🫁 CHRONIC INTERSTITIAL (RESTRICTIVE) LUNG DISEASES (ILDs)

📌 Definition

Chronic interstitial lung diseases (ILDs) are a heterogeneous group of disorders characterized by:

- Bilateral
- Often patchy
- Progressive interstitial fibrosis
- Predominantly involving alveolar walls

They are also called:

- Restrictive lung diseases
- Infiltrative lung diseases

🎯 Core Pathophysiologic Hallmark

✔ Reduced lung compliance ("stiff lungs")
✔ Increased work of breathing
✔ Progressive dyspnea

🔬 Pathophysiology

Interstitial fibrosis → Thickened alveolar septa →
Impaired diffusion → V/Q mismatch → Hypoxemia

Advanced disease →
- Pulmonary hypertension
- Cor pulmonale
- Respiratory failure

🩻 Radiologic Features

- Small nodules
- Irregular linear opacities
- Ground-glass shadows

- Honeycombing (late stage)

🍯 End-Stage Lung

All ILDs, when advanced, may result in:

👉 Diffuse scarring
👉 Cystic spaces
👉 "Honeycomb lung"

At this stage, the original cause may be impossible to determine.

📚 Major Categories of Chronic Interstitial Lung Disease

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❶ Fibrosing

- Idiopathic pulmonary fibrosis (UIP pattern)

- Nonspecific interstitial pneumonia
- Cryptogenic organizing pneumonia
- Collagen vascular disease-associated
- Pneumoconiosis
- Therapy-associated (drugs, radiation)

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2 Granulomatous

- Sarcoidosis
- Hypersensitivity pneumonitis

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3 Eosinophilic

- Loeffler syndrome
- Drug-associated
- Chronic eosinophilic pneumonia

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4 Smoking-Related

- Desquamative interstitial pneumonia
- Respiratory bronchiolitis

🔥 Fibrosing Disease: Idiopathic Pulmonary Fibrosis (IPF)

🫁 Idiopathic Pulmonary Fibrosis (IPF)

Also called:

- Usual interstitial pneumonia (UIP pattern)
- Cryptogenic fibrosing alveolitis

⚠ IPF is a diagnosis of exclusion.

📌 Epidemiology

- Age > 50 years
- More common in males

- Rare before age 50

🔬 Pathogenesis

Central concept:

Repeated alveolar epithelial injury

- Abnormal repair
  → Progressive fibrosis

🧬 Genetic Factors

Important genetic associations:

- Telomerase mutations → cellular senescence
- MUCSB gene variant (~35% cases)
- Surfactant gene mutations

These genes are expressed in epithelial cells, suggesting epithelial injury is the initiating event.

🔁 Pathogenic Sequence

Chronic epithelial injury → Defective regeneration → Fibroblast & myofibroblast proliferation → Collagen deposition → Progressive interstitial fibrosis

🔥 Important Mediators

- TGF-β (major profibrotic cytokine)
- M2 macrophages (pro-fibrotic phenotype)

Inflammation is secondary — fibrosis is primary.

🔬 MORPHOLOGY (UIP Pattern)

🫁 Gross Features

- Cobblestone pleural surface

- Retraction scars along septa
- Firm, rubbery white fibrosis
- Lower lobes predominantly affected

🔬 Histologic Hallmarks

1️⃣ Patchy interstitial fibrosis

2️⃣ Subpleural and basilar predominance

3️⃣ Fibroblastic foci (early lesion) ⭐

4️⃣ Temporal heterogeneity

- Early cellular lesions
- Late dense collagenous scars coexist

5️⃣ Honeycomb fibrosis

- Cystic spaces
- Lined by type II pneumocytes or bronchiolar epithelium

🧪 Inflammatory Component

- Lymphocytes
- Occasional plasma cells
- Mast cells
- Eosinophils

But inflammation is mild compared to fibrosis.

🫀 Secondary Changes

- Pulmonary hypertension
- Intimal fibrosis of pulmonary arteries
- Medial thickening

🩺 Clinical Features of IPF

🔹 Symptoms

- Gradual onset dyspnea
- Nonproductive cough

🔹 Physical Findings

- "Velcro-like" inspiratory crackles
- Cyanosis (late)
- Clubbing (common)
- Cor pulmonale (late)
- Peripheral edema

🩻 Radiology

- Subpleural fibrosis
- Basilar predominance
- Reticular pattern
- Honeycombing

Often diagnostic without biopsy.

💊 Treatment

Anti-inflammatory drugs → Not effective

Antifibrotic agents:

- Nintedanib (tyrosine kinase inhibitor)
- Pirfenidone (TGF-β inhibitor)

Definitive treatment:

→ Lung transplantation

📉 Prognosis

Poor.

Median survival:

3-5 years after diagnosis.

🧪 Pulmonary Function Tests (Restrictive Pattern)

Parameter	Finding
FEV1	↓
FVC	↓ ↓ ↓
FEV1/FVC	Normal or ↑
TLC	↓
DLCO	↓

Restrictive 🆚 Obstructive

Feature	Restrictive	Obstructive
Compliance	↓	Normal/ ↑

TLC	↓	↑
FEV1/FVC	Normal/ ↑	↓
Cause	Fibrosis	Airway narrowing

🎓 Viva Pearls

- ✔ IPF = diagnosis of exclusion
- ✔ UIP pattern required
- ✔ Lower lobe + subpleural involvement
- ✔ Fibroblastic foci = early lesion
- ✔ Honeycomb lung = end-stage
- ✔ TGF-β central mediator
- ✔ Poor prognosis (3–5 yrs)

🧠 Summary

Idiopathic pulmonary fibrosis is a progressive, fibrosing interstitial lung disease caused by repeated epithelial injury and abnormal repair, leading to patchy subpleural fibrosis, honeycomb lung, and fatal respiratory failure. 🫁🔥

🫁 Other Fibrosing Interstitial Lung Diseases

When evaluating fibrosing ILDs, several entities must be differentiated from IPF (UIP pattern), because prognosis and treatment differ significantly.

🅽 Nonspecific Interstitial Pneumonia (NSIP)

📌 Definition

A chronic bilateral interstitial lung disease of unknown cause with uniform (temporally homogeneous) inflammation and/or fibrosis.

🔬 Key Histologic Feature

Unlike UIP (IPF), NSIP shows:

- Patchy involvement
- BUT uniform stage of fibrosis in affected areas
- No temporal heterogeneity
- No classic fibroblastic foci pattern of UIP

🤝 Association

Frequently associated with collagen vascular diseases such as:

- Rheumatoid arthritis
- Systemic sclerosis

🩺 Clinical Significance

⭐ Much better prognosis than IPF
⭐ Often steroid-responsive
⭐ Important exam differentiation from UIP

2️⃣ Cryptogenic Organizing Pneumonia (COP)

(Formerly called bronchiolitis obliterans organizing pneumonia — BOOP)

📌 Definition

An interstitial lung disease characterized by intraalveolar plugs of loose organizing connective tissue.

🧠 Pathology

- Patchy airspace consolidation
- Subpleural or peribronchial distribution
- Intraalveolar fibroblastic plugs

- Interstitium relatively preserved

🩺 Clinical Features

- Cough
- Dyspnea
- Patchy consolidation on imaging

💊 Significance

- Some recover spontaneously
- Most respond well to oral steroids
- Much better prognosis than IPF

3️⃣ Autoimmune-Associated Pulmonary Fibrosis

Diffuse pulmonary fibrosis can complicate systemic autoimmune diseases such as:

- Systemic sclerosis

- Rheumatoid arthritis
- Systemic lupus erythematosus

🎯 Clinical Importance

✔ Must rule out before diagnosing IPF

✔ Treating underlying autoimmune disease may improve lung disease

✔ Better prognosis than idiopathic fibrosis

🏭 Pneumoconioses

📌 Definition

Originally: lung diseases caused by inhalation of mineral dusts

Now broadened to include:

- Organic particulates
- Inorganic particulates
- Some chemical fumes/vapors

Most common mineral pneumoconioses:

- Coal dust
- Silica
- Asbestos

🧬 Pathogenesis of Pneumoconiosis

🧪 Particle Size Matters

Particle Size	Fate
>10 μm	Trapped in upper airway
<0.5 μm	Exhaled

1–5 μm ⭐	Lodge in distal airways → most dangerous

🔥 Role of Alveolar Macrophages (Key Mechanism)

1. Particle inhalation
2. Phagocytosis by macrophages
3. Inflammasome activation
4. IL-1 release
5. Cytokine cascade
6. Fibroblast activation
7. Collagen deposition

→ Progressive fibrosis

🧠 Immunologic Amplification

Particles may:

- Drain to lymphatics
- Modify self-proteins

- Trigger immune response

This amplifies lung injury.

🏭 Major Mineral Pneumoconioses

1️⃣ Coal Workers' Pneumoconiosis (CWP)

- Coal dust relatively inert
- Requires heavy exposure
- Can progress to massive fibrosis

Smoking worsens disease.

2️⃣ Silicosis

Silica is highly fibrogenic.

- Strong inflammatory response
- Nodular fibrosis

- Increases TB risk
- Lower exposure needed compared to coal

3️⃣ Asbestosis

Most clinically significant.

- Interstitial fibrosis
- Subpleural plaques
- Increased risk of:
    - Lung carcinoma
    - Mesothelioma

⚠️ Risk extends to family members (via contaminated clothing).

Smoking + asbestos = synergistic increase in lung cancer risk.

🚬 Effect of Smoking

Smoking worsens all pneumoconioses.

Most dramatic interaction:

👉 Smoking + asbestos → markedly increased lung carcinoma risk.

🎓 High-Yield Comparison

Feature	IPF (UIP)	NSIP	COP	Pneumoconiosis
Cause	Unknown	Often autoimmune	Unknown	Dust exposure
Fibrosis pattern	Patchy + temporal heterogeneity	Uniform	Intraalveolar plugs	Nodular/interstitial
Steroid response	Poor	Good	Good	Variable

Prognosis	3–5 yrs	Better	Good	Depends on exposure

🧠 Revision Points

- ✔ NSIP = uniform fibrosis + better prognosis
- ✔ COP = intraalveolar plugs + steroid responsive
- ✔ Autoimmune diseases commonly cause ILD
- ✔ Pneumoconiosis = dust-induced fibrosis
- ✔ Macrophage + inflammasome activation central
- ✔ Particle size 1–5 μm most dangerous

🏭 Coal Workers' Pneumoconiosis (CWP)

CWP is a lung disease caused by inhalation of coal mine dust. While dust control has reduced new cases, prevalence remains significant among older miners, especially in the Appalachian region (USA).

📊 Spectrum of Coal-Induced Lung Disease

Coal exposure produces a wide range of pulmonary findings:

1️⃣ Anthracosis (Benign Carbon Deposition)

- Carbon pigment accumulation
- No significant cellular reaction
- No functional impairment
- Also seen in:
  - Urban dwellers
  - Smokers

2️⃣ Simple CWP

Characterized by:

- Coal macules
- Coal nodules

- Minimal to no pulmonary dysfunction

Less than 10% progress to PMF.

3️⃣ Complicated CWP (Progressive Massive Fibrosis – PMF)

PMF = Confluent pulmonary fibrosis (>2 cm nodules)

⚠ PMF is a general term and may occur in any pneumoconiosis.

🧬 Pathogenesis

Coal dust contains:

- Carbon (relatively inert)
- Silica
- Trace metals
- Inorganic minerals

Higher mineral contamination → higher risk of disease.

Dust particles (1–5 μm) → Ingested by macrophages → Cytokine release → Fibrosis

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🔬 MORPHOLOGY

🖤 Anthracosis

- Carbon-laden macrophages
- Accumulate along:
  - Pulmonary lymphatics
  - Pleural lymphatics
  - Lymph nodes
- No fibrosis

🟤 Simple CWP

Coal Macule (Hallmark Lesion)

- Dust-laden macrophages

- Delicate collagen network
- Upper lobes predominantly involved

Over time → Centrilobular emphysema may develop

⚫ Complicated CWP (PMF)

- Coalescence of nodules
- Large black scars
- 2 cm (can reach 10 cm)
- Dense collagen + pigment
- Progressive lung destruction

Once PMF develops → Progression continues even without further exposure.

🩺 Clinical Features

Simple CWP

- Usually benign

- Minimal functional impairment

PMF

- Progressive dyspnea
- Pulmonary hypertension
- Cor pulmonale

🧠 Important Exam Point

Unlike silica and asbestos:

❌ No increased lung carcinoma risk (after adjusting for smoking)

This is a key distinguishing feature.

🪨 Silicosis

📌 Definition

Silicosis is caused by inhalation of crystalline silica.

It is the most common chronic occupational lung disease worldwide.

👷 High-Risk Occupations

- Sandblasting
- Hard-rock mining
- Quarrying
- Stone cutting

🧬 Types of Silica

Crystalline forms (most toxic):

- Quartz (most common cause)
- Cristobalite
- Tridymite

Crystalline forms are highly fibrogenic.

🔥 Pathogenesis

Silica inhalation → Macrophage ingestion → Lysosomal damage → Inflammasome activation → Release of:

- IL-1
- TNF
- Free radicals
- Fibrogenic cytokines

→ Fibroblast activation → Collagen deposition → Nodular fibrosis

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🔬 MORPHOLOGY

Early Lesions

- Tiny nodules
- Upper lung zones
- Pale to black (if mixed with coal)

Microscopy (Classic Exam Feature)

Silicotic nodules show:

✔ Concentric layers of hyalinized collagen
✔ "Whorled" pattern ⭐
✔ Amorphous center

Under polarized light:

✔ Weakly birefringent silica particles

Advanced Disease

- Nodule coalescence
- Hard collagenous scars
- PMF development

- Honeycomb lung (late)

May involve:

- Hilar lymph nodes
- Pleura

🩺 Clinical Features

- Often asymptomatic early
- Detected on routine chest X-ray

Radiology:

- Fine nodularity
- Upper lobe predominance

Dyspnea appears late (after PMF).

🫀 Complications

1. Pulmonary hypertension
2. Cor pulmonale
3. Increased susceptibility to tuberculosis ⭐
4. Modestly increased lung cancer risk

🦠 Silicosis & Tuberculosis

Silica impairs macrophage killing of Mycobacterium. → Increased TB risk → Silicotuberculosis → Caseating center in nodules

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📊 CWP vs Silicosis Comparison

Feature	CWP	Silicosis
Dust	Coal (carbon)	Crystalline silica
Fibrogenicity	Low	High

Nodules	Macules + nodules	Whorled collagen nodules
TB risk	No	Increased ⭐
Lung cancer	No increase	Modest increase
PMF	Possible	Common in advanced disease
Upper lobe	Yes	Yes

🎓 Exam Pearls

✔ Coal macule = dust macrophages + delicate collagen

✔ PMF = nodules >2 cm

✔ Silicotic nodule = whorled hyalinized collagen

✔ Polarized light → birefringent silica

✔ Silicosis → ↑ TB risk

✔ CWP → no carcinoma increase

🧱 Asbestos-Related Diseases

Asbestos = fibrous crystalline hydrated silicates used in construction, insulation, shipbuilding.

Occupational exposure is associated with both fibrotic and malignant diseases.

📌 Major Asbestos-Related Pathologies

1. Asbestosis (interstitial fibrosis)
2. Pleural plaques
3. Pleural effusion
4. Lung carcinoma
5. Malignant mesothelioma (pleural/peritoneal)
6. Laryngeal carcinoma

⚠ Family members can also be affected due to fibers carried home on clothing.

🧬 Pathogenesis

Mechanism is similar to silica but with important oncogenic effects.

🔬 Stepwise Mechanism

Asbestos inhalation → Macrophage phagocytosis → Lysosomal damage → Inflammasome activation → Cytokine release (IL-1, TNF) → Fibroblast activation → Interstitial fibrosis

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🧨 Oncogenic Effects

Asbestos acts as:

- Tumor initiator
- Tumor promoter

Mechanisms include:

- Free radical generation
- Preferential localization near mesothelium

- Adsorption of carcinogens from tobacco smoke

🚬 Smoking + asbestos = strong synergy for lung carcinoma

❌ No synergistic effect for mesothelioma

🔬 MORPHOLOGY

🫁 Asbestosis (Parenchymal Disease)

Hallmark: Asbestos Bodies ⭐

- Golden-brown
- Fusiform or beaded rods
- Translucent center
- Iron-coated fibers
- Iron derived from ferritin

Formed when macrophages attempt to phagocytose fibers.

🧭 Distribution

Unlike CWP and silicosis (upper lobe predominant):

✔ Begins in lower lobes
✔ Subpleural distribution
✔ Progresses upward

This is a classic exam differentiator.

🧱 Fibrotic Changes

- Diffuse interstitial fibrosis
- Distorted architecture
- Enlarged air spaces
- Honeycomb lung (late)

🫀 Vascular Effects

- Pulmonary artery narrowing

- Pulmonary hypertension
- Cor pulmonale

🧱 Pleural Involvement

1️⃣ Pleural Plaques (Most Common Manifestation)

- Well-circumscribed dense collagen plaques
- Often calcified
- Located on:
  - Anterior parietal pleura
  - Posterolateral pleura
  - Dome of diaphragm

Usually asymptomatic.

Radiographically seen as calcified densities.

2️⃣ Pleural Effusion

May occur, sometimes recurrent.

3️⃣ Diffuse Pleural Fibrosis

Less common but can impair lung expansion.

🩺 Clinical Features of Asbestosis

- Latency: 10–20 years after exposure
- Progressive dyspnea
- Productive cough

May progress to:

- Cor pulmonale
- Congestive heart failure
- Death

Clinically indistinguishable from other chronic ILDs.

🎗️ Malignancy Risk

🫁 Lung Carcinoma

- Risk increased ~5-fold
- Smoking dramatically increases risk further
- Very poor prognosis

🧱 Malignant Mesothelioma

- Risk increased >1000-fold ⭐
- Rare tumor in general population
- Not increased by smoking
- Extremely poor prognosis

Common sites:

- Pleura (most common)
- Peritoneum

📊 Asbestosis vs Silicosis vs CWP

Feature	Asbestosis	Silicosis	CWP
Lobe involvement	Lower ⭐	Upper	Upper
Pleural plaques	Yes ⭐	No	No
TB risk	No	Yes ⭐	No
Lung cancer	Yes (↑ ↑ with smoking)	Modest ↑	No ↑
Mesothelioma	Yes ⭐	No	No
Asbestos bodies	Yes ⭐	No	No

💊 Drug- and Radiation-Induced Pulmonary Disease

💉 Drug-Induced Lung Injury

Certain drugs cause pneumonitis and fibrosis.

1️⃣ Bleomycin

- Direct toxic effect
- Pneumonitis
- Interstitial fibrosis

2️⃣ Amiodarone

- Causes pneumonitis
- Progressive fibrosis

Mechanism:

- Direct toxicity
- Inflammatory cell recruitment

☢️ Radiation Pneumonitis

Occurs after thoracic irradiation.

Acute Radiation Pneumonitis

- Occurs 1–6 months post therapy
- Fever
- Dyspnea (disproportionate)
- Pleural effusion
- Infiltrates in irradiated lung

May resolve with steroids or progress.

Chronic Radiation Pneumonitis

- Persistent fibrosis
- Reduced lung compliance
- Chronic respiratory impairment

🎓 Exam Pearls

✔ Lower lobe + subpleural = think asbestos

✔ Pleural plaques = most common asbestos finding

✔ Asbestos bodies = iron-coated fibers

✔ Smoking ↑ lung carcinoma risk but NOT mesothelioma

✔ Mesothelioma risk ↑ 1000-fold

✔ Silicosis → TB risk

✔ CWP → no cancer risk

🧠 Summary

Asbestos exposure causes lower-lobe interstitial fibrosis with asbestos bodies and pleural plaques, and markedly increases the risk of lung carcinoma and mesothelioma, especially in smokers.

🟣 Granulomatous Diseases

🌍 Sarcoidosis

📌 Definition

Sarcoidosis is a multisystem disease of unknown etiology characterized by:

✔ Noncaseating granulomas
✔ Involvement of multiple organs
✔ Most commonly affecting lungs and hilar lymph nodes

Because many other diseases can cause noncaseating granulomas, sarcoidosis is a diagnosis of exclusion.

🫁 Why It Is Important in Respiratory Pathology

Sarcoidosis commonly presents as:

- Restrictive lung disease
- Bilateral hilar lymphadenopathy
- Interstitial lung involvement

On chest X-ray, the classic finding is:

👉 Bilateral hilar lymphadenopathy (BHL)

🌍 Epidemiology

Sarcoidosis shows unique epidemiologic patterns:

📌 Age

- Most common in adults < 40 years

📌 Ethnicity

- High incidence in Danish and Swedish populations
- 2–3× more common in African Americans (USA)

📌 Smoking

⭐ Higher prevalence among nonsmokers
(Almost unique among pulmonary diseases)

🧬 Pathogenesis

Exact cause: Unknown

Strong evidence for:

👉 Disordered immune regulation
👉 Genetically predisposed individuals
👉 Environmental trigger (unknown antigen)

🧠 Immunologic Mechanism (Core Concept)

Sarcoidosis is a CD4+ T-cell–mediated disease.

🔬 Stepwise Immune Events

1️⃣ Unknown antigen exposure
2️⃣ Activation of CD4+ Th1 cells
3️⃣ Cytokine production
4️⃣ Macrophage activation
5️⃣ Granuloma formation

🧪 Key Immunologic Findings

🟣 In the Lung

✔ Accumulation of CD4+ Th1 cells
✔ Oligoclonal expansion of T cells
✔ Increased Th1 cytokines:

- IL-2 → T-cell proliferation
- IFN-γ → macrophage activation
- TNF → granuloma formation
- IL-8 & MIP-1α → recruitment of inflammatory cells

🔵 In the Blood

Interestingly:

✔ Low circulating CD4+ T cells
✔ Anergy to skin tests (e.g., Candida, PPD)

This paradox = immune cells concentrated at disease site.

🧱 Granuloma Characteristics

Granulomas are:

✔ Noncaseating
✔ Well-formed
✔ Tight clusters of epithelioid macrophages
✔ Multinucleated giant cells

Unlike tuberculosis:

❌ No caseous necrosis

🔁 Recurrence After Transplant

After lung transplantation:

- Recurrence occurs in ~1/3 patients
- Suggests systemic immune dysregulation

🧪 Differential Diagnosis of Noncaseating Granulomas

Must exclude:

- Mycobacterial infections
- Fungal infections
- Berylliosis

Hence: Sarcoidosis = diagnosis of exclusion.

👁️ Extra-Pulmonary Manifestations

Occurs in ~25% each:

👁️ Eye

- Uveitis
- Visual disturbances

🩺 Skin

- Erythema nodosum
- Lupus pernio

📊 Summary Table

Feature	Sarcoidosis
Etiology	Unknown
Immune mechanism	CD4+ Th1-mediated
Granulomas	Noncaseating
Common CXR finding	Bilateral hilar lymphadenopathy
Age group	< 40 years
Smoking	More common in nonsmokers
Skin test response	Anergy

🎓 Exam Pearls

✔ CD4+ Th1 driven disease
✔ Noncaseating granulomas
✔ Bilateral hilar lymphadenopathy
✔ Anergy to PPD
✔ Recurs after transplant
✔ Diagnosis of exclusion

🧠 Summary

Sarcoidosis is a CD4+ T cell–mediated multisystem granulomatous disease of unknown cause, classically presenting with bilateral hilar lymphadenopathy and noncaseating granulomas in young nonsmokers.

🔬 MORPHOLOGY

🧱 Cardinal Lesion: Noncaseating Epithelioid Granuloma

The hallmark of sarcoidosis is the nonnecrotizing (noncaseating) epithelioid granuloma.

Structure of the Granuloma

- Central collection of epithelioid macrophages
- Multinucleated giant cells (macrophage fusion)
- Outer rim rich in $CD4^+$ T cells
- Peripheral fibroblasts (early stage)

With time:
→ Fibroblast proliferation → Collagen deposition → Hyalinized scar replaces granuloma

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🔎 Special Microscopic Findings (Not Diagnostic)

Sometimes seen inside giant cells:

☐ Schaumann bodies

- Laminated concretions
- Composed of calcium + proteins

2️⃣ Asteroid bodies

- Stellate (star-shaped) inclusions
- Found within giant cells

⚠ Not specific to sarcoidosis.

Rarely → Small foci of central necrosis may occur (especially nodular form)

🫁 Pulmonary Involvement (90% of Patients)

Granulomas predominantly involve:

- Interstitium (not airspaces)
- Around bronchioles
- Around pulmonary venules
- Pleura

This pattern is called:

👉 Lymphangitic distribution

🧪 Bronchoalveolar Lavage

- Increased $CD4^+$ T cells
- Elevated CD4/CD8 ratio (classic finding)

🍯 Advanced Disease

In 5–15%:

→ Diffuse interstitial fibrosis → Honeycomb lung → Chronic respiratory impairment

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🫀 Lymph Node Involvement

Occurs in 75–90% of patients.

Features:

- Bilateral hilar and paratracheal lymphadenopathy
- Painless
- Firm, rubbery
- Nonmatted

- No necrosis

⚠ Key difference from tuberculosis (which shows caseation and matted nodes)

🌺 Skin Involvement (~25%)

1️⃣ Erythema Nodosum (Acute Sarcoidosis Hallmark)

- Bilateral red, tender nodules
- Anterior legs
- Panniculitis
- Granulomas uncommon in these lesions

Associated with good prognosis.

2️⃣ Subcutaneous Sarcoid Nodules

- Painless
- Contain classic noncaseating granulomas

👁️ Ocular Involvement (20–50%)

Common manifestations:

- Iritis
- Iridocyclitis
- Choroiditis
- Retinitis
- Optic nerve involvement

Complications:

- Corneal opacities
- Glaucoma
- Visual loss

Often associated with lacrimal gland involvement:

→ Reduced tears → Sicca syndrome

🦠 Salivary Gland Involvement

- Parotid enlargement (≤10%)
- Xerostomia

Combined uveitis + parotitis:

👉 Mikulicz syndrome

🩸 Other Organ Involvement

🟤 Spleen

- Granulomas in ~75%
- Splenomegaly in ~10%

🟤 Liver

- Portal triad granulomas
- Hepatomegaly in ~30%

🟤 Bone marrow

- Up to 40% involvement
- Rarely severe manifestations

🩺 Clinical Features

📌 Asymptomatic Cases

Many patients:

- Incidentally detected
- Bilateral hilar lymphadenopathy on X-ray

📌 Symptomatic Cases

Gradual onset of:

Respiratory

- Dyspnea
- Dry cough
- Substernal discomfort

Constitutional

- Fever
- Fatigue
- Weight loss
- Night sweats

🧪 Laboratory Findings

Hypercalcemia & Hypercalciuria ⭐

Cause:

Macrophages in granulomas produce active vitamin D (calcitriol).

Important exam point.

🗒️ Diagnosis

No single definitive test.

Diagnosis requires:

1️⃣ Compatible clinical and radiologic findings

2️⃣ Noncaseating granulomas on biopsy

3️⃣ Exclusion of other causes (especially tuberculosis)

⚠ TB must always be ruled out.

📉 Clinical Course & Prognosis

Sarcoidosis has an unpredictable course.

Outcomes:

✔ 65–70% recover completely

✔ 20% develop permanent lung/eye damage

✔ 10–15% die from:

- Progressive pulmonary fibrosis
- Cor pulmonale

Remissions may be:

- Spontaneous

- Steroid-induced

  Often permanent

📊 Comparison: Sarcoidosis vs Tuberculosis

Feature	Sarcoidosis	Tuberculosis
Granuloma	Noncaseating	Caseating
Lymph nodes	Nonmatted	Matted
Necrosis	Absent	Present
$CD4^+$ T cells	Increased in lung	Variable
PPD test	Anergy	Positive

🎓 Viva Pearls

- ✔ Noncaseating granulomas
- ✔ $CD4^+$ Th1 mediated
- ✔ Bilateral hilar lymphadenopathy
- ✔ Lymphangitic interstitial distribution
- ✔ Elevated CD4/CD8 ratio
- ✔ Hypercalcemia (vitamin D production)
- ✔ Erythema nodosum = good prognosis
- ✔ Diagnosis of exclusion

🧠 Summary

Sarcoidosis is a multisystem $CD4^+$ T-cell–mediated granulomatous disease characterized by noncaseating granulomas with lymphangitic pulmonary distribution, bilateral hilar lymphadenopathy, and potential progression to interstitial fibrosis.

🌾 Hypersensitivity Pneumonitis (HP)

(Also called Allergic Alveolitis)

📌 Definition

Hypersensitivity pneumonitis is an immunologically mediated inflammatory lung disease that primarily affects the alveoli.

Because alveoli are involved →
It presents as a restrictive lung disease.

🌍 Etiology

Caused by inhalation of organic antigens.

Common sources:

- Moldy hay (Farmer's lung)
- Bird droppings (Bird fancier's lung)
- Contaminated humidifiers
- Fungi, thermophilic actinomycetes

Unlike sarcoidosis, the inciting antigen is usually identifiable.

🧬 Pathogenesis

HP is an immune-mediated disease involving both:

- Type III hypersensitivity (immune complex-mediated)
- Type IV hypersensitivity (T-cell mediated)

🧪 Immunologic Evidence

✔ Increased $CD4^+$ and $CD8^+$ T cells in bronchoalveolar lavage
✔ Serum antibodies to offending antigen
✔ Complement + immunoglobulin deposits in vessel walls
✔ Noncaseating granulomas (≈2/3 patients)

🔬 MORPHOLOGY

📌 Core Histologic Features

1️⃣ Patchy interstitial mononuclear infiltrates

- Especially around bronchioles
- Lymphocytes predominate
- Plasma cells + epithelioid macrophages present

2️⃣ Poorly formed, noncohesive noncaseating granulomas

- Peribronchiolar location
- No necrosis

3️⃣ Acute cases:

- Neutrophils may be present

4️⃣ Chronic advanced cases:

- Upper-lobe-predominant interstitial fibrosis
- May resemble UIP pattern

🫁 Physiologic Effects

Because alveoli are primarily involved:

- ↓ Diffusion capacity (↓ DLCO)
- ↓ Lung compliance
- ↓ Total lung capacity
- Restrictive pattern on PFTs

🩺 Clinical Features

❗ Acute Form

Occurs 4–8 hours after antigen exposure.

Symptoms:

- Fever
- Cough

- Dyspnea
- Malaise
- Constitutional symptoms

Diagnosis is often obvious due to clear temporal relation.

If antigen removed → complete resolution within days.

2️⃣ Chronic Form

Occurs with persistent exposure.

- Insidious cough
- Progressive dyspnea
- Weight loss
- Malaise

If exposure continues → Irreversible interstitial fibrosis

📊 Hypersensitivity Pneumonitis vs Sarcoidosis

Feature	HP	Sarcoidosis
Cause	Known antigen	Unknown
Granulomas	Poorly formed	Well-formed
Distribution	Peribronchiolar	Lymphangitic
CD4/CD8 ratio	Often normal or ↓	Increased
Reversibility	Yes (early)	Variable

🟠 Pulmonary Eosinophilia

📌 Definition

Group of disorders characterized by:

- Pulmonary infiltrates

- Eosinophil-rich inflammation

🧬 Causes

- Helminth infections
- Drug reactions (e.g., Allopurinol)
- Vasculitis
- Often idiopathic

📉 Course

- Variable
- Chronic forms may lead to fibrosis

🚬 Smoking-Related Interstitial Diseases

Smoking is not only associated with COPD but also restrictive ILDs.

🟤 Desquamative Interstitial Pneumonia (DIP)

🔬 Histology (Key Feature)

- Numerous macrophages in alveolar spaces
- Dusty-brown pigment ("smoker's macrophages")
- Mild septal thickening
- Mild interstitial fibrosis

🫁 Physiology

- Mild restrictive pattern
- Usually good prognosis

💊 Management

- Smoking cessation
- Steroids (good response)

Some patients may still progress.

🟤 Respiratory Bronchiolitis

🔬 Histology

- Pigmented macrophages
- Bronchiolocentric distribution
- Mild peribronchiolar fibrosis

Less diffuse than DIP.

🩺 Clinical Features

- Gradual dyspnea
- Dry cough
- Improves with smoking cessation

📊 DIP vs Respiratory Bronchiolitis

Feature	DIP	Respiratory Bronchiolitis
Distribution	Diffuse alveoli	Bronchiolocentric
Macrophages	Numerous	Localized
Fibrosis	Mild	Mild
Smoking related	Yes	Yes
Prognosis	Good	Good

🎓 Exam Points

- ✔ HP = immune reaction to inhaled antigen
- ✔ Poorly formed granulomas
- ✔ Acute onset 4–8 hrs after exposure
- ✔ Reversible if antigen removed

✔ Chronic exposure → fibrosis

✔ DIP = smoker's macrophages in alveoli

✔ Respiratory bronchiolitis = bronchiolocentric macrophages

🧠 Summary

Hypersensitivity pneumonitis is an immune-mediated alveolar disease caused by inhaled organic antigens, characterized by poorly formed noncaseating granulomas and potentially reversible restrictive lung disease.

-> The End <-