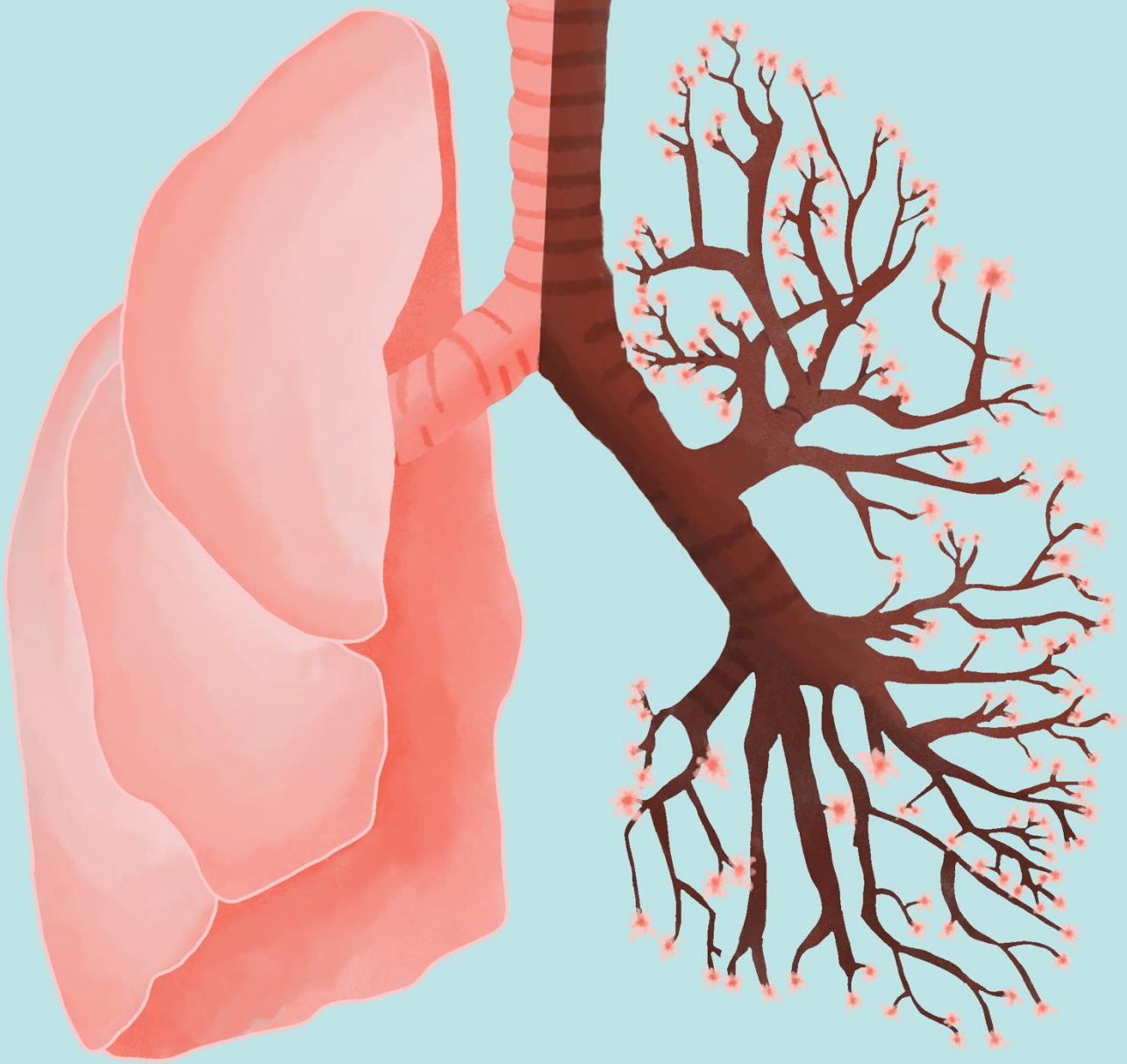
RESPIRATORY SYSTEM PATHOLOGY



Title: Sheet 4 - chronic lung diseases

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- In the previous lectures we discussed the main obstructive lung diseases, in this lecture we are going to discuss the chronic interstitial (restrictive, infiltrative) lung diseases.

❋ Chronic interstitial (restrictive) lung diseases

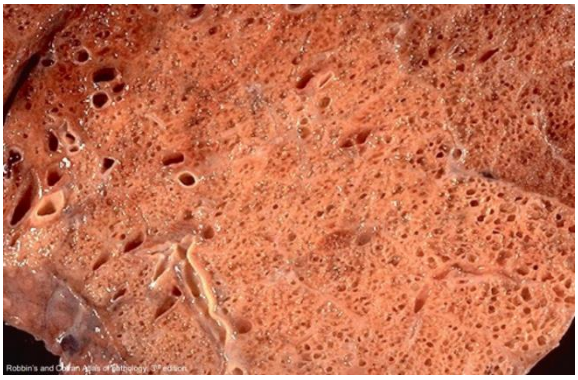
- There are more than 100 restrictive diseases. In these diseases the lungs are restricted from filling so air entry is difficult and the patient can't get air in, this happens because in restrictive lung diseases the lung volumes and capacity are decreased.
- Rrestrictive diseases are characterized by **reduced expansion** of the lungs parenchyma and decreased total lungs capacity which means **decreased lung compliance** (ability to expand), which in turn **increases the effort** to breath. Therefore, patients usually present to you with dyspnea and cough.
- The **severity** of these diseases is determined by the **total lung capacity**.
- These diseases are called restrictive and infiltrative, restrictive because the lungs are restricted from filling, and infiltrative because they are associated with cellular and non-cellular infiltrations of the interstitium and the alveoli.
- They are defined as heterogenous group of disorders that are characterized by bilateral, often patchy, pulmonary fibrosis. Pulmonary fibrosis mostly affects the **alveolar walls**.
- Many of these entities are of unknown cause and pathogenesis
- These diseases show frequent overlaps especially in histologic features. The shared histologic features and the similarity in clinical symptoms and the radiographic findings and the pathophysiologic changes justify their consideration as one group. It is so difficult to classify these diseases.

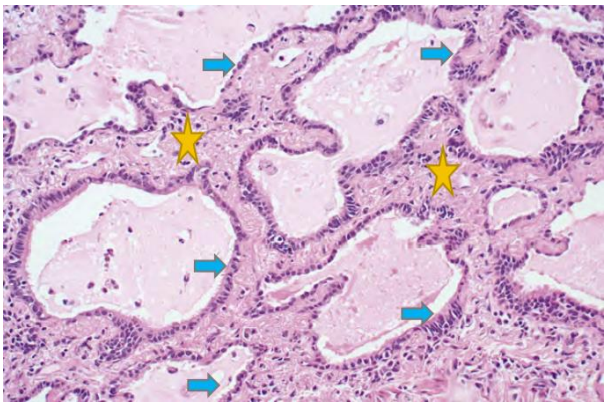
- One of the classifications is based on the clinicopathologic features and characteristic histology, in this classification there are four main categories:
  1. Fibrosing diseases
  2. Granulomatous diseases
  3. Eisonophilic diseases
  4. Smoking related diseases

- The **hallmark** of these diseases is reduced compliance (stiff lungs) because of the decreased lungs ability to expand so the patients usually show breathing difficulties.
- The damage to the alveolar epithelium and interstitial vasculature results in **abnormal ventilation-perfusion ratio** which leads to **hypoxia**. In restrictive lung diseases we are talking about **fibrosis** or **scarring** in the interstitium and alveolar walls. This means that the changes are **irreversible** and with time this may lead to ventilation-perfusion **miss-match** leading to hypoxia.
- These diseases have similar radiographic findings. They may show small nodules, irregular lines, or ground-glass shadows.

- With progression patients may develop respiratory failure, pulmonary hypertension and cor pulmonale
- In the cases of advanced restrictive lung diseases the etiology of the underlying diseases may be difficult to determine, this happens because of diffuse scarring and gross destruction of the lung which obscures the characteristic features of the underlying etiology, the **diffuse scarring** and **gross destruction** of the lung is referred to as **end-stage or "honeycomb" lung**.

The following figure shows the gross appearance of **honeycomb lung**. As you can see the lung shows irregular residual small dilated air spaces, these irregular air spaces are present between bands of dense fibrous interstitial connective tissue. At this stage and regardless of the cause of the restrictive lung disease, the majority of cases show the same gross and microscopic findings with extensive pulmonary interstitial fibrosis. Because the lung is converted by fibrosis into irregular small dilated air spaces you can't differentiate the underlying etiology.





This figure shows the histologic findings of honeycomb lung, there is **dense fibrous connective** tissue highlighted by **the yellow star**. This dense connective tissue surrounds the residual air spaces which are filled with a pink proteinaceous material. The **blue arrow** points to the **residual air spaces**, as you can see the air spaces have become dilated and lined with metaplastic bronchiolar epithelium instead of the pneumocytes, so gas exchange is affected, this produces a marked diffusion block to the gas exchange resulting in abnormal ventilation-perfusion ratio which leads to hypoxia.

- The following table will be discussed in details in next 3 lectures. The doctor just read it.

Fibrosing
Usual interstitial pneumonia (idiopathic pulmonary fibrosis)
Nonspecific interstitial pneumonia
Cryptogenic organizing pneumonia
Associated with collagen vascular disease
Pneumoconiosis
Associated with therapies (drugs, radiation)
Granulomatous
Sarcoidosis
Hypersensitivity pneumonia
Eosinophilic
Loeffler syndrome
Drug allergy–related
Idiopathic chronic eosinophilic pneumonia
Smoking-Related
Desquamative interstitial pneumonia
Respiratory bronchiolitis

❋ Granulomatous diseases

- As the name implies, these diseases show granulomatous reactions histologically
- Granulomatous diseases include:

a) **Sarcoidosis**: a disease with an unknown etiology and characteristic lung infiltration by granulomas

b) **Hypersensitivity pneumonia**: an immune reaction to an inhaled antigen

A) Sarcoidosis

- It is a **multisystem** disease of **unknown** etiology. This means that the disease process can involve more than one system and the exact underlying cause is still unknown.
- The most common organs include: the lungs, hilar lymph nodes and the paratracheal lymph nodes
- Histologically the disease is characterized by **noncaseating granulomas** in many tissues and organs
- Sarcoidosis has multiple different presentations; this disease can present as an **acute** or **chronic** illness.
- One of the presentations of sarcoidosis is as a restrictive lung disease which is our topic.

• DIAGNOSIS:

- The histologic diagnosis of sarcoidosis is considered a **diagnosis of exclusion**, because noncaseating granulomas are **not** considered **pathognomic** for sarcoidosis, they can be seen in other diseases such as mycobacterial or fungal infections.
- **Clinically**, sarcoidosis can manifest in different ways, **however bilateral hilar lymphadenopathy** or **lung involvement** or both are the **most common presentation**, eye and skin involvement each can occur in about 25% of cases, and can be also the only presenting feature of the disease.

• INTERESTING EMIPEMIOLOGIC TRENDS:

- Sarcoidosis occur throughout the world affecting **both genders** and **all races** and **age groups**, however there are some epidemiologic trends such as a **consistent** predilection of adults **less than the age 40** and a **high prevalence among non-smokers**

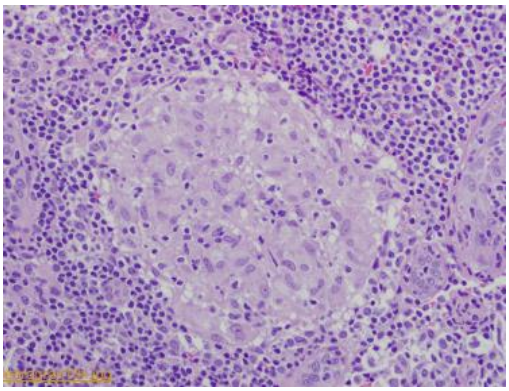
• ETIOLOGY AND PATHOGENESIS:

- Research evidence suggests that sarcoidosis shows a **disordered immune regulation** in **genetically predisposed** persons exposed to certain environmental agents
- Several immunologic abnormalities in sarcoidosis suggest a development of cell mediated response to an unidentified antigen, driven by CD4+ helper T cells

• MORPHOLOGY

- The characteristic histopathologic features of sarcoidosis is the presence of noncaseating epithelioid granuloma. It can be seen in any organ involved by sarcoidosis.

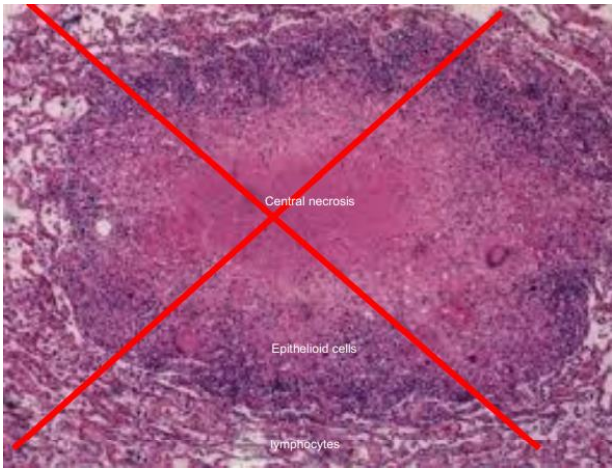
- It is made by a discrete, compact collection of **epithelioid cells** (activated macrophages) rimmed by an outer zone rich in **CD4+ T cells** with intermixed **multinucleated giant cells** (formed by fusion of these macrophages).



In this figure you can see a pale center while the periphery is a little bit dark blue purple. In the center of the **noncaseating granuloma** you can see a cluster of epithelioid cells, those are activated macrophages rimmed by peripheral blue T lymphocytes.

- Note that caseation necrosis typical of tuberculosis is **ABSENT**.

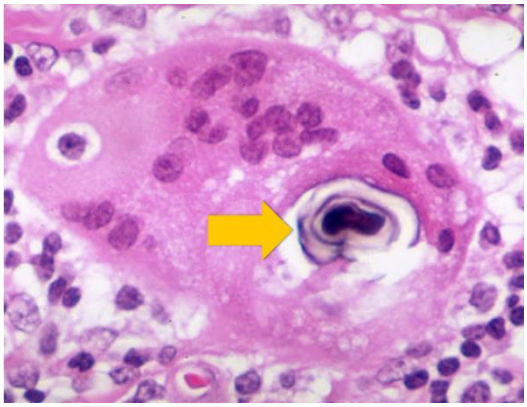
In this figure, you can see a centre of pale **epithelioid** macrophages rimmed by a fence of T lymphocytes. At the very centre we can find a dark pink area called central necrosis **(caseating or necrotizing granulomatous reaction)** . This type of granuloma is present in some infections such as tuberculosis, but is absent in sarcoidosis. In some cases of sarcoidosis, you may identify a small focus of necrosis especially in the nodular form, but the central extensive caseation as shown in this figure is not seen in sarcoidosis and is considered typical for TB.



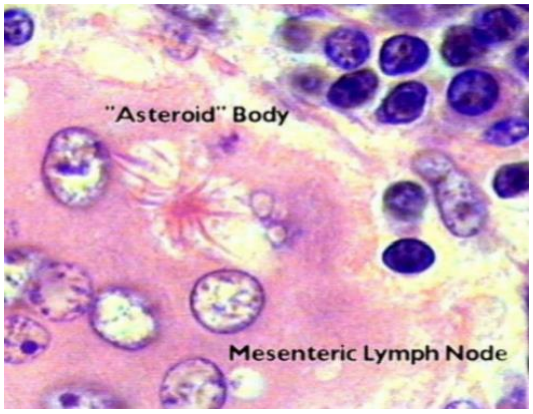
- Early on, a thin layer of fibroblasts is found peripheral to the granuloma and over time those fibroblasts start to proliferate and lay down collagen that **replaces** the granuloma with **hyalinized scars**.

- **Microscopic Features**
  - Two microscopic features can be seen in granulomas in some cases of sarcoidosis:
    a) Schaumann bodies
    b) Asteroid bodies

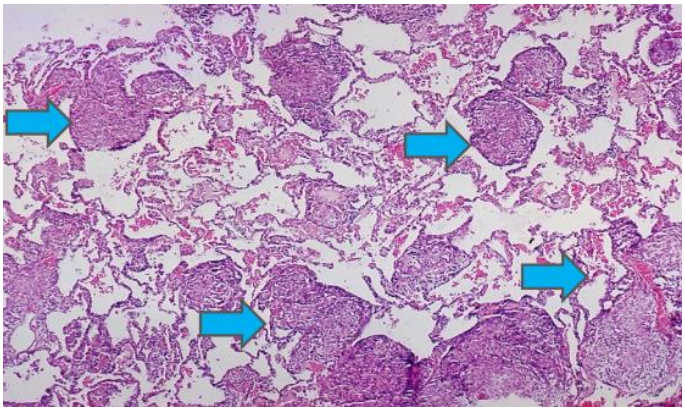
a) **Schaumann bodies** are defined as laminated concretions composed of calcium and proteins. The following figure shows a central multinucleated giant cell. This cell is engulfing a schaumann body, pointed at by the yellow arrow. This laminated appearance looks like **the onion skin.**



b) **Asteroid bodies** are stellate inclusions within the giant cells. As you can see there are blue lymphocytes at the right upper side and multinucleated giant cell at the left lower side. **The giant cell engulfing a star shaped structure** is what we call asteroid body.



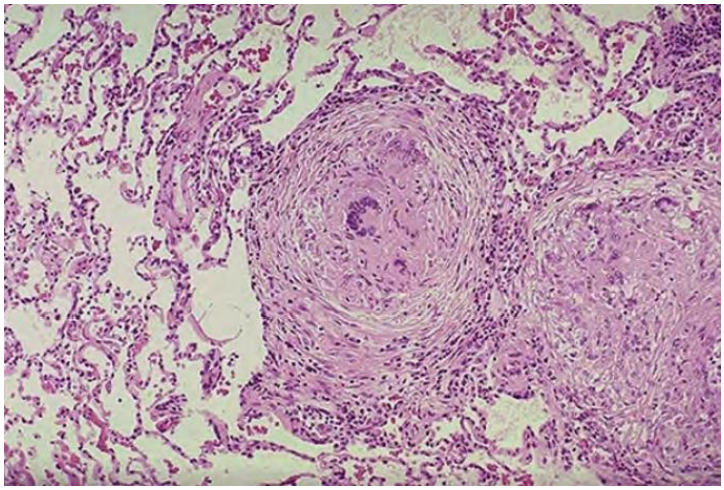
☑ You must know that schaumann bodies and asteroid bodies are **not specific for sarcoidosis**, you can see them in granulomas related to other causes as well. Therefore, their presence is not required for the diagnosis, as we said before sarcoidosis is a diagnosis of exclusion, so if you exclude all other causes (clinically, by radiology, microbial studies and histology) and you are left with sarcoidosis, you don't need to see schaumann or asteroid bodies because they are not specific and not necessary to run the diagnosis.

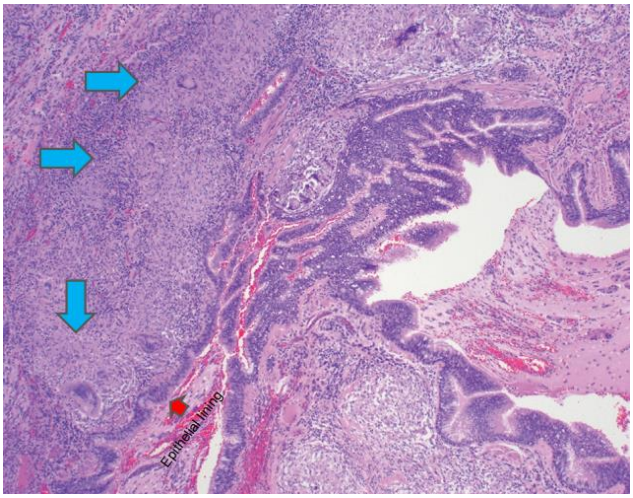


This figure shows involvement of the lungs in sarcoidosis. As you can see, the **alveolar spaces are patent** while there are some **pink purple collections** in the **walls** of alveoli (blue arrow). These collections are made of noncaseating granulomas (epithelioid cells rimmed by T-cells)

Note that this involvement is only seen in the walls of the alveoli, which means there **is no plugging of alveolar spaces**.

- This figure shows lung involvement in cases of sarcoidosis but at a higher power view. As you can see there is a central noncaseating granulomatous with giant cells, present in the interstitium of the alveolar walls while alveolar spaces are still patent (not plugged by those granulomas).





▪ This figure shows a peri-bronchial noncaseating granuloma with many giant cells. They are present just beneath the epithelial lining.
Note that those lesions have some tendency to be localized in the connective tissue around the bronchioles

Sarcoidosis mainly involves the lungs, hilar and paratracheal lymph nodes, skin, eye and lacrimal glands, spleen, liver and bone marrow.

❋ Morphology of lungs involvement:

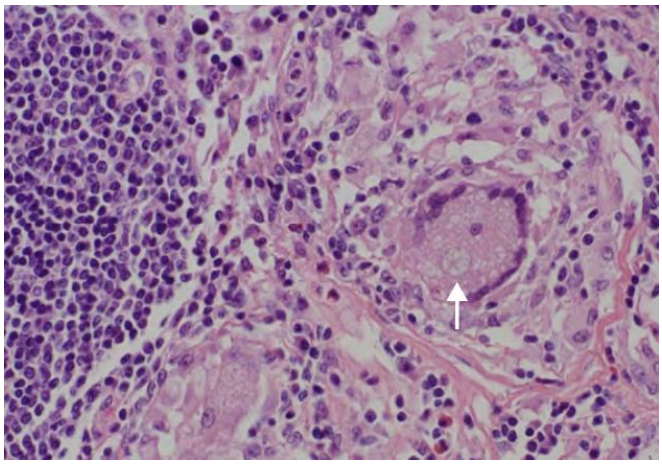
- Lungs are involved in about 90% of the cases
- Granuloma involves the interstitium rather than the air spaces
- The granulomatous involvement shows some tendency to be localized in the connective tissue around the bronchioles, pulmonary venules and pleura

- **DIAGNOSIS**:
  - One of the diagnostic methods for lung disease is the bronchoalveolar lavage (BAL) in which a bronchoscope is passed through the mouth or nose → appropriate airway in the lung, with a measured amount of fluid collected for examination.
  - When you perform BAL in cases of sarcoidosis the result will be **abundant CD4+ T lymphocytes.**
  - The progression into honeycomb (end-stage) lung occur in about 5-15% of patients

❋ Morphology of hilar and paratracheal lymph nodes involvement:

- They are enlarged in 75-90% of patients
- 1/3 are present with peripheral lymphadenopathy
- The lymph nodes in cases of sarcoidal involvement are **painless with firm, rubbery texture**.
- Unlike tuberculosis, the lymph nodes of sarcoidosis are **non-matted, non-adherent and do not ulcerate.**

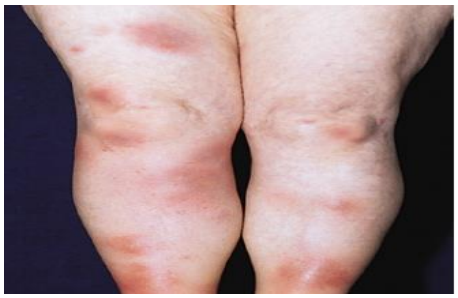
- This figure shows the histologic findings in a lymph node that is involved by sarcoidosis. As you can see, there is some lymphoid tissue at the left and to the right there is non-caseating granuloma with central multinucleated giant cells and asteroid bodies. The findings should raise the possibility of sarcoidosis after ruling out all other entities in the differential diagnosis because sarcoidosis is diagnosed by exclusion.



❋ Morphology of skin involvement:

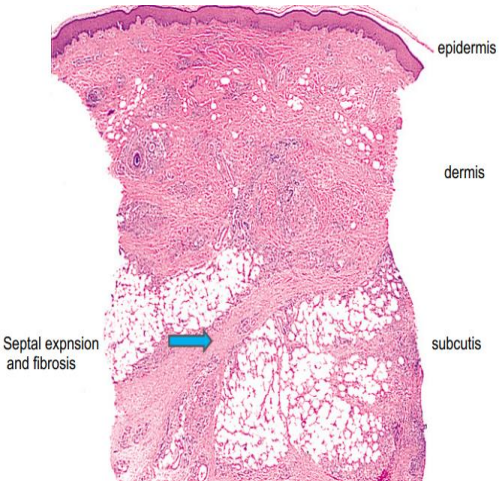
- Skin lesions are encountered in about 25% of patients
- Patients may have erythema nodosum or/and subcutaneous nodules

a) Erythema nodosum is considered **the hallmark** of acute sarcoidosis, clinically the patient presents with **raised, red, tender nodules** on the **anterior** aspects of **legs**. Histologically, the sarcoidal granulomas are **uncommon** in EN instead you may see some sort of inflammation of the subcutaneous fat which we call **septal panniculitis**.



b) The subcutaneous nodules are discrete painless lesions that are usually presented with abundant noncaseating granulomas histologically

- The following figure presents the histologic findings in erythema nodosum. Remember that noncaseating granulomas are considered **uncommon** in erythema nodusum.
- The lesion is centred in the **subcutis** so the dermis and epidermis are almost unremarkable. The **main finding** is expansion and widening of the interlobular septa by inflammation, and fibrosis by a pattern we call **septal panniculitis**.



- In other words, erythema nodosum is Inflammation and fibrosis of the deep subcutaneous tissue (subcutis). The dermis and epidermis show no histologic findings.

❋ Morphology in cases of eye and lacrimal glands involvement:

- Occurs in 20-50% of the cases
- Ocular involvement takes the form of iritis or iridocyclitis. The involvement may be unilateral or bilateral
- This results in corneal opacities, glaucoma and less commonly the total loss of vision
- The posterior uveal tract may be also affected with resultant coriditis, retinitis and optic nerve involvement
- The involvement of lacrimal glands may show **Sicca Syndrome**, which is am inflammation in the lacrimal glands with suppression of lacrimation
- Unilateral or bilateral parotitis with painful enlargement of the parotid glands occurs in less than 10% of the patients
- Some of these patients develop dry mouth (xerostomia)
- There could be combined uveoparotid involvement. This case is called **Mikulicz syndrome.**

❋ Morphology in cases of spleen, liver and bone marrow

- The spleen in about ¾ cases contains granulomas
- In around 10%, it becomes clinically enlarged
- The liver shows granulomatous regions usually in the portal triads in about ¾ cases
- About 1/3 of patients show hepatomegaly or abnormal liver function
- The bone marrow involvement by sarcoidosis is reported in about 40% of patients
- Other findings in BM involvement may include hypercalcemia and hypercalciuria
- Hypercalcemia and Hypercalciuria are not related to bone destruction. They are caused by **increased calcium absorption** secondary to production of active vitamin D by the macrophages that form the granulomas

• Clinical features of sarcoidosis

- In most of the patients the disease is entirely asymptomatic and usually discovered in routine chest radiographs as bilateral hilar lymphadenopathy or as incidental finding at autopsy. These are the most common presentations.
- In other patients the disease present with some symptoms such as peripheral lymphadenopathy, cutaneous lesions, eye involvement, splenomegaly or hepatomegaly
- In 2/3 of symptomatic cases the patients shows gradual **respiratory symptoms** such as dyspnea, dry cough or chest discomfort or **constitutional signs and symptoms** such as fever, fatigue, weight loss, anorexia and night sweats

- **Diagnosis of sarcoidosis**
  - Diagnosis is considered somehow tricky because there is no definitive diagnostic test for sarcoidosis
  - It requires the presence of clinical and radiologic findings that are consistent with the disease, but because both are non-specific; we still need **to exclude** other disorders with similar presentations, and then to **identify the noncaseating granuloma** in the involved tissue and organ by histology
  - In particular, TB must be excluded along other infections

- **The course of sarcoidosis (The development)**
  - The course in considered **unpredictable** in sarcoidosis because patients may show progressive chronicity or periods of activity interspersed with remissions
  - The remissions may be spontaneous or initiated by steroid therapy

- **The outcome of sarcoidosis**
  - 65-70% of patients recover with minimal or no residual manifestation (majority)
  - 20% of patients face permanent lung dysfunction or visual impairment
  - 10-15% of patients face progressive pulmonary fibrosis and cor pulmonale

B) Hypersensitivity pneumonitis

- It is an immune mediated inflammatory lung disease. The immune reaction is mainly related to an inhaled antigen and this antigen is mostly occupational (related to work place).
- It primarily affects the alveoli so it is often called (allergic alveolitis)

- This table shows different sources of inhaled antigens that can cause hypersensitivity pneumonitis. Mushroom's fungal structure and yeast can be a source of antigen.
- Farmer's lung is a disease caused by inhaled mold of certain crops. Farmers are most likely to get it as it's usually caused by breathing in dust.
- The antigen can be a mold like aspergillus species or a bacteria.
- Mycobacteria can be related to sauna and hot tubs.
- Bird feathers and chemicals also can trigger this disease

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

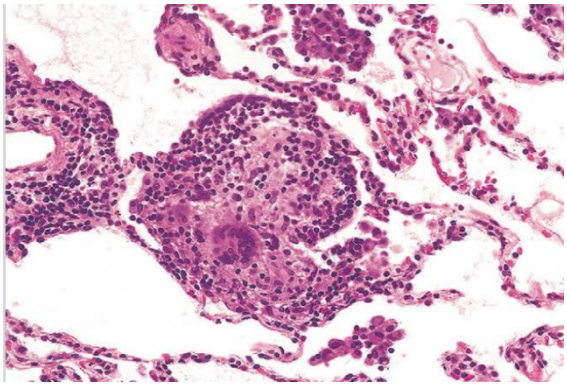
Immunologic Basis

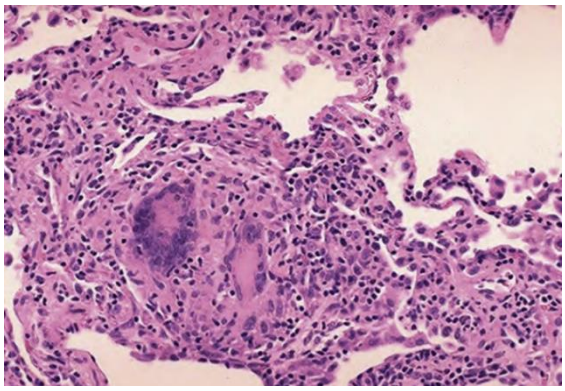
- BAL specimens show increased number of both CD4+ and CD8+ lymphocytes
- Most affected patients have specific antibodies against the offending antigen in their serum
- The presence of complement and immunoglobulins within vessel walls is seen in immunofluorescence test
- Noncaseating granulomas are seen in the lungs of 2/3 of affected patients

Morphology

- Histologically, the findings include a patchy mononuclear cell infiltrates in the pulmonary interstitium, with a characteristic peribronchiolar accentuation
- It is predominated by lymphocytes, but plasma cells and epithelioid cells are also present
- In acute forms of the disease, neutrophils may be seen
- In more than 2/3 of cases a loose, poorly formed granulomas without necrosis are presented mainly in a peribronchiolar location
- In advanced chronic cases, **bilateral, upper lobe dominant interstitial Fibrosis** (which we can also call **UIP pattern**) occurs

- This figure shows the histologic findings of hypersensitivity pneumonitis. As you can see there is a central loosely formed granulomatous reaction within the interstitium of the alveolar wall. This reaction is surrounded by chronic inflammation and one multinucleated giant cell. **The alveolar spaces are still patent**.





- This figure shows the same findings as the previous figure but there are two multinucleated giant cells instead of one.

- **Clinical features**
  - It can present as acute or chronic disease
  - **In cases of acute reactions** patients usually present with fever, cough, dyspnea and constitutional signs and symptoms arising 4 to 8 hours after exposure.
  - Within the acute form the diagnosis is usually obvious because of the temporal relationship between the symptom's onset and the exposure to the causing agent
  - If antigenic exposure is terminated after acute attacks of the disease, complete resolution of pulmonary symptoms occurs within days
  - Failure to remove the causing agent from the environment results in irreversible chronic disease
  - **Chronic disease** is characterized by insidious onset of cough, dyspnea, malaise and weight loss

➔ **Now let's solve this question:**

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, 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