Doctor.021

no. 4

RS PATHOLOGY

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CHRONIC INTERSTITIAL (RESTRICTIVE, INFILTRATIVE) LUNG DISEASES, PART 1

Restrictive lung diseases:

It's hard to get the air IN (it is hard to fill the lungs).
It's hard to Inhale.
lung compliance is Decreased (stiff lungs).
The stretchability of the lung is decreased like new rubber that is difficult to expand or stretch.
Lung volume and capacity are Decreased.

- More than 100 diseases under the umbrella of chronic restrictive or interstitial lung diseases

- Total lung capacity: (TLC) is the volume of air in the lungs upon the maximum effort of inspiration.
- lung compliance: is a measure of the lung's ability to stretch or expand.

CHRONIC INTERSTITIAL LUNG DISEASES

Why **interstitial**?
Because they are characterized by the presence of infiltration either cellular or acellular within the interstitium.

• Called RESTRICTIVE or INFILTRATIVE
Why **restrictive**?
Because the lungs are restricted from filling, meaning that the lungs have limitation so it can't fill.
Why **infiltrative**?
Because they are characterized by the presence of cellular and acellular infiltration mainly in the interstitium
• are a heterogeneous group of disorders characterized predominantly by inflammation and fibrosis of the lung interstitium (+/- intra-alveolar) associated with pulmonary function studies indicative of restrictive lung disease. (reductions in lung volume, and lung compliance).

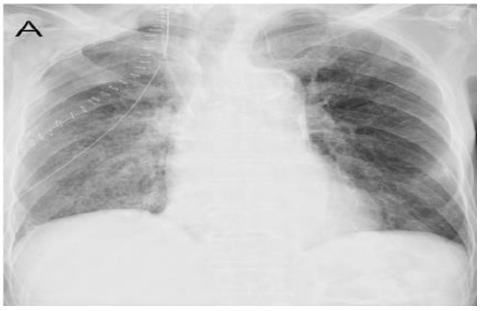
• Many entities in this group are of unknown cause and pathogenesis. (Idiopathic or cryptogenic)
* Cryptogenic a disease uncertain origin

• Frequent overlap between these entities

• Clinically: dyspnea (increased effort to breathe), tachypnea (increased respiratory rate), end-inspiratory crackles, and eventual cyanosis.
Dyspnea is the first and the most common symptom.
end-inspiratory crackles: during inflation, we heard crackles sound that comes from the opening of the closed airways.
The patient may have cyanosis because it's difficult to get the air in so there is a problem with oxygenation and CO2 retention. Eventually, the patient will have accumulation of CO2 and bluish discoloration of the mucous membrane (cyanosis).

• Chest radiographs: bilateral lesions → small nodules, irregular lines, or ground-glass shadows.

Ground-glass shadow: it is like you're looking to the lungs from broken glass, so they appear hazy.



EXTRA PIC FROM GOOGLE FOR ground-glass shadow →

Remember: in chronic interstitial lung diseases, it's a bilateral change.

• Accumulation of cellular and acellular component within the interstitium mainly causes damage to the alveolar epithelium and interstitial vasculature that responsible for gas exchange. This affects the diffusion and gas exchange within the membranes and results in **abnormal ventilation–perfusion ratio → hypoxia.**

Hypoxia → leads to vasoconstriction to reroute the blood from the areas of less oxygenation to the areas of higher oxygenation

But if it progresses to Chronic hypoxia this will be associated with vasoconstriction and structural change of the blood vessel's wall (smooth muscles proliferation and thickening of the wall) and this will lead to pulmonary hypertension

So, the right side of the heart will bump against resistance → right side heart failure and pulmonary failure.

• With progression → pulmonary hypertension → respiratory failure and cor pulmonale

• categorized based on **clinical features and histology** into 4 main categories in the table below:

Table 15.5 Major Categories of Chronic Interstitial Lung Disease

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Connective tissue disease–associated
Pneumoconiosis
Drug reactions
Radiation pneumonitis
Granulomatous
Sarcoidosis
Hypersensitivity pneumonitis
Eosinophilic
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis–associated interstitial lung disease
Other
Langerhans cell histiocytosis
Pulmonary alveolar proteinosis
Lymphoid interstitial pneumonia

asic pa

• the entities can be distinguished in their early stages, but advanced forms are hard to differentiate

• **When advanced all result in:**

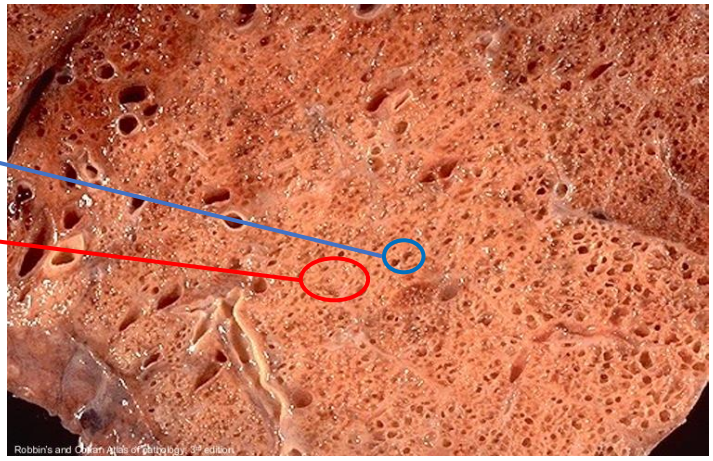
1- diffuse scarring (diffuse fibrosis on both sides) and gross destruction of the lung, referred to as **end-stage or "honeycomb" lung**.

• this leads to hypoxia →secondary pulmonary hypertension → cor pulmonale.

• At this stage, the etiology of the underlying diseases may be difficult to determine

HONEYCOMB LUNG

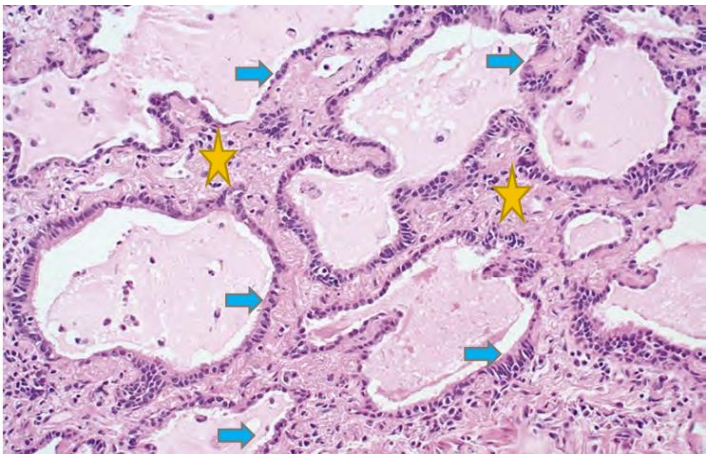
Macroscopically:
- loss of alveolar spaces and residual irregular dilated spaces remain
- Dense and thick bands fibrous CT between them



Extensive pulmonary interstitial fibrosis

- Blue arrows → the lining of the dilated spaces "Metaplastic bronchiolar epithelium" (no type 1 or type 2 pneumocytes)

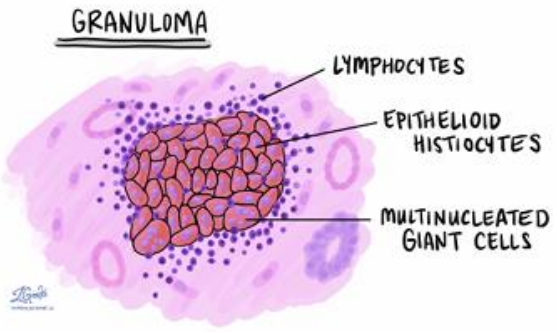
-Yellow stars →thickening of the wall by deposition of dense fibrous CT
So, this is what we call: End stage lung.
In this stage, you cannot distinguish the primary etiology.



GRANULOMATOUS DISEASES

Interstitial lung diseases that associated with granuloma formation.

Granuloma: type of chronic inflammation made of activated macrophages (epithelioid histocytes) that fused together to form multinucleated giant cells and they are usually cuffed (surrounded) by other inflammatory cells like lymphocytes and plasma cells.



Under the umbrella of granulomatous diseases:
1) **Sarcoidosis**
2) Hypersensitivity pneumonitis

SARCOIDOSIS

Before you start watch this short video for further understanding
https://youtu.be/9p3UVhk3TWU?si=Juk0tj2svk8KiNV8

• Systemic **granulomatous** disease of **unknown etiology**

Systemic: more than one organ is going to be involved, (can affect many organs and any organ of the body)

• characterized by **noncaseating granulomas** in many tissues and organs.

Noncaseating granuloma: granuloma without central necrosis.

Not specific for sarcoidosis, it can be seen in bacterial, fungal, TB infections.

• So, Diagnosis of exclusion.

So, if we found a noncaseating granuloma +affecting multiple organs and tissues, this going to be suggestive of sarcoidosis, but the defiant diagnosis will be after excluding all other possible causes that can cause the noncaseating granuloma, because it is not specific for sarcoidosis.

• Clinically

can present as an acute or chronic illness or restrictive lung disease.

ETIOLOGY AND PATHOGENESIS

• the etiology is **unknown**.

• research evidences suggest that it's a Disordered immune regulation in **genetically predisposed** persons exposed to certain environmental agents.

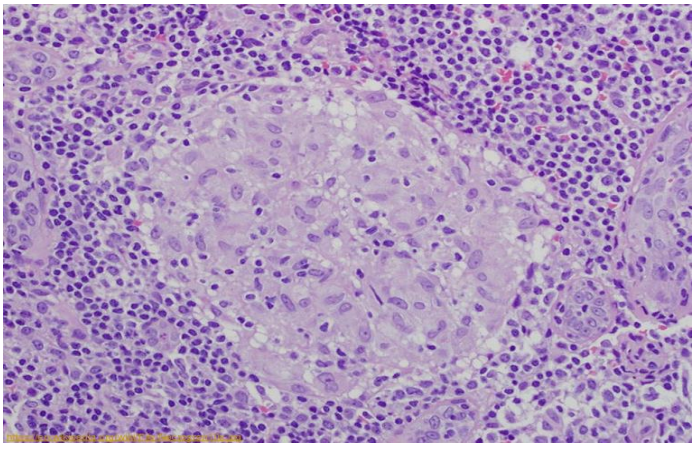
• Cell-mediated response to an unidentified antigen, driven by CD4+ helper T cells.

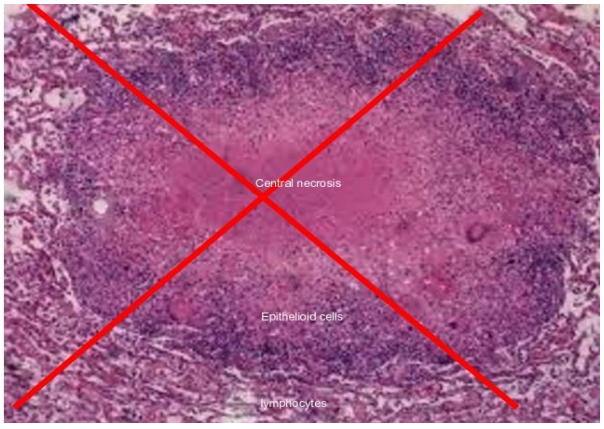
Morphology

- Noncaseating epithelioid granuloma:

❑ discrete (sharply-defined, well-circumscribed), compact collection of epithelioid cells rimmed by an outer zone rich in CD4+ T cells with intermixed multinucleate giant cells.

Noncaseating granuloma:
- Pale center: there is a collection of activated macrophages (have open chromatin, vesicular nucleus, prominent nuclei and indistinct cell order)
- Sharply defined.
- In the periphery, we have lymphocytes and other inflammatory cells.
- It is **not** diagnostic for sarcoidosis.





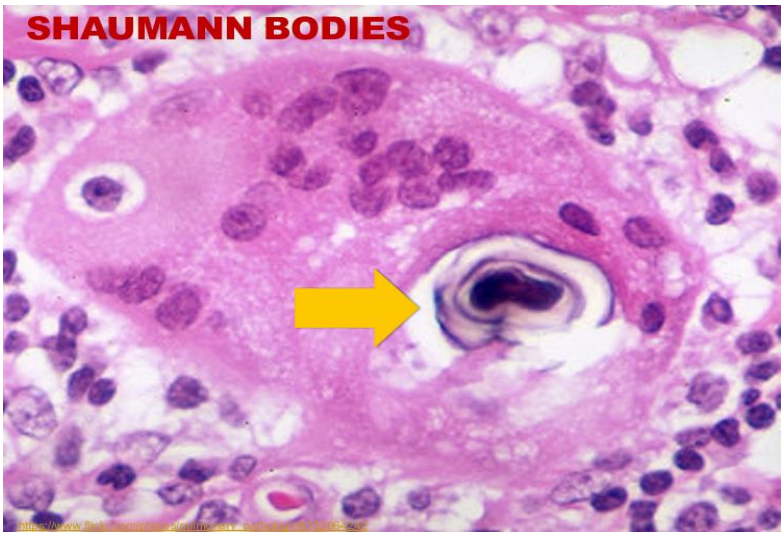
→ Caseation necrosis typical of tuberculosis is **ABSENT**.

- Overtime, granulomas replaced by hyalinized scars.
- Sarcoidosis granuloma may show two types of bodies that are **not** needed for diagnosis and are **not** characteristic.
Meaning that their presence is **not** required for diagnosis of sarcoidosis and they are **not** specific, so they **can** be found in other types of granulomas.

❑ In the granulomas:

1- Shaumann bodies:

✓ laminated (layer by layer, onion pattern) concretions composed of calcium and proteins seen in activated macrophages or multinucleated giant cells.



2-Asteroid bodies:

- stellate or star shaped inclusions within giant cells.

The presence of both bodies is not required for diagnosis of sarcoidosis, and they may also occur in granulomas of other origins.

MOST COMMONLY INVOLVES:

- Lungs
- lymph nodes
- Skin
- eye and lacrimal glands
- Spleen, Liver, BM

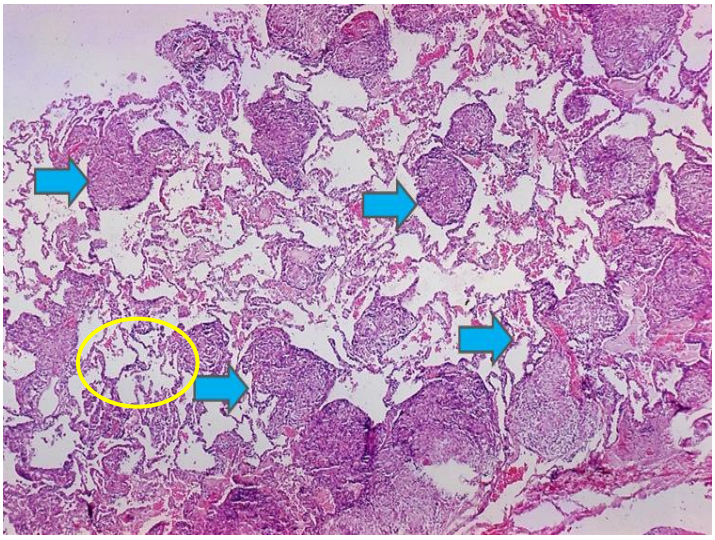
MORPHOLOGY, LUNGS:

- 90% of patients.
- Granulomas involve the **interstitium +/- alveolar lesions and pleural involvement**
- **Lesions are common along the lymphatics, around bronchi and blood vessels**
- high frequency of granulomas in **the bronchial submucosa**
- The BAL fluid contains abundant CD4+ T cells.

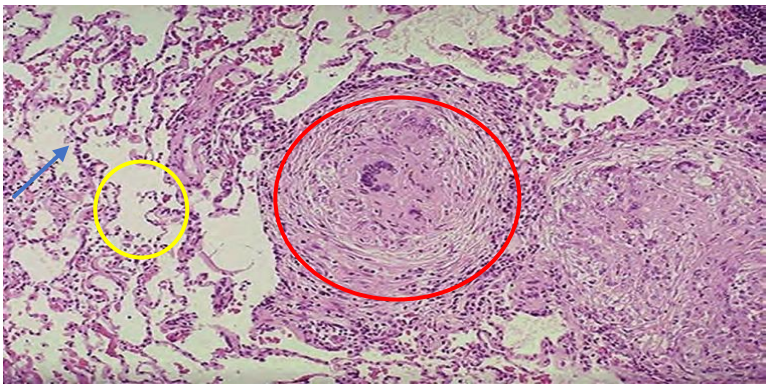
Bronchoalveolar lavage (BAL) is a diagnostic procedure used usually to diagnose the LRTD or lung diseases mainly. You interduce fluid in the mouth or the nose to part of the lungs and then you are going to collect the fluid and send it to the pathology lab to see the dominant cell type in it.

Please watch this short video to further understanding:
https://youtu.be/EAmsdmrZWig?si=TNmJJalaMLRjlw2R

• strong tendency for lesions to heal in the lungs → varying stages of fibrosis and hyalinization are often found.
• In 5-15% of cases may progress to end stage lung → honeycomb lung (we cannot distinguish the primary etiology in this stage).

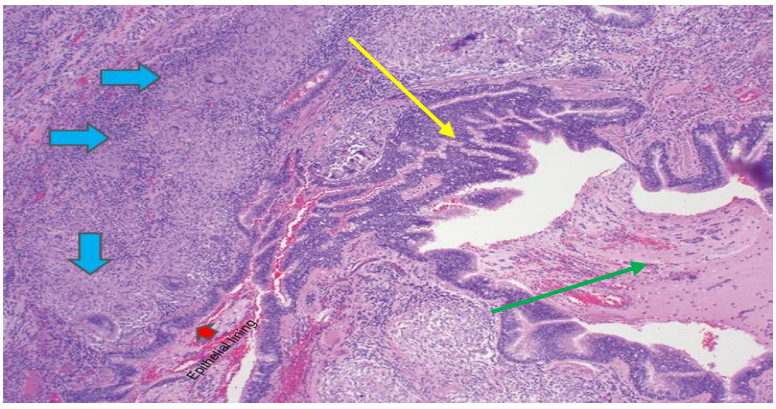


about this histological section:
- Yellow circle →patent alveolar spaces
- Normal wall thickness.
- Blue arrows → Pink lesions → well-defined granulomas.
There are lymphocytes around them.



* This is a higher power of the previous histological section:
Yellow circle: alveolar spaces patent full of air
Blue arrow: walls of normal thickness
Red circle: the wall expanded with well-defined circumscribe granuloma and multinucleated giant cells in the center

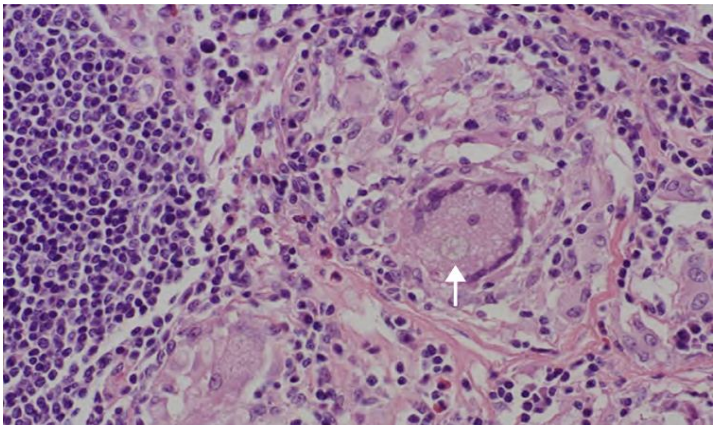
Also, you can see granuloma in interalveolar space, around the vessels, in the pleura and in bronchial submucosa
Yellow arrow →mucosa lining one of the bronchi
Green arrow → mucous secretions within the lumen
Blue arrows → area of noncaseating granuloma within submucosa (pale area)



MORPHOLOGY, LYMPH NODES:

• in almost all cases, any node can be affected.
• Particularly the hilar and mediastinal nodes
• The nodes:
• Enlarged painless.
• firm, rubbery texture.
• Discrete "nonmatted" (not fused with each other that means adjacent nodes can be separated), nonadherent to adjacent structures and do not ulcerate "unlike TB"
TB: necrosis within the lymph node, fused with each other, adherent to adjacent structures and may develop ulceration
+/- sometimes calcified

White arrow → asteroid body within the giant cell



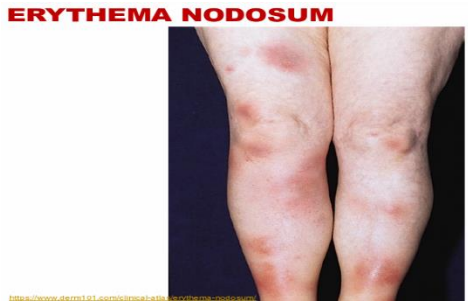
MORPHOLOGY, SKIN:

• 25% of patients.

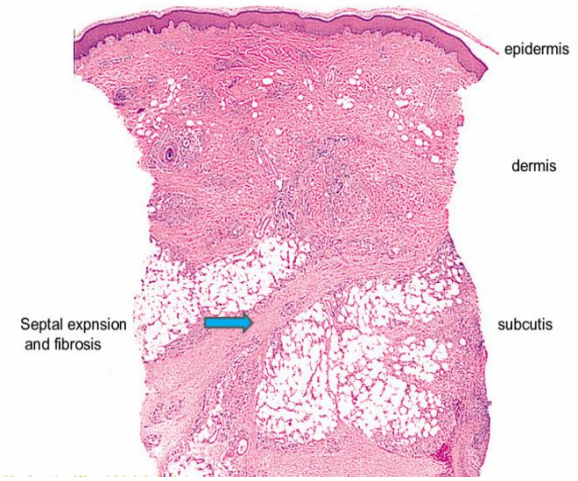
1) Erythema nodosum:

Erythema: redness, nodosum: nodules

• **Hallmark of acute sarcoidosis but not specific for sarcoidosis.**
• Raised, red, tender **(painful)** nodules on the anterior aspects of legs.
- The lesions disappear after 24 hours if the patient takes steroids.
• Sarcoidal granulomas are uncommon in EN.



Microscopically: Septal panniculitis can be seen
Panniculitis: inflammation of the fat in **superficial subcutis layer**
- Blue arrow → expansion and **widening** of the fibrous septa between the fat lobules. This expansion is due to fibrosis and chronic inflammatory infiltration by lymphocytes, histocytes and other inflammatory cells



2) Subcutaneous nodules:

• discrete painless.
• abundant noncaseating granulomas (seen in subcutaneous nodules but **not** in erythema nodosum).

3) Others: erythematous plaques; or flat lesions:

These lesions are not specific because they can be seen in lupus.

MORPHOLOGY, EYE AND LACRIMAL GLANDS:

• 20-50% of cases.

1) UVEITITS (MOST COMMON): inflammation of any part of the uveal tract
Uveal tract = iris, ciliary body and choroid.
• iritis or iridocyclitis, unilateral or bilateral.
• posterior uveal tract disease (choroiditis)

2) Corneal opacities and the involvement of the optic nerve, will lead to **glaucoma, and even total loss of vision.**

3) SICCA SYNDROME: Inflammation in the lacrimal glands, with suppression of lacrimation.

• < 10% of patients; Unilateral or bilateral parotitis with painful enlargement of the parotid glands.
• Xerostomia (dry mouth) due to inflammation affecting the salivary glands.
• **Mikulicz syndrome:** Combined uveoparotid involvement. (involvement of both the uveal tract and the parotid gland).

MORPHOLOGY, SPLEEN, LIVER, BM:

• Spleen:
  - In ¾ of cases spleen contains granulomas.
  - In 10% only it becomes enlarged. (splenomegaly).

• Liver:
  - Granulomas in portal triads
  - 1/3 hepatomegaly or abnormal liver function.

• Bone marrow:
  - 40% of patients.

• Hypercalcemia and hypercalciuria.
  - not related to bone destruction
  - caused by increased calcium absorption secondary to production of active vitamin D by the activated macrophages that form the granulomas.
  - activated macrophages activate 1- alpha hydroxylase, which activates vit D and this leads to increase absorption of calcium from the intestine and resorption of calcium from distal convoluted tubules in the kidney.
  - Those patients are in risk of developing calcium kidney stones.

CLINICAL FEATURES

• **Mostly, entirely asymptomatic.**
• Symptomatic in others:
  - 2/3 → gradual respiratory symptoms (shortness of breath **(MOST COMMOM)**, dry cough, or chest discomfort) or Constitutional signs and symptoms (fever, fatigue, weight loss, anorexia, night sweats).
  - **Based on the organ involvement:** peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly, or hepatomegaly.

DIAGNOSIS

• A definitive diagnostic test for sarcoidosis does **not** exist
• Noncaseating granulomas is suggestive of sarcoidosis, but exclusion of other causes is a must.

• Diagnosis:
  - ✓ Clinical findings
  - ✓ Radiologic findings
    Chest x-ray → find a bilateral hilar lymphadenopathy.
    CT scan → find reticular nodular infiltration in both lungs.
    → This patient has restrictive pattern so you have to find restrictive lung disease.
  - ✓ Histologic findings: Identification of noncaseating granulomas in involved tissues.
  - ✓ Exclusion of other disorders mainly infections and TB with similar presentations, radiology or histologic findings.
    - In particular, tuberculosis must be excluded.
    - TB most commonly causes caseating granuloma but it can cause noncaseating granuloma too.
    - Sarcoidosis **cannot** cause caseating granuloma.

COARSE:

• Unpredictable course.
• Progressive chronicity.
• Periods of activity interspersed with remissions.
• Remissions may be spontaneous or by steroid therapy.

OUTCOME:

• 65% -70% → recover with minimal or no residual manifestations.
• 20% → permanent lung dysfunction or visual impairment.
• 10% to 15% → progressive pulmonary fibrosis and cor pulmonale.

GRANULOMATOUS DISEASES

• Sarcoidosis.
• **Hypersensitivity pneumonitis.**

HYPERSENSITIVITY PNEUMONITIS

• a spectrum of immunologically mediated, predominantly interstitial lung disorders caused by intense, prolonged exposure to inhaled organic antigens (Often **occupational**) → etiology is **known.**
- First time exposure → activation of immune system (T-calls, B cells and plasma cells) and formation of antibodies.
- After the re-exposure to the same antigen → antigen-antibody immune complex formation → so, it almost a type 3 of hypersensitivity reaction.
- Pneumonitis because the inflammation affects the lungs.

• Called **allergic alveolitis:**
  - Primarily affects the alveoli.
  - Related to the inhalation of organic dust containing antigens made up of the spores of thermophilic bacteria, fungi, animal proteins, or bacterial products.

• Numerous syndromes are described depending on the occupation or exposure of the individual, examples:

- **Farmer's lung** → exposure to dusts generated from humid, warm, newly harvested hay that permits the rapid proliferation of the spores and mold.
- **Humidifier or air-conditioner lung:** caused by thermophilic bacteria in heated water reservoirs.
- **Hot tub lung:** nontuberculous Mycobacterium.
- **Pigeon breeder's lung:** proteins from serum or feathers.

• >300 allerogen → development of hypersensitivity pneumonitis most of which are related to occupational exposure.

Table 13.4 Sources of Antigens Causing Hypersensitivity Pneumonitis

Source of Antigen	Types of Exposures
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Birds	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto painters), zinc, dyes

From Lacasse Y, Girard M, Cormier Y: Recent advances in hypersensitivity pneumonitis, Chest 142:208, 2012.

IMMUNOLOGIC BASIS

• BAL specimens demonstrate increased numbers of both CD4+ and CD8+ lymphocytes **but cytotoxic T-cells (CD8+) are much more common.**
• specific antibodies against the offending antigen in serum. (antigen- antibody immune complex)
• Complement and immunoglobulins within vessel walls by (immunofluorescence) IF.
• 2/3 of patients, Noncaseating granulomas in the lungs by activation a cell-mediated immune reaction and type 4 hypersensitivity reaction.

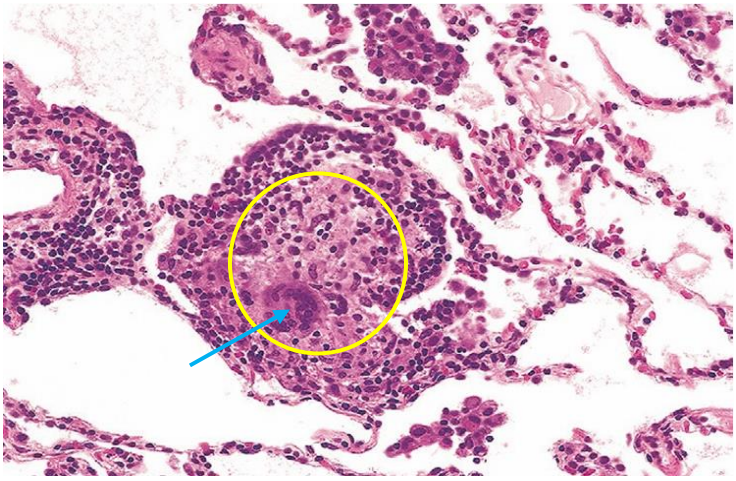
MORPHOLOGY

• Histologic changes are centered on **bronchioles**, including:

- "**Loose**," (**not** well-defined, not well-circumscribe) poorly formed granulomas, without necrosis (noncaseating) in > 2/3 of cases, usually in a peribronchiolar location.
- interstitial pneumonitis: lymphocytes, plasma cells, and macrophages (eosinophils are rare) in the pulmonary interstitium.
- interstitial fibrosis with fibroblastic foci, honeycombing, and obliterative bronchiolitis (in late stages).

• > 50% intra-alveolar infiltrate is seen.
• In advanced chronic cases, **bilateral, upper - lobe - dominant** interstitial fibrosis (Usual interstitium pattern UIP of fibrosis) occurs.

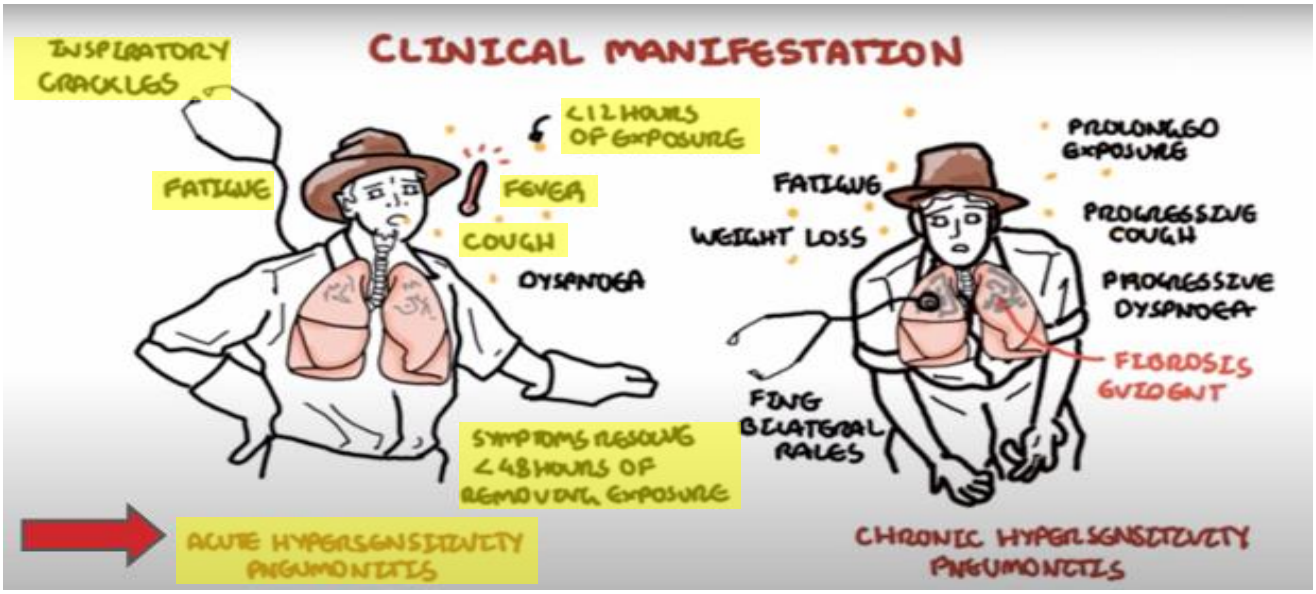
Expanded alveolar septum with a loosely formed granuloma (yellow circle) that is not well-defined
Blue arrow → multinucleated giant cell
- There are patent alveolar spaces.
- Normal thickness of walls.
- That's not enough for diagnosis.



CLINICAL FEATURES

May be come with:
1) **Acute reaction** (called Acute Hypersensitivity Pneumonitis): fever, cough, dyspnea, and constitutional signs and symptoms arising **4 to 8** hrs after exposure to large amount of allergens in a short period of time (influenza like).
• If antigenic exposure is terminated after acute attacks of the disease, **complete resolution (no fibrosis)** of pulmonary symptoms occurs within days (mainly in 48 hours).
• With the acute form, the **diagnosis** is obvious because of the **temporal relationship** of symptom onset and exposure to the antigen. (easy diagnosis).
- There is **No** relationship between this acute reaction and chronic interstitial lung disease.

• Failure to remove the agent from the environment results in Irreversible chronic interstitial pulmonary disease.
- Exposure to these antigens (in low doses +for a long period of time) during the patients' job result in a chronic hypersensitivity pneumonitis
2) **Chronic disease**: characterized by insidious onset of progressive cough, dyspnea, malaise, fatigue and weight loss.
- These **progressive** symptoms are due to fibrosis and inflammation of the lungs.
- Symptoms become worse over time
• Restrictive pattern on PFT.
• Dx:
• clinical, radiological (high resolution CT: ground glass opacity) and pathological examination.



Clinical Case

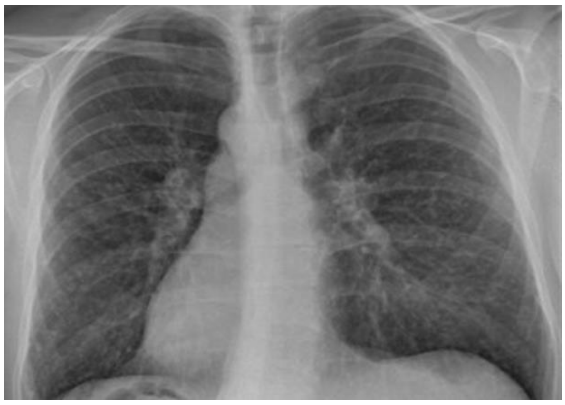
A 61-year-old lady noted increasing dyspnea and a nonproductive cough for 5 months. On examination, her temperature is 37.7° C. A CXR shows prominent hilar lymphadenopathy with reticulonodular infiltrates bilaterally. A transbronchial biopsy showed interstitial fibrosis and small, discrete noncaseating granulomas. One granuloma contains an asteroid body in a giant cell. The medical history indicates that she smoked cigarettes for 10 years, but stopped 5 years ago. Which of the following is the most likely cause of her illness?

A) T cell-mediated response to unknown antigen
B) Deposition of immune complexes
C) Infection with atypical mycobacteria
D) Smoke inhalation with loss of bronchioles

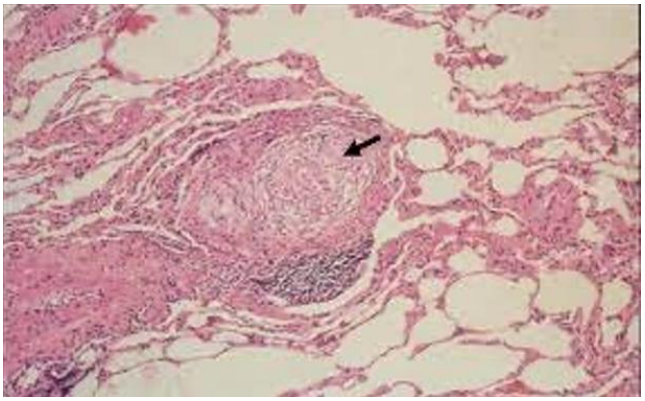
THE ANSWER IS: (A).

Clues:
1- Increasing dyspnea so she has chronicity
2- Non-productive cough and almost normal temperature → no infection
3- Multiorgan involvement (lungs and lymph nodes)
4- Interstitial fibrosis and noncaseating granuloma
5- The patient now is not a smoker
6- There is no history for exposure to a known antigen → no deposition of immune complexes

- Bilateral hiler lymphadenopathy
- Increase the opicities in both sides
- Reticulonodular infiltration



- **Black arrow** →discrete well-defined granuloma
- There is some lymphocytes
- The alveolar spaces are patent



	sarcoidosis	Hypersensitivity pneumonitis
Workplace related	no	yes
Noncaseating granuloma	Well defined	Poorly defined
Bilateral hilar lymphadenopathy	yes	no
Hypercalcimia and hypercalciuria	yes	no
BAL:	T helper are dominant	Both increased but T cytotoxic are more
Other organs involvement: eye, skin, bone..etc	yes	no

Past papers

1) True about sarcoidosis:
   A) higher prevalence in smokers
   B) Mainly occupational disease
   C) In liver it manifests as granuloma surrounding central veins
   D) In more than 50%, it causes granuloma in spleen
   E) Noncaseating granuloma are common in erythema nodosum

2) What's specific about sarcoidosis:
   A) Non-caseating granuloma
   B) Shaumann bodies
   C) Asteroid bodies
   D) None of the above

3) Regarding sarcoidosis, one of the following is correct:
   A) Hypercalcemia in sarcoidosis isn't related to bone destruction
   B) The presence of noncaseating granuloma in lung biopsy is diagnostic
   C) Asteroid bodies are laminated concretions that contain calcium
   D) The noncaseating granulomas are centered within the alveolar spaces
   E) Corneal opacification is the most common presentation of eye involvement.

Answers: D, D, A

V1

We have added the clinical features of hypersensitivity pneumonitis, which is included in the first 10 minutes of lecture 5.