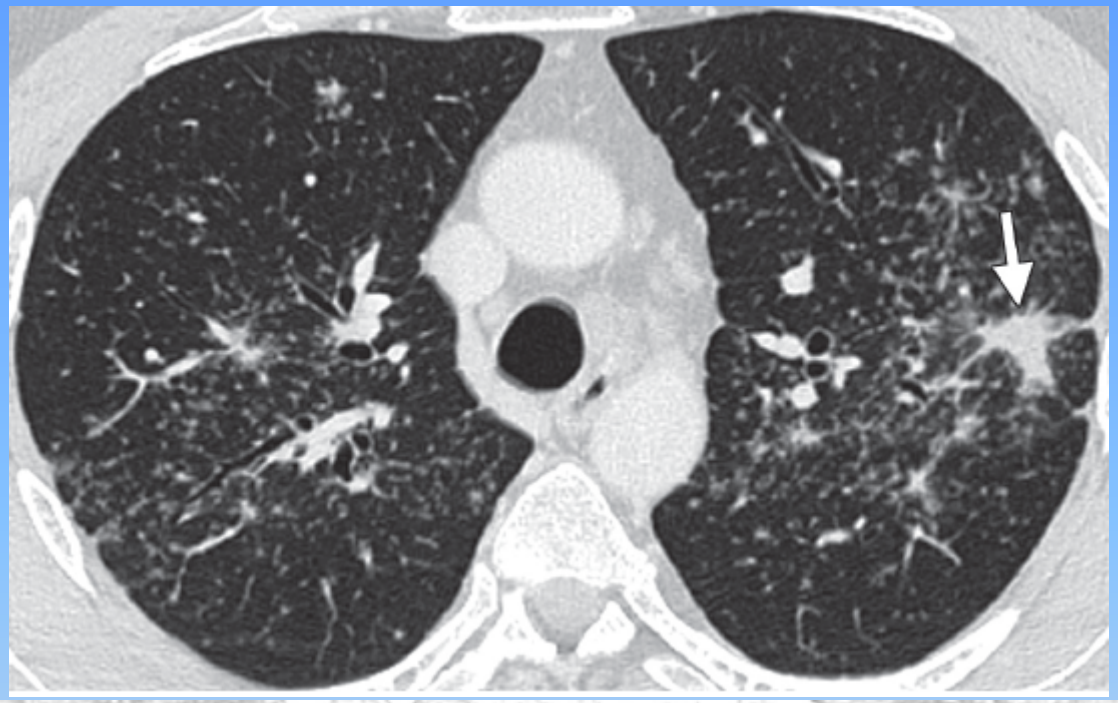
Collagen disorders

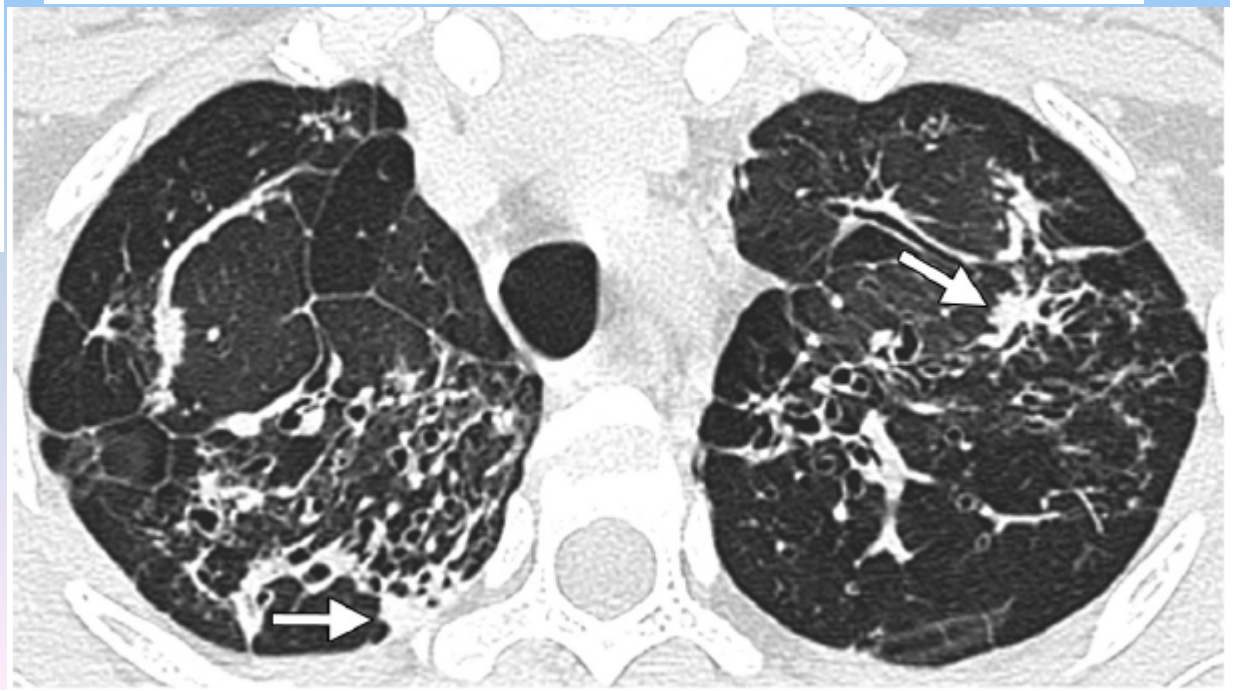
Parasitic infection

Plain films


Widening of right paratracheal stripe
Obliteration of AP window
Multiple small pulmonary nodules
Bilateral hilar prominence







HRCT findings

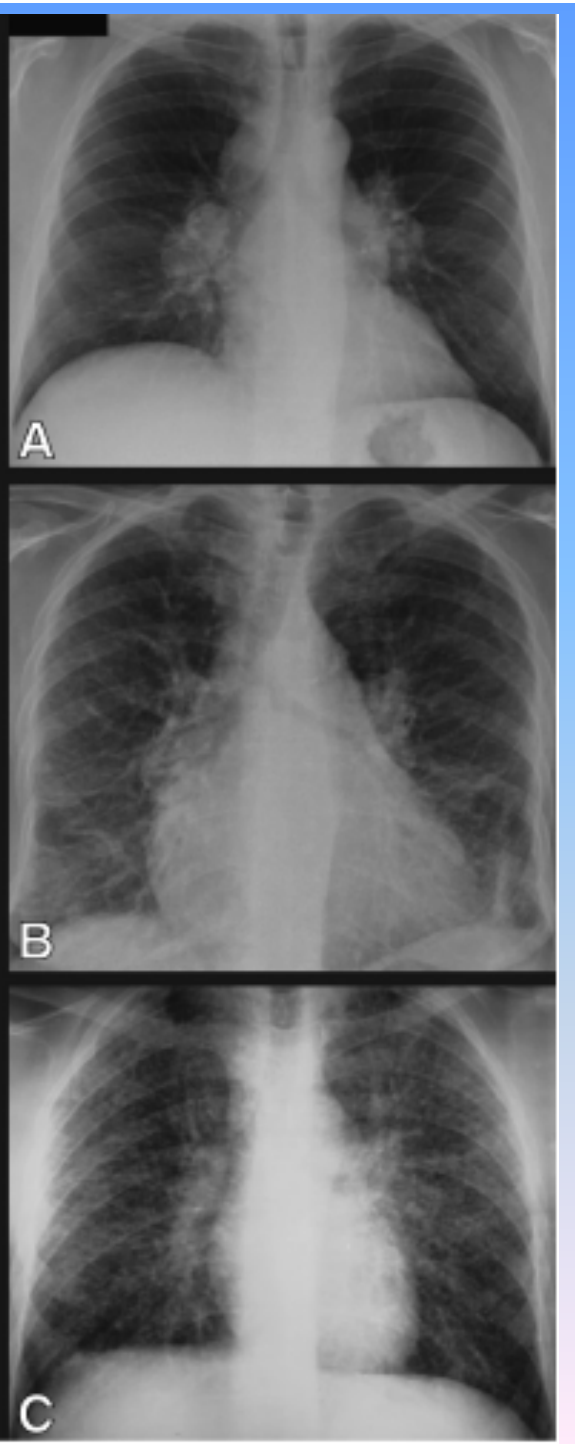
Table 2
Reversible and Irreversible Abnormalities of Pulmonary Sarcoidosis at High-Resolution CT

Reversible parenchymal abnormalities*
Micronodules, macronodules
Airspace consolidation: confluent alveolar opacities
Ground-glass opacities
Interlobular septal thickening
Intralobular linear opacities
Irreversible parenchymal abnormalities†
Honeycomb-like opacities, cysts, bullae, emphysema
Architectural distortion
Traction bronchiectasis, bronchiolectasis
Volume loss in upper lobes, retraction of hila
Mycetoma (in 10% of patients with end-stage sarcoidosis and a preexisting cavity)

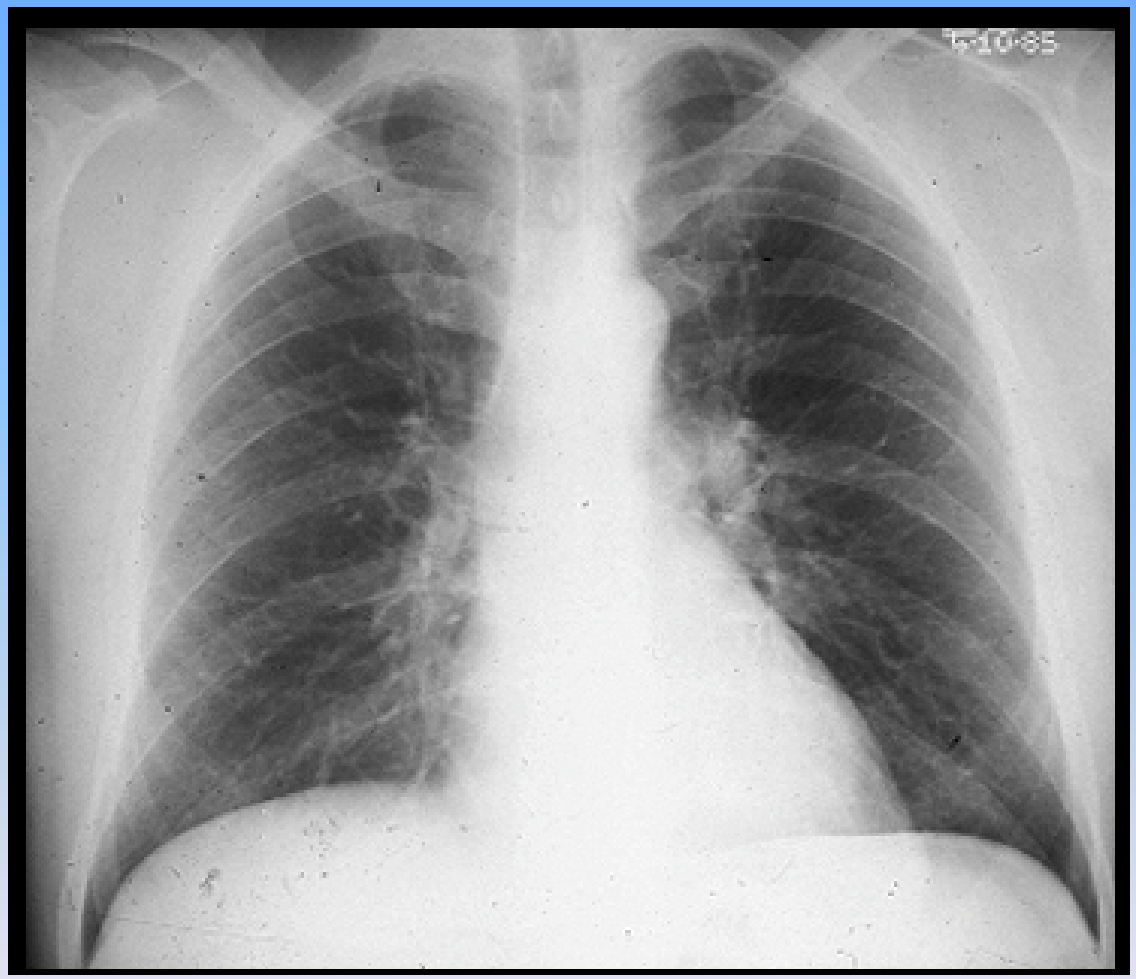
*These features are suggestive of granulomatous inflammation.
†These features are indicative of chronicity and fibrosis.

Staging of Sarcoidosis on the Basis of Chest Radiographs

STAGE 0	No abnormalities	5%–10%
STAGE 1	Lymphadenopathy (fig. A)	50%
STAGE 2	Lymphadenopathy + pulmonary infiltration (fig. B)	25%–30%
STAGE 3	Pulmonary infiltration (fig. C)	10%–12%
STAGE 4	Fibrosis	5% (up to 25% during the course of the disease)

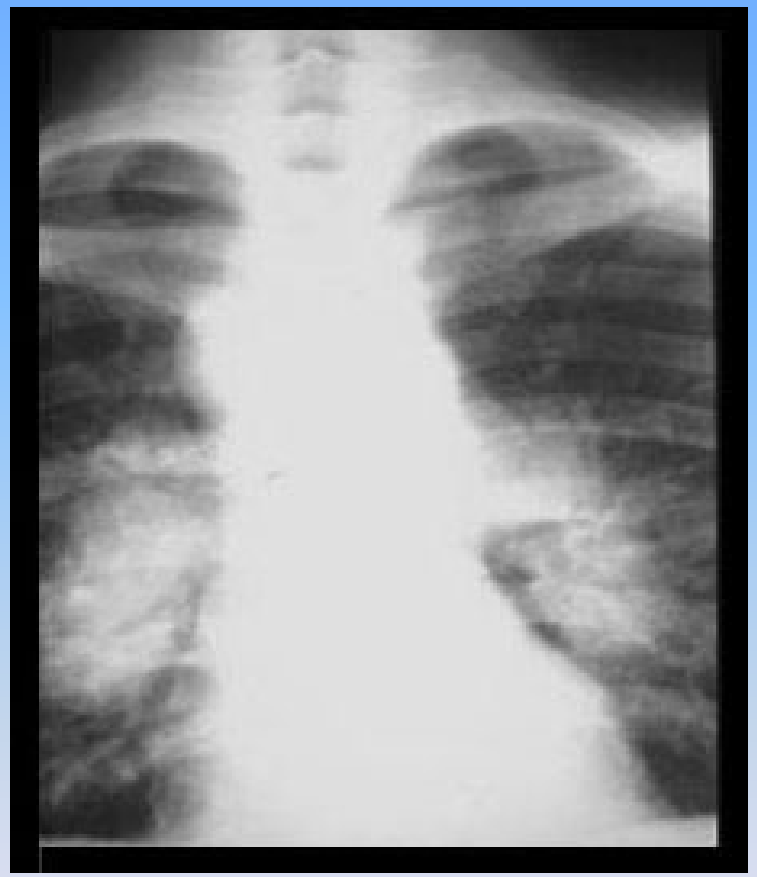


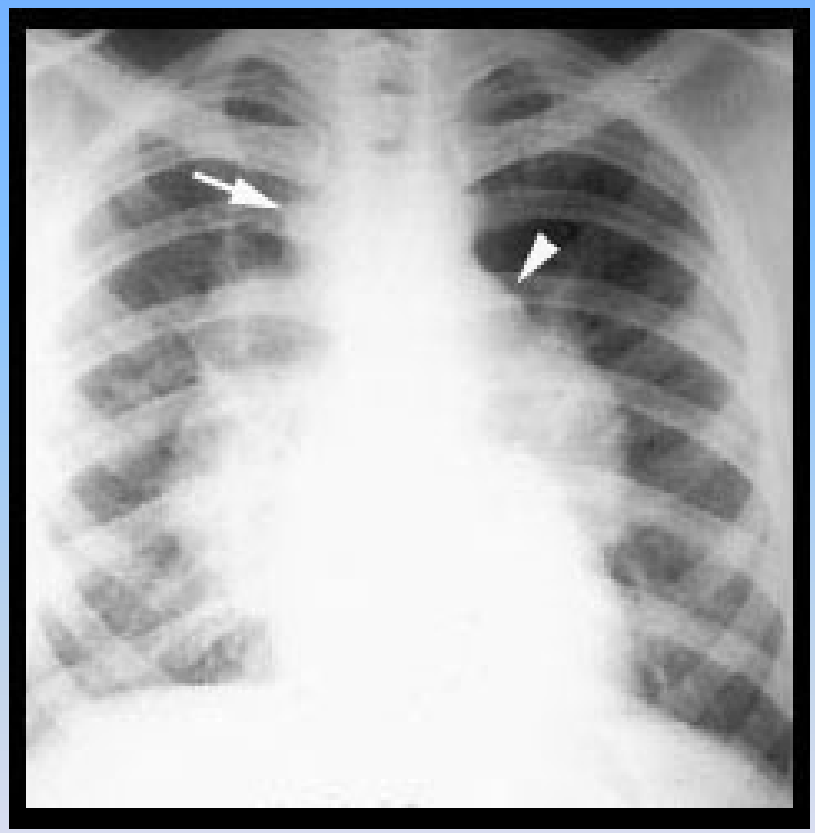
Stage 0



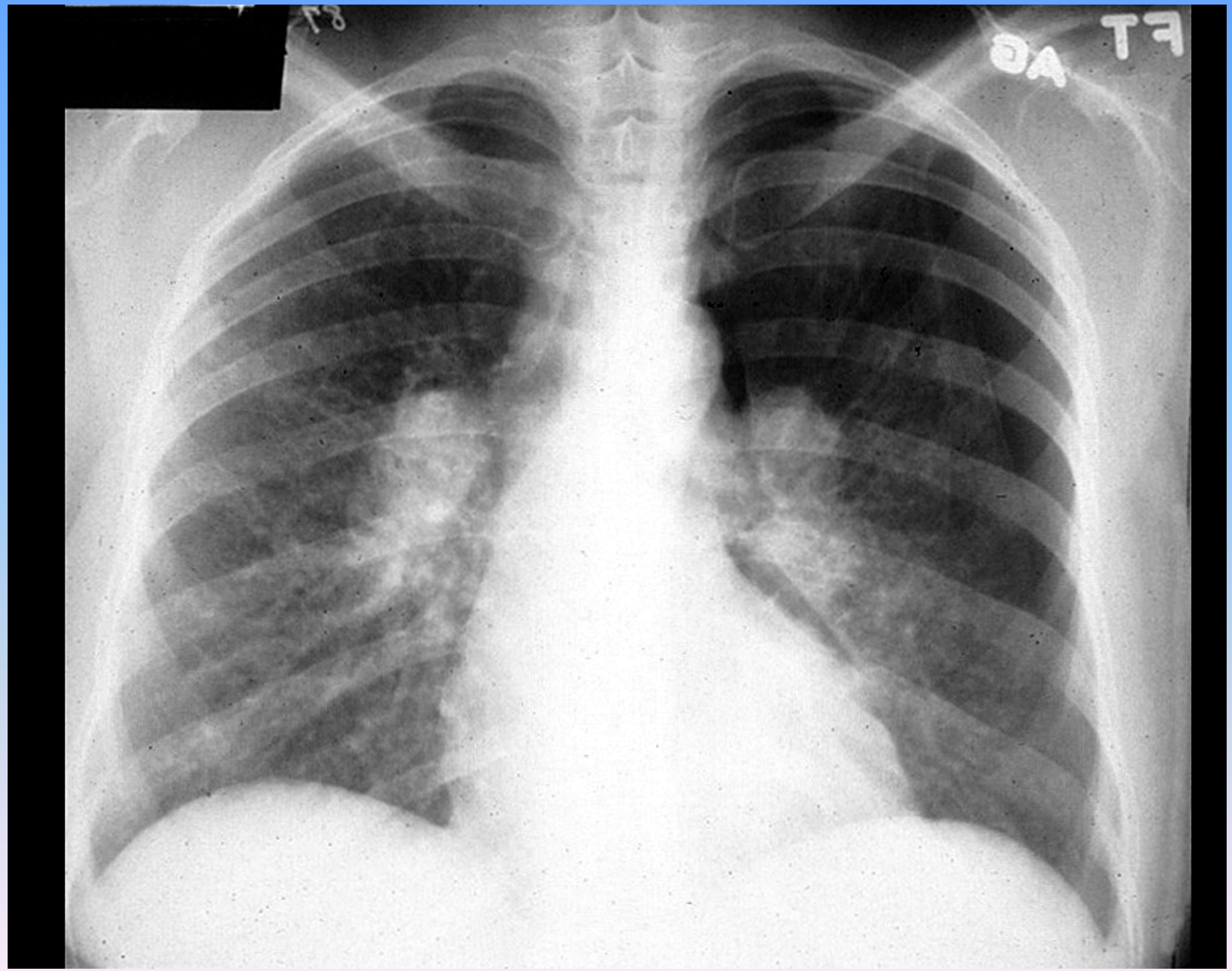
- Stage 0 - Normal findings on chest radiograph

Stage I

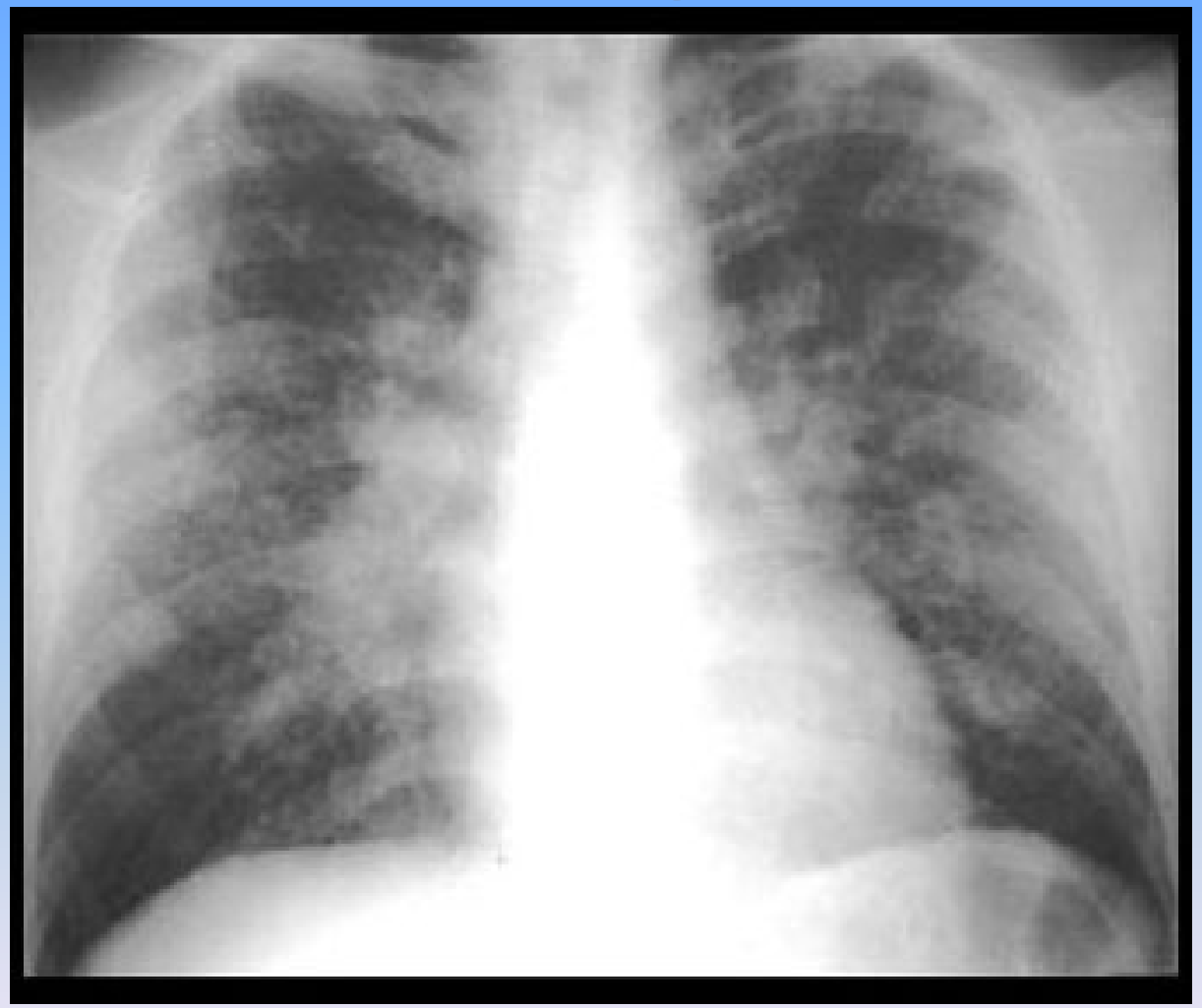




- Stage I - Bilateral hilar lymphadenopathy, which may be accompanied by paratracheal adenopathy

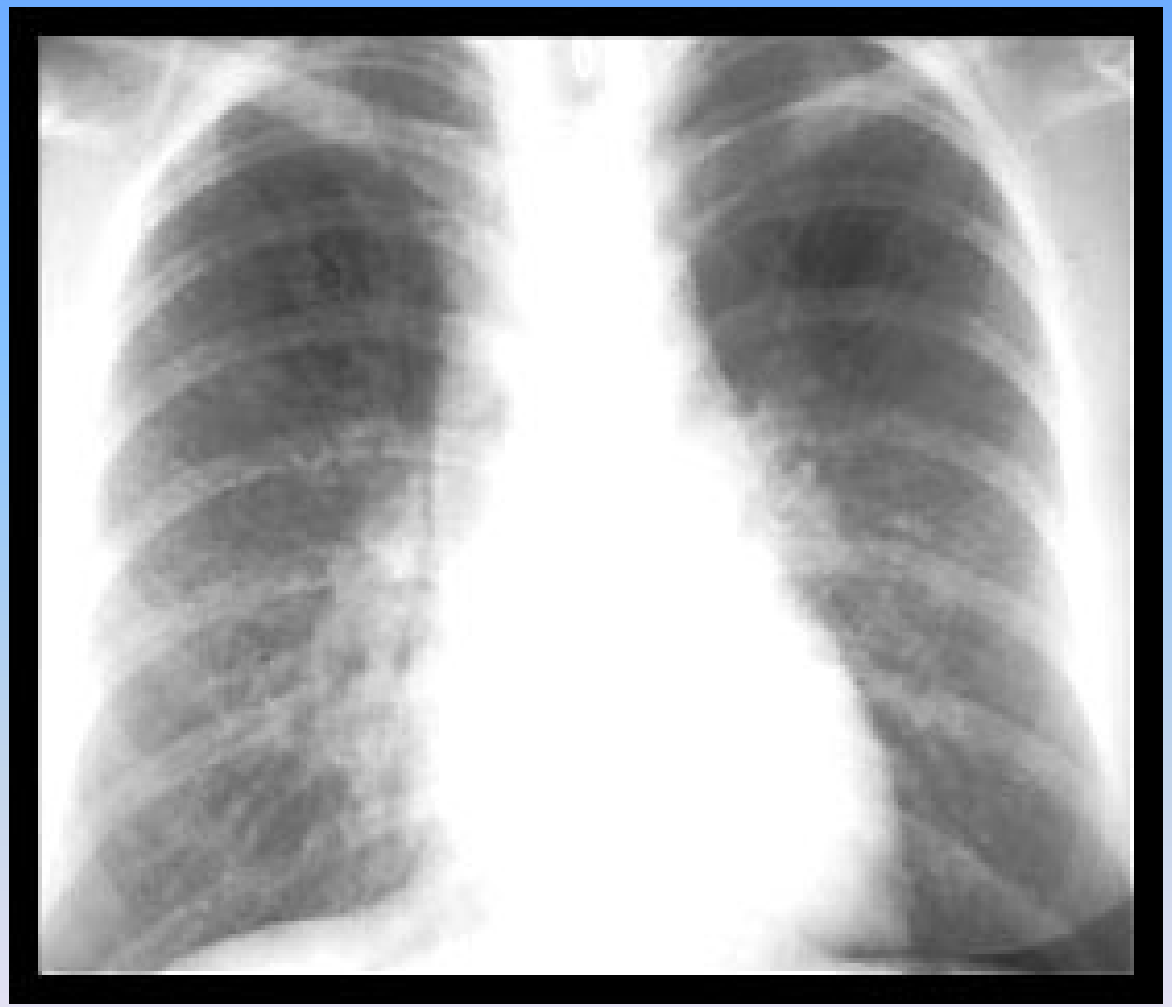


Stage II

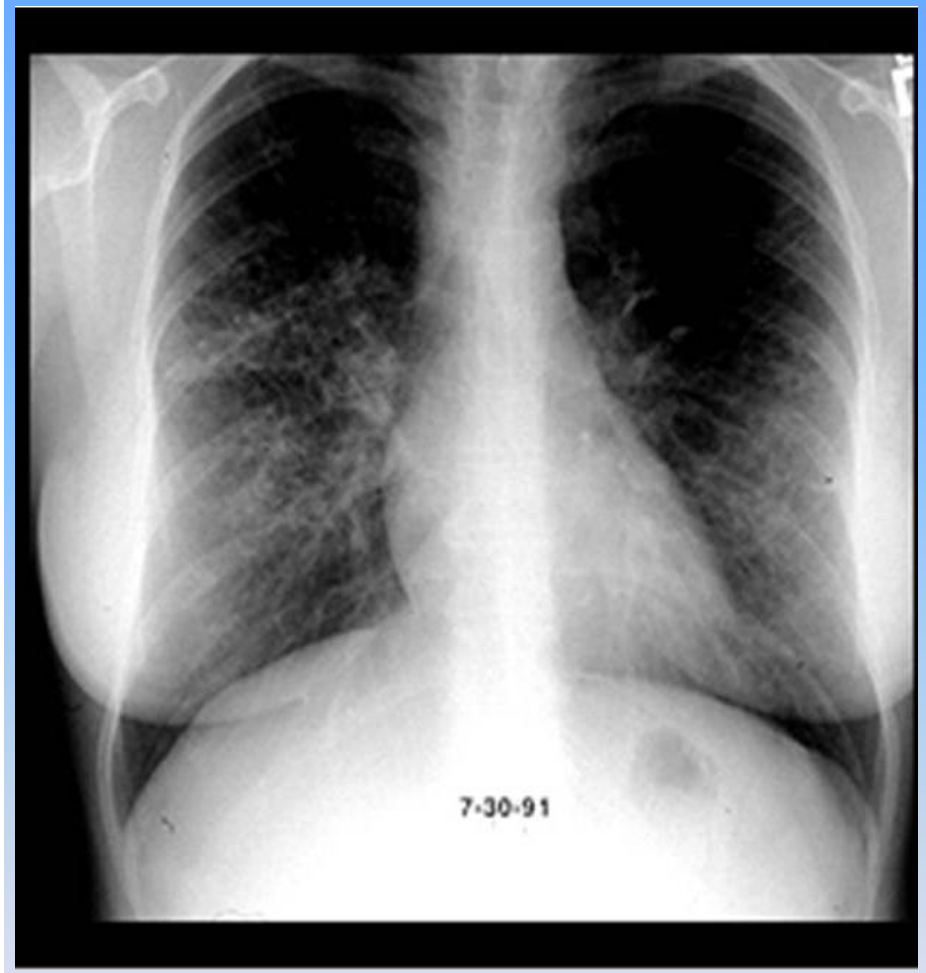


Bilateral hilar adenopathy with pulmonary infiltrates

Stage III



Parenchymal infiltrates without hilar adenopathy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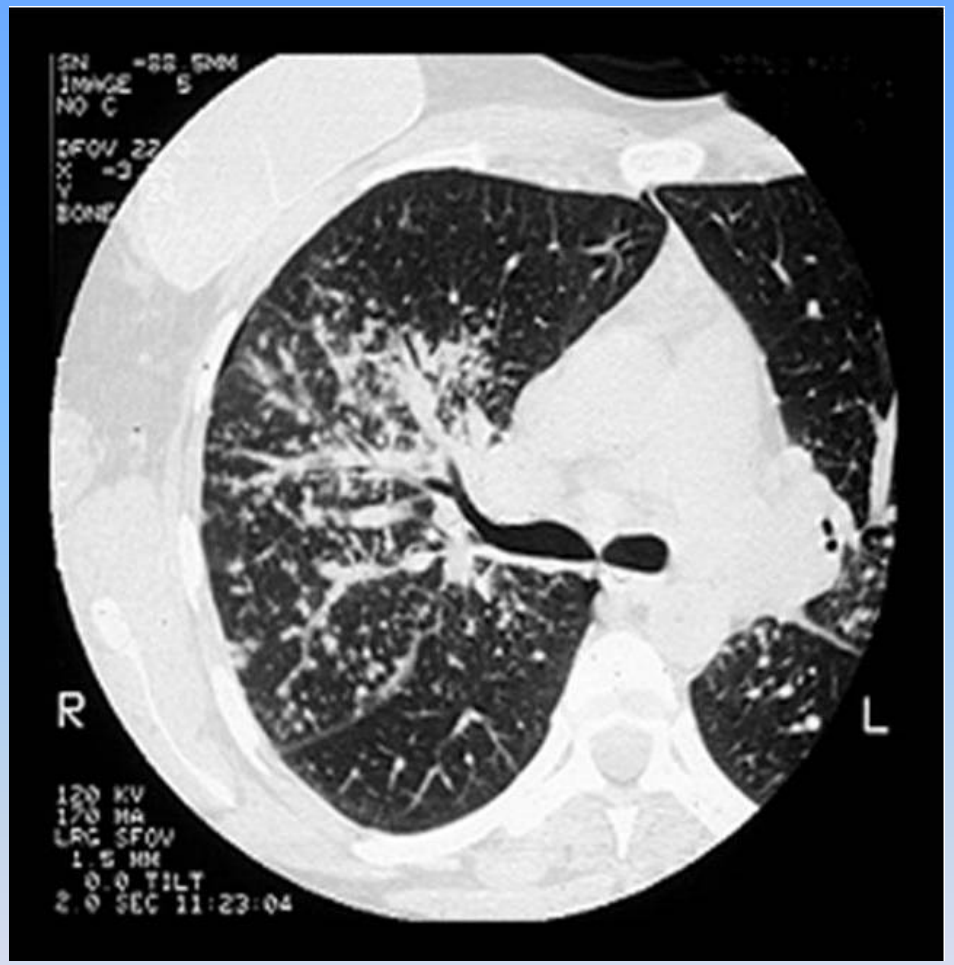
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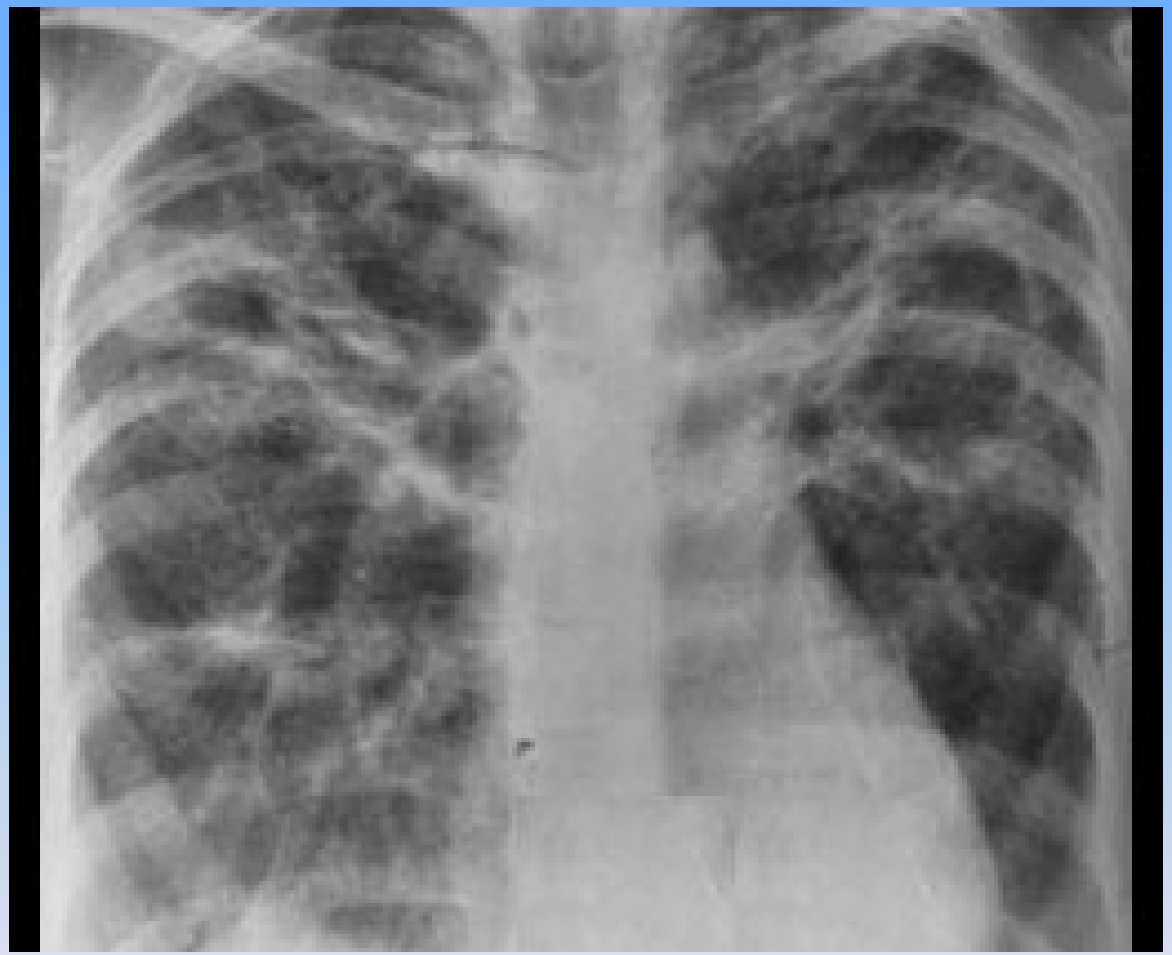
Stage IV



- Stage IV - Advanced fibrosis with evidence of honey-combing, hilar retraction, bullae, cysts, and emphysema

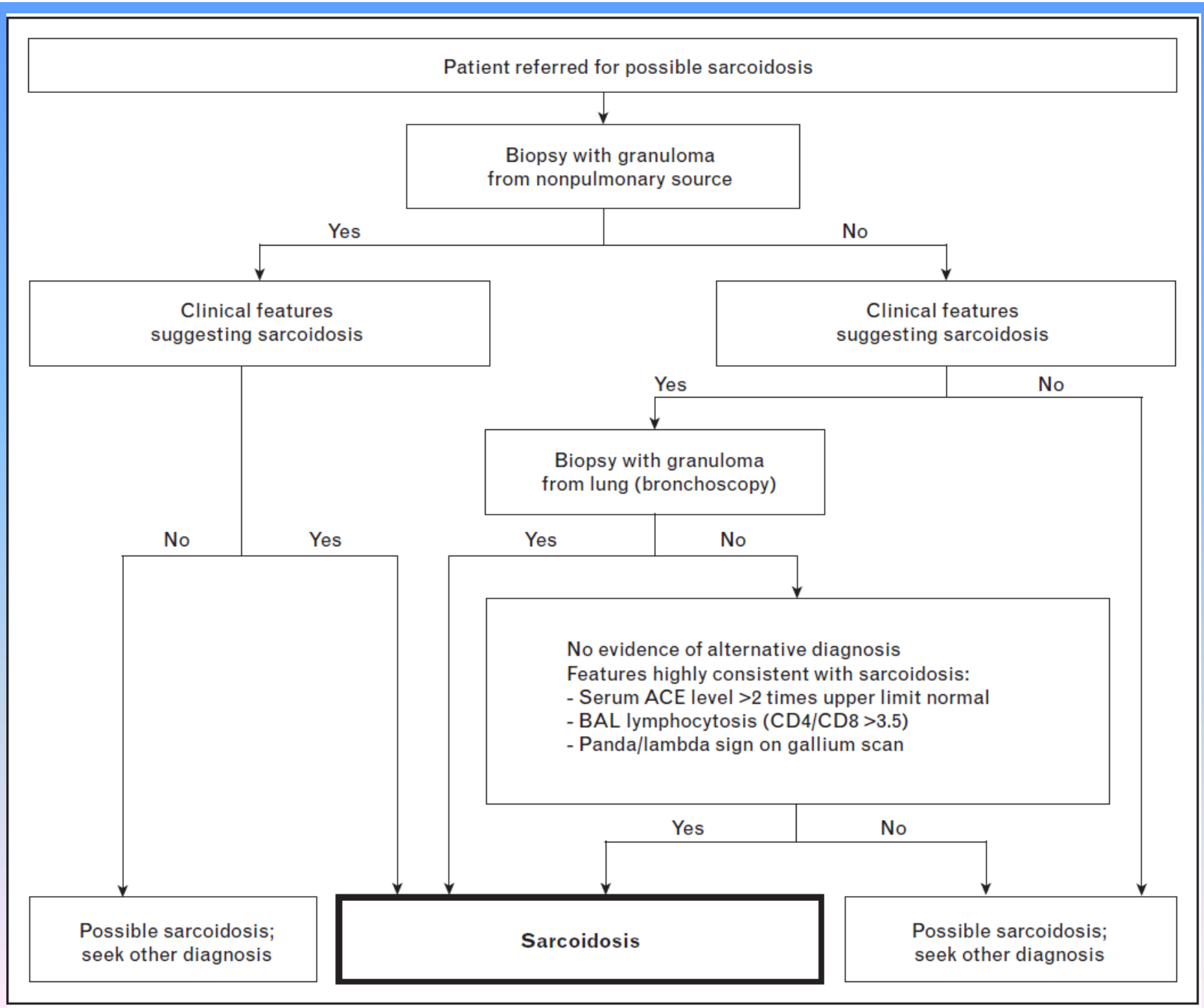
Diagnosis

Three criteria:

1. Compatible clinical picture

2. Demonstration of noncaseating granulomas in one or more tissues (requires biopsy)

3. Exclusion of other granulomatous diseases, particularly AFB (very important)


Patient referred for possible sarcoidosis
Biopsy with granuloma from nonpulmonary source
Yes
No
Clinical features suggesting sarcoidosis
Clinical features suggesting sarcoidosis
Yes
No
Biopsy with granuloma from lung (bronchoscopy)
No
Yes
Yes
No
No evidence of alternative diagnosis
Features highly consistent with sarcoidosis:
- Serum ACE level >2 times upper limit normal
- BAL lymphocytosis (CD4/CD8 >3.5)
- Panda/lambda sign on gallium scan
Yes
No
Possible sarcoidosis; seek other diagnosis
Sarcoidosis
Possible sarcoidosis; seek other diagnosis

Diagnostic modalities

- **Imaging**
- **Histopathology (TBLB, Lymph node biopsy, TBNA)**
- Serum angiotensin converting enzyme levels
- Mantoux test
- Serum electrolytes, RFT,
- ECG, holter monitoring
- PFT

Laboratory Abnormalities

- Vary with site of organ involvement
- Calcium- Increased GI absorption common; hypercalciuria 10-30%, sustained hypercalcemia in only 2% due to Vit. D production by granulomas
- Anemia- 5%
- Lymphopenia common
- Polyclonal gammopathy common
- Cutaneous anergy common

Angiotensin Converting Enzyme

- ACE produced by epithelioid cells in granulomas
- Serum ACE increased in 60% of patients
- Diagnostic use limited

  False negative rate of 40%

  False positive rate of 10%

- May be valuable in ***following disease activity***

Pulmonary Function Tests

- **Normal**
- **Decreased diffusing capacity**: Often earliest PFT abnormality. Tends to remain low in spite of clinical remission
- **Restrictive changes**: Decreased VC, TLC. May improve with clinical remission
- **Obstructive changes:** Rarely in Stage 1 disease due to endobronchial granulomas. More common in Stage 3 disease due to traction, distortion of airways by fibrotic tissue

Biopsy Procedures in Sarcoidosis

	Diagnostic Yield
1. Transbronchial biopsy	40-90
2. Scalene node biopsy	60-79%
3. Conjunctival biopsy	17-55%
4. Liver Biopsy	24-94%
5. Skin lesion biopsy (not E. nodosum)	100%
6. Lymph node biopsy	85% (if palpable)

Do you always need a biopsy?

- Bilateral hilar adenopathy alone (Stage 1)

  If the patient is asymptomatic (except for fever) and has no evidence of extrapulmonary disease (except for erythema nodosum), s/he can be watched without a biopsy.

  (Not true, if patient HIV+ !)

- 65% will remit spontaneously

All bilateral hilar lymphadenopathy is not sarcoidosis

Important to exclude lymphoma and tuberculosis

Not all patients with sarcoidosis require treatment

1. Sarcoidosis has a high likelihood of spontaneous remission
2. Treatment of end-stage pulmonary fibrosis (honeycombing, bullae) is of no value
3. It is not clear that steroids alter the natural history of the disease

Remission rates in sarcoidosis stages

Stage 1 (BHL)	55-90%
Stage 2 (BHL + infiltrates)	40-70%
Stage 3 (Pulm. infiltrates)	10-20
Overall:	20-25% permanent loss of lung function
	5-10% die

Indications for Steroids

1. Symptomatic pulmonary disease
2. Progressive parenchymal lung disease over 2 years
3. Posterior ocular disease (uveitis, iridocyclitis) or anterior disease not responding to topical steroids
4. Persistent fever, weight loss, anorexia, etc.
5. Significant liver disease
6. CNS disease
7. Hypercalcemia
8. Myocardial disease
9. Thrombocytopenia
10. Lupus pernio
11. Symptomatic bone cysts

Treatment options- first line

CONSIDER NOT TREATING!

- Can wait up to 6 months to see if spontaneous remission occurs (especially pulmonary)

Treatment options

Steroids are the mainstay of treatment

- Start at 20-40 mg/day of prednisone
- May need more or intravenous if severe, difficulty expected, or acute disease
- Slowly taper over 2-3months with monitoring for clinical/ radiological worsening, to lowest dose (5-10 mg every alternate day) and continue
- Total duration usually 9-12 months, may be prolonged

WATCH FOR STEROID SIDE EFFECTS

- *Weight gain*
- *Blood sugar*
- *Blood pressure*
- *Thinning of skin*
- *osteoporosis*

Treatment options- second line

If prednisone intolerance, contraindicated or to spare its effects

Methotrexate (5-20mg/week)

- Liver toxicity, lung toxicity, mouth sores, abortion
- Blood counts, Cr, and liver function monthly, biopsy?

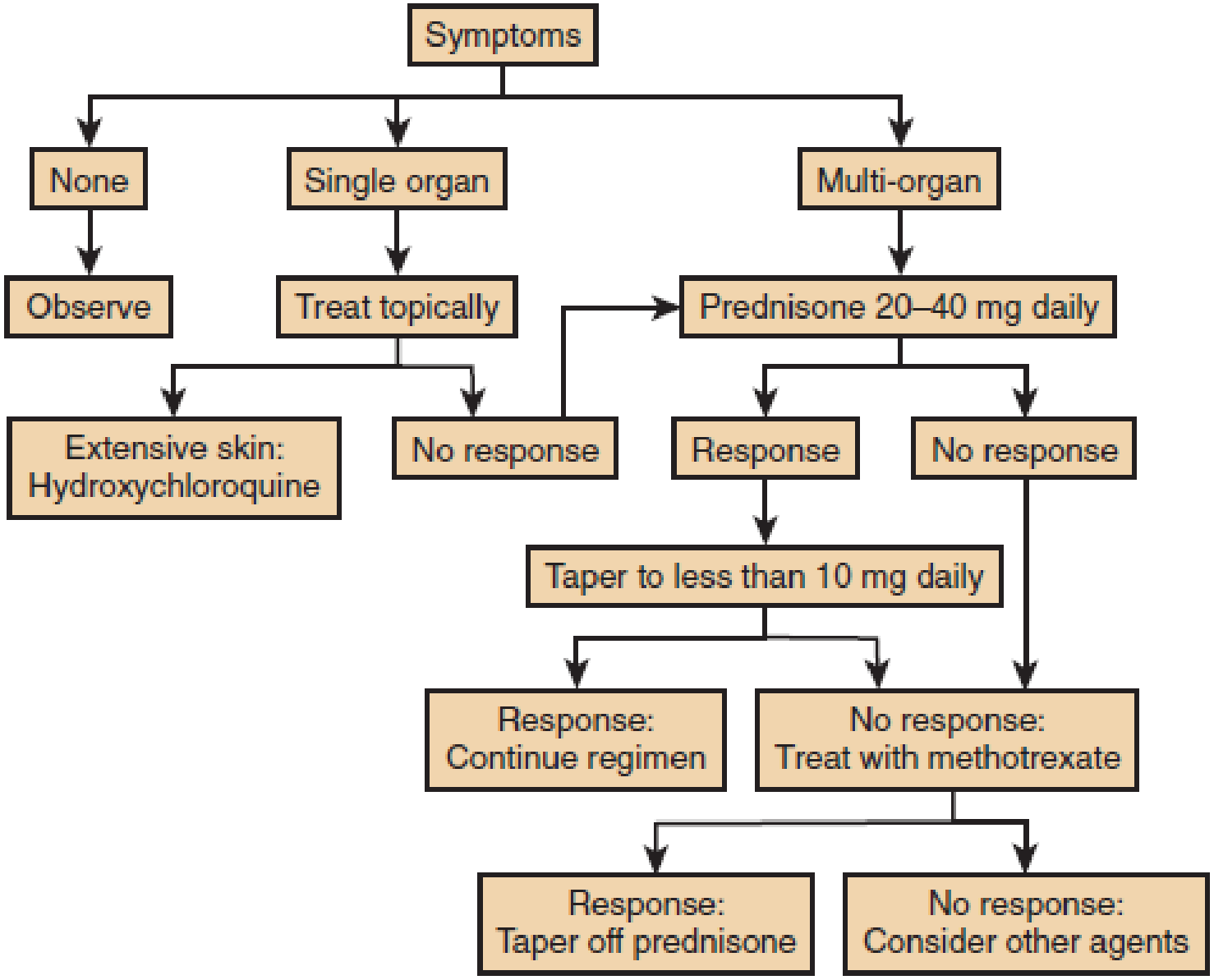
Azathioprine (1-3mg/kg/day)

- Low blood counts, diarrhea, small increase in malignancy
- Blood counts and liver function monthly

Hydroxychloroquine

mainly used in hypercalcemia and skin involvement

Organ	Clinical Findings	Treatment
Lungs	Dyspnea plus FEV_1, FVC <70%	Prednisone, 20–40 mg/day
	Cough, wheezing	Inhaled corticosteroid
Eyes	Anterior uveitis	Topical corticosteroid
	Posterior uveitis	Prednisone, 20–40 mg/day
	Optic neuritis	Prednisone, 20–40 mg/day
Skin	Lupus pernio	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day Thalidomide, 100–150 mg/day Methotrexate, 10–15 mg/wk
	Plaques, nodules	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day
	Erythema nodosum	NSAID
Central nervous system	Cranial-nerve palsies	Prednisone, 20–40 mg/day
	Intracerebral involvement	Prednisone, 40 mg per day Azathioprine, 150 mg/day Hydroxychloroquine, 400 mg/day
Heart	Complete heart block	Pacemaker†
	Ventricular fibrillation, tachycardia	AICD
	Decreased LVEF (<35%)	AICD; prednisone, 30–40 mg/day
Liver	Cholestatic hepatitis with constitutional symptoms	Prednisone, 20–40 mg/day Ursodiol, 15 mg/kg of body weight per day
Joints and muscles	Arthralgias	NSAID
	Granulomatous arthritis	Prednisone, 20–40 mg/day
	Myositis, myopathy	Prednisone, 20–40 mg/day
Hypercalciuria and hypercalcemia	Kidney stones, fatigue	Prednisone, 20–40 mg/day Hydroxychloroquine, 400 mg/day


Symptoms
None
Single organ
Multi-organ
Observe
Treat topically
Prednisone 20–40 mg daily
Extensive skin: Hydroxychloroquine
No response
Response
No response
Taper to less than 10 mg daily
Response: Continue regimen
No response: Treat with methotrexate
Response: Taper off prednisone
No response: Consider other agents

THANK YOU