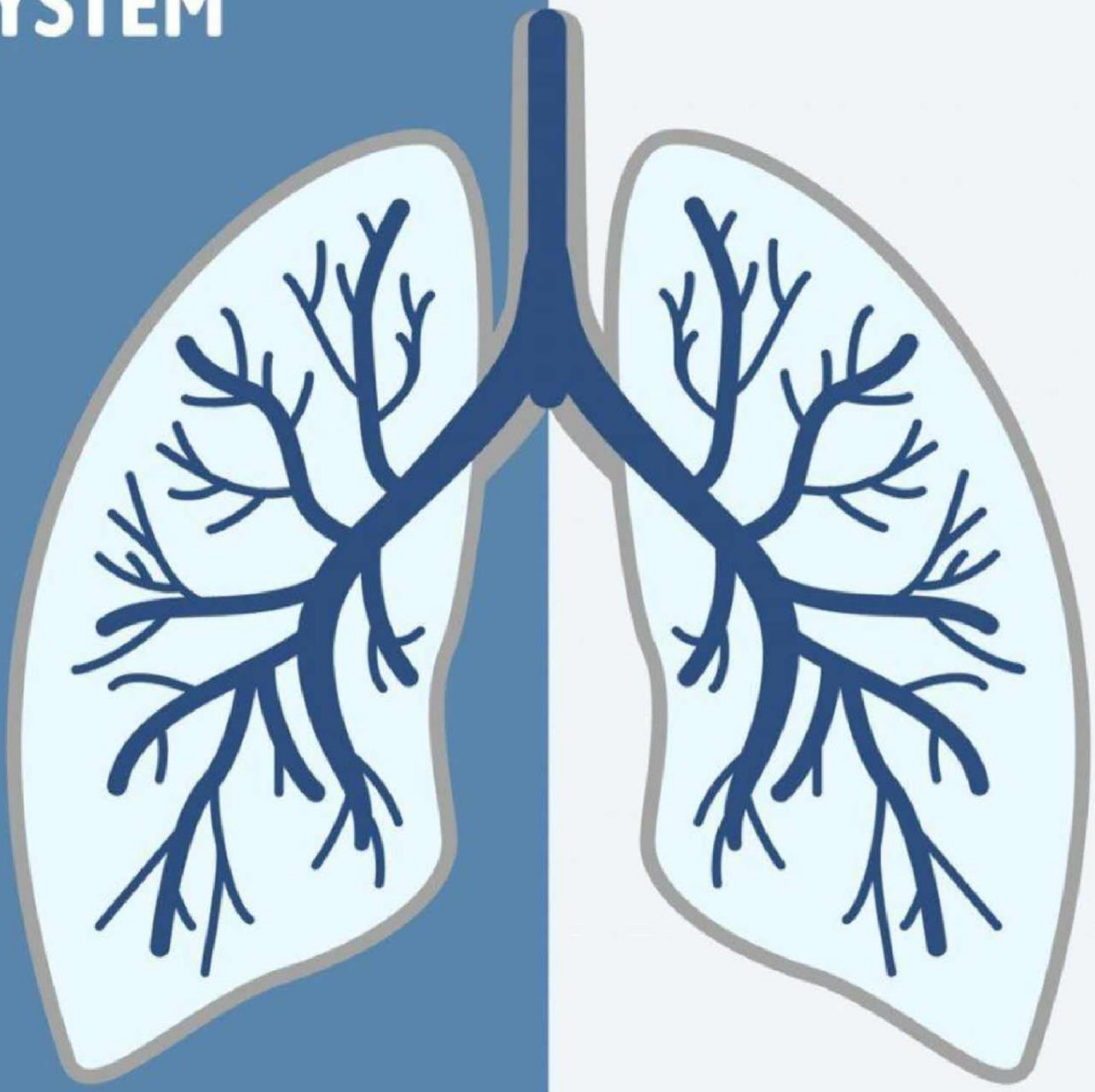
RESPIRATORY SYSTEM

PATHOLOGY



WRITER: 018 sheets

CORRECTOR: Ahmad T Qatawneh

DOCTOR: Maram abdaljaleel

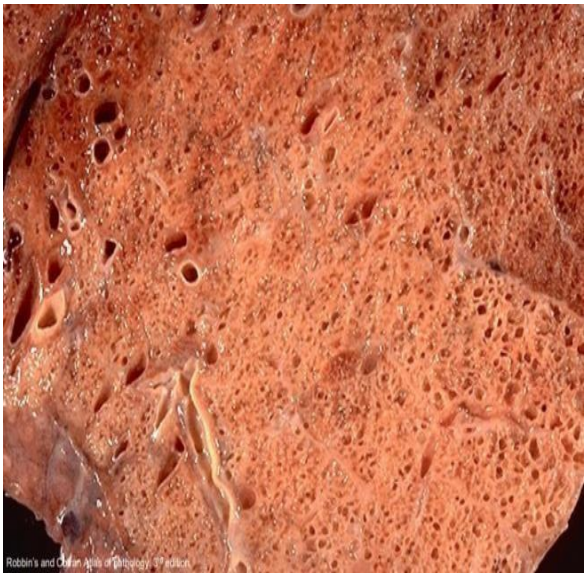
In this lecture we are going to discuss the **chronic interstitial (restrictive, infiltrative) lung diseases** which are defined histologically and clinically.

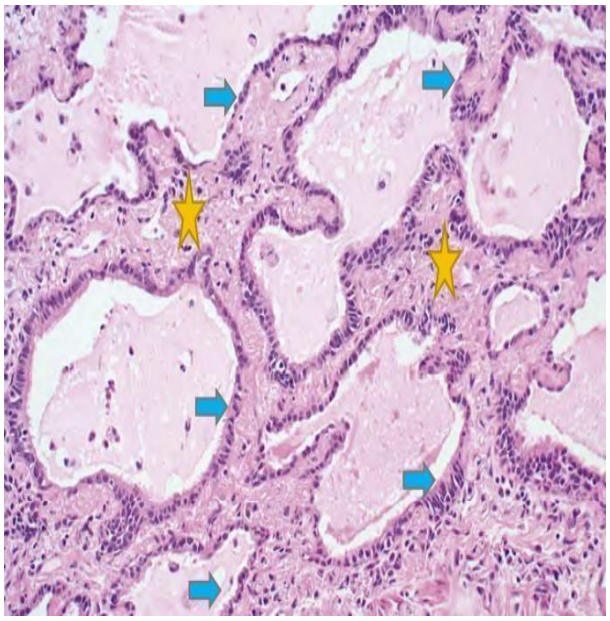
Chronic interstitial (restrictive) lung diseases

- Are a heterogenous group of disorders (more than 100 diseases with frequent overlapping) characterized predominately **by inflammation and fibrosis of lung interstitium (+/- intra-alveolar inflammation**) associated with **pulmonary function studies indicative of restrictive lung diseases (reduction in lung volumes and capacities)**
- In these diseases, the lungs are restricted from filling so air entry is difficult, and the patient can't get air in.
- Restrictive 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 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 cellularand non-cellular infiltrations of the interstitium and the alveoli.
- 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.
- **Clinically:** Dyspnea (increased effort to breath), tachypnea, end-inspiratory crackles, and eventual cyanosis.
- **Chest radiographs:** Bilateral nodular lesions (small nodules, irregular lines, or ground-glass shadows)
- The damage to the alveolar epithelium and interstitial vasculature results in **abnormal ventilation-perfusion ratio leading to hypoxia.** With progression, the state of hypoxia leads to vascular spasm leading pulmonary hypertension and thus respiratory failure and cor pulmonale.

- The **hallmark** of these diseases is reduced compliance (stiff lungs) because of the decreased lung's ability to expand so the patients usually show breathing difficulties.
- The entities can be distinguished in their early stages, but advances forms are hard to differentiate because In the cases of advanced restrictive lung diseases, diffuse scarring and gross destruction of the lung will obscure 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**, cystically 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 lungdisease, most 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**. The air spaces have become dilated and lined with metaplastic bronchiolar epithelium insteadof the pneumocytes, so gas exchange is affected, this produces a marked diffusion blockage to gas exchange resulting in abnormal ventilation-perfusion ratio which leads to hypoxia.

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

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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 granulomatous disease** of **unknown** etiology. That is, 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** (No center of necrosis) 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 diagnosis of sarcoidosis is considered a **diagnosis of exclusion**, because noncaseating granulomas are **not** considered **pathognomonic** for sarcoidosis as they can be seen in other diseases such as mycobacterial or fungal infections.
- Clinically, sarcoidosis can manifest in different ways as an **acute, chronic illness or restrictive lung disease**,
- **bilateral hilar lymphadenopathy,** or **lung involvement** or both are the **most common presentations**.Eye, and skin involvement each can occur in about 25% of cases and can be also the only presenting feature of the disease.

• Interesting epidemiological trends:

- Sarcoidosis occurs 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**

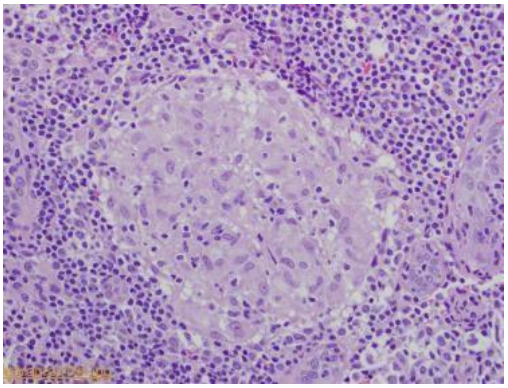
• ETIOLOGY AND PATHOGENESIS:

- Etiology is unknown, yet 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 feature of sarcoidosis is the presence of **noncaseating epithelioid granuloma**. It can be seen in any organ involved by sarcoidosis (However it is not pathognomonic).

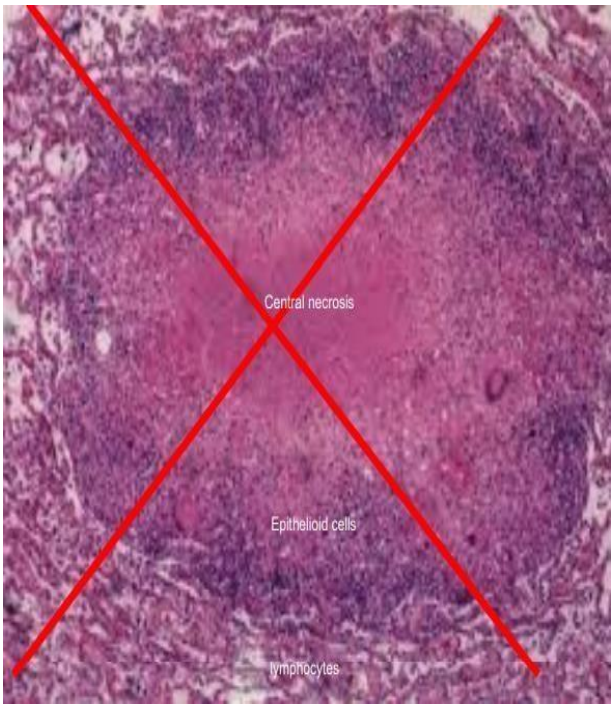
- It is made by a discrete (well-circumscribed), compact collection of **epithelioid cells** (activated macrophages) rimmed by an outer zone rich in **CD4+ T cells** with intermixed **multinucleated giant cells** (formed by fusion of these macrophages) **without any center of necrosis**.



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**.

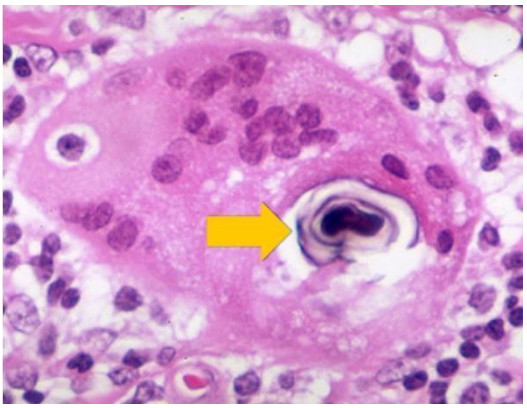
In this figure, you can see a center of pale **epithelioid** macrophages rimmed by a fence of T lymphocytes. At the very center we can find a dark pink area called central necrosis **(caseating or necrotizing granulomatous reaction)** . This type of granuloma is present in some infections such as tuberculosis 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.



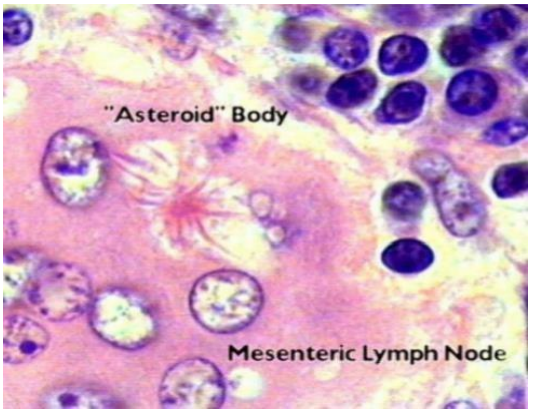
- Early on, a thin layer of fibroblasts is found peripheral to the granuloma and over time those fibroblasts start to proliferate and lay down collagen that **replaces** the granuloma with **hyalinized scars** which results the interstitial lung disease.

- **Microscopic Features**
  - Two microscopic features can be seen in granulomas in some cases of sarcoidosis (however these are non-specific and not essential for diagnosis) :
    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 called an asteroid body.**



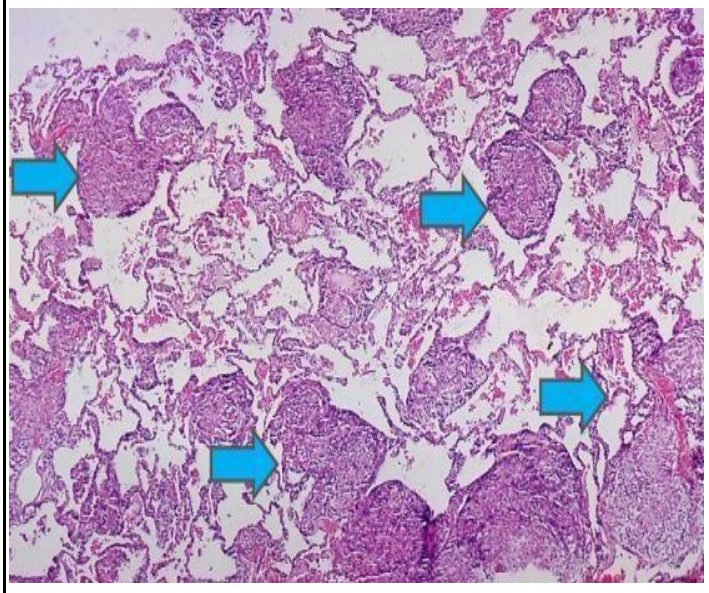
☑ Schumann bodies and asteroid bodies are **not specific for sarcoidosis**, you can see them in granulomas related to other causes as well. Therefore,their presence is not required for the diagnosis, as we said before sarcoidosis is a diagnosis of exclusion and so by exclusion of all other causes (clinically,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

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

Morphology of lungs involvement:

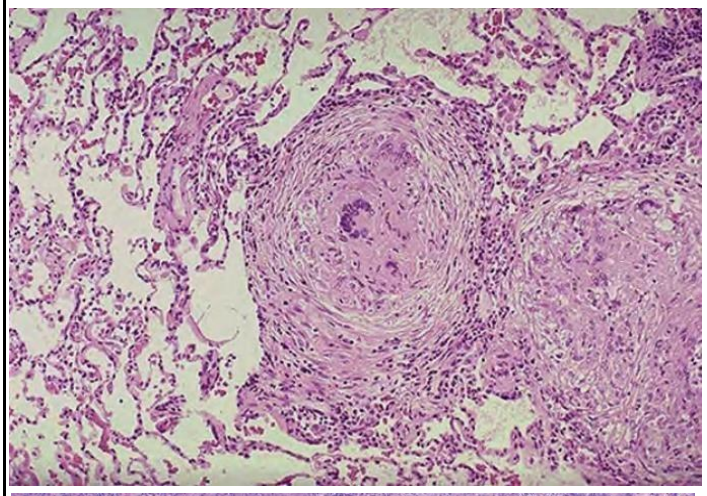
- Lungs are involved in about 90% of the cases
- Granuloma involves the interstitium (+/- alveolar lesions and pleural involvement) rather than the air spaces (the airspaces are patent)
- The granulomatous involvement shows some tendency to be localized around the lymphatics, bronchi,connective tissue around the bronchioles, pulmonary venules (blood vessels) and pleura with a **high frequency of granulomas in bronchial submucosa**.
- The granulomatous lesions also show high tendency to heal with fibrosis with variable stages of fibrosis (with earliest stage being: formation of fibroblastic fossae and latest one being the formation of honey-comb lung)

- **DIAGNOSIS**:
  - A bronchoalveolar lavage (BAL) is used inwhich 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 occurs in about 5-15% of patients.

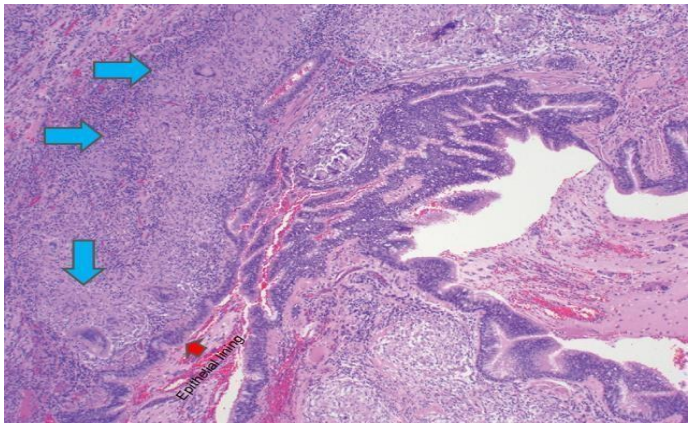


This figure shows involvement of the lungs in sarcoidosis. As you can see, the **alveolar spaces are patent** while there are some **pink, purple collections** in the **walls** of alveoli (blue arrow). These collections are made of noncaseating granulomas (epithelioid cells rimmed by T-cells)

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 at a higher power view, there is a central noncaseating granuloma with giant cells present in the interstitium of the alveolar walls while the **alveolar spaces are still patent (not plugged by those granulomas).**

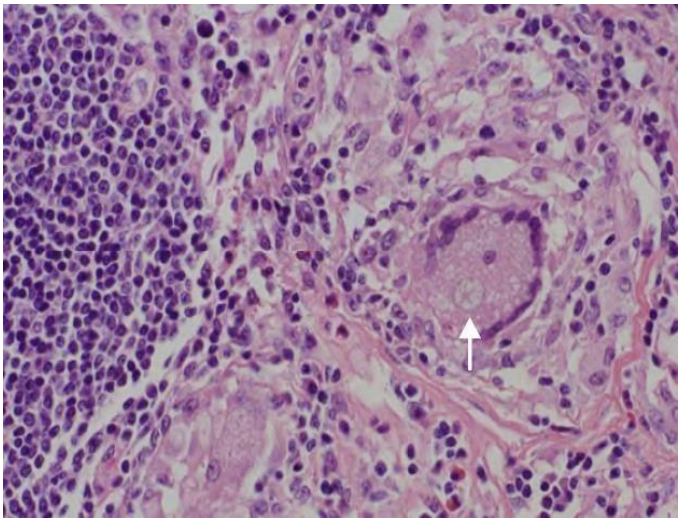


This figure shows a peri-bronchial non caseating granuloma with many giant cells. The pink areas below the epithelial lining represent epithelioid macrophages.

Remember: noncaseating granulomas in sarcoidosis tend to develop in the connective tissue of bronchioles.

❋ Morphology of hilar and paratracheal lymph nodes involvement:

- In almost all cases, any node can be affected. **Particularly the hilar and mediastinal**.
- 1/3 are present with peripheral lymphadenopathy.
- The lymph nodes in cases of sarcoidal involvement are **enlarged painless with firm, rubbery texture**.
- the lymph nodes of sarcoidosis are **non-matted, non-adherent (non-fused) and do not ulcerate "unlike TB".**
- **+/- sometimes calcified** (part of inflammation).

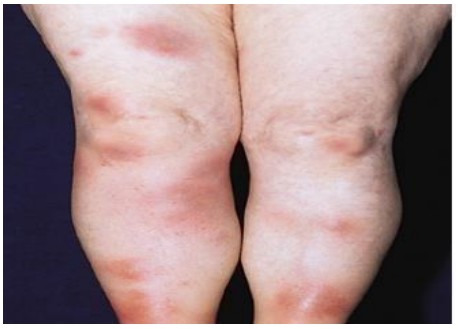


This figure shows the histologic findings ina lymph node that is involved by sarcoidosis. As you can see, there is some lymphoid tissue at the left and to the right there is non-caseating granuloma with central multinucleated giant cells and asteroid bodies. The findings should raise the possibility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

❋ Morphology of skin involvement:

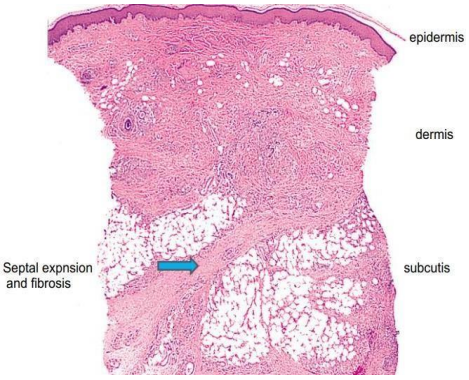
- Skin lesions are encountered in about 25% of patients
- Patients may have erythema nodosum or/and subcutaneous nodules:

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



b) **The subcutaneous nodules** are **discrete painless lesions** presented **with abundant noncaseating granulomas**.

- The lesion is centered in the **subcutis,** so the dermis and epidermis are almost unremarkable. The **main finding** is expansion and widening of the interlobular septa (normally thin) by inflammation, and fibrosis in 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.

c) Other skin lesions that can be found : **Erythematous plaques; or flat lesions.**

❋ Morphology in cases of eye and lacrimal glands involvement:

- Occurs in 20-50% of the cases
- **UVEITITS (**Inflammation inside the eyes) is most common in the form of:
  - iritis or iridocyclitis. The involvement may beunilateral or bilateral.
  - Posterior uveal tract disease resulting retinitis, choroiditis, and optic nerve involvement.
- This results in **corneal opacities, glaucoma** (due to optic nerve involvement) and less commonly **the total loss of vision**.
- The involvement of lacrimal glands may show **Sicca Syndrome**, which is an 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 (may cause kidney stones). **Hypercalcemia and Hypercalciuria** are not related to bone destruction. They are caused by **increased calcium absorption secondary to production of active vitamin Dby the macrophages** that form the granulomas. (These macrophage release 1-alpha hydroxylase which activates the inactive form of vitamin D found in our body).

• Clinical features of sarcoidosis

- Generally, The disease can present as **acute, chronic or insidious** onset of restrictive lung disease.
- **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** show 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 tricky because there is no definitive diagnostic test for sarcoidosis and therefore is dependent on:
    - **Clinical findings:** as mentioned above
    - **Radiological findings:** Bilateral hilar lymphadenopathy and bilateral reticular nodular infiltrates.
    - **Histological findings:** identification of the noncaseating granuloma in the involved tissue and organ.
    - **Exclusion of other disorders:** those with similar presentations, radiological or histological findings. **In particular, TB must be excluded.**

- **The course of sarcoidosis (The development)**
  - The course in considered **unpredictable** in sarcoidosis because patients may show **progressive chronicity** or **periods of activity (acute attacks) interspersed with remissions** or even sometimes **patients plateau without any complications throughout life and with minimal symptoms**.
  - 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 (resulting honey-comb lungs) and cor pulmonale

B) Hypersensitivity pneumonitis

- A spectrum of **immunologically mediated** predominately **interstitial lung disorders** caused by intense, prolonged exposure to **inhaled organic antigens mostly occupational** (related to workplace)..
- Referred to as **Allergic alveolitis**; because it primarily affects the alveoli and is related to inhalation of organic dust containing antigens composed of spores of thermophilic bacteria, fungi animal proteins, or bacterial products.
- More than 300 allergens leading to the development of hypersensitivity pneumonitis.
- Numerous syndromes depending on the occupation or exposure of the individual:
  - **Farmers lung**: exposure to dusts generated from humid, warm, newly harvested hay the permit the rapid proliferation of spores and mold.
  - **Humidifier or air-conditioner lung**: caused by thermophilic bacteria in heated water reservoirs.
  - **Hot tub lung:** non-tuberculous mycobacterium.
  - **Pigeon breeder's lung**: proteins from the serum or feathers of birds.

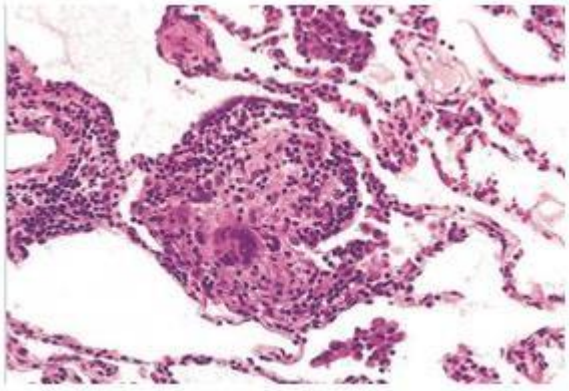
Source of Antigen	Types of Exposures
Mushrooms, fungi, yeasts	Contaminated wood, humidifiers, central hot air heating ducts, peat moss plants
Bacteria	Dairy barns (farmer's lung)
Mycobacteria	Metalworking fluids, sauna, hot tub
Birds	Pigeons, dove feathers, ducks, parakeets
Chemicals	Isocyanates (auto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

Immunologic Basis

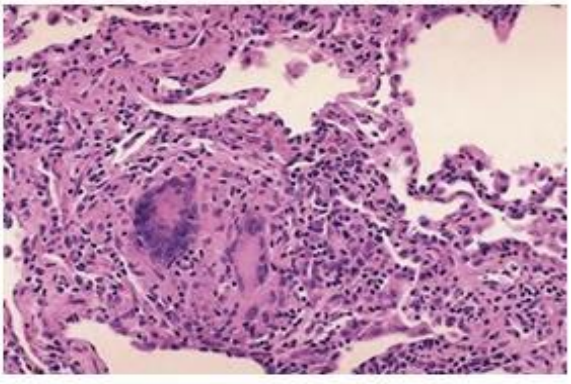
- BAL specimens show **increased number of both CD4+ and CD8+ lymphocytes.**
- Most affected patients have specific antibodies against the offending antigen in their serum.
- The presence of complement and immunoglobulins within vessel walls is seen in immunofluorescence test.
- Noncaseating granulomas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

Morphology

- Histological changes are centered around the bronchioles including:
  - **Interstitial pneumonitis:** lymphocytes (mainly), plasma cells and macrophages(eosinophils are rare) in the pulmonary interstitium.
  - "**Loose" poorly formed granulomas** (Not well circumscribed histologically) **without necrosis in 2/3 of cases,** usually in a **peribronchiolar location.**
  - **Interstitial fibrosis** with fibroblastic foci, honeycombing and obliterative bronchiolitis (in late stages).
- It is predominated by lymphocytes, but plasma cells and epithelioid cells are also present and in acute forms of the disease, neutrophils may be seen.
- In more than 50% of cases, intra-alveolar infiltrate is seen.
- In advanced chronic cases, **bilateral, upper lobe dominant interstitial Fibrosis** (also known as **unusual interstitial pattern (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 one but there are two multinucleated giant cells rather than one.

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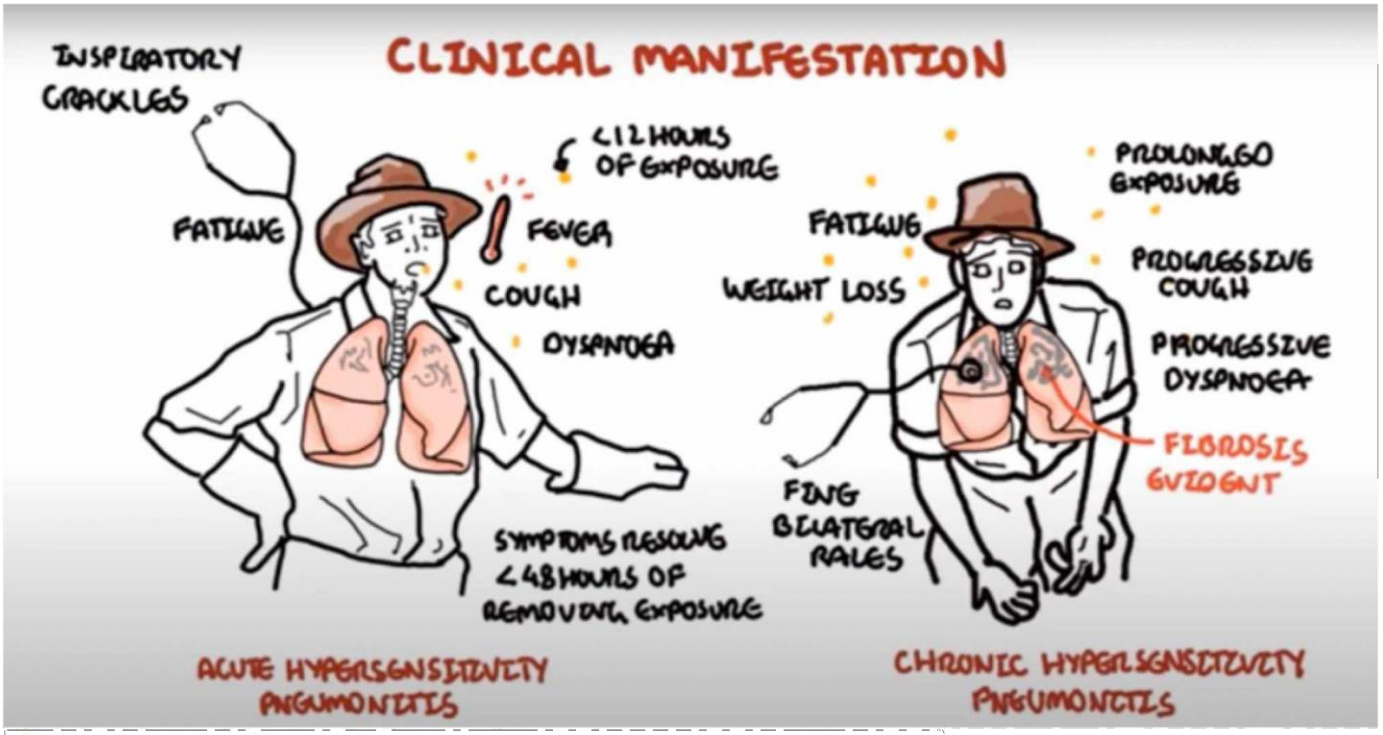
- **Clinical features**
  - It can present as acute or chronic disease
  - **In cases of acute reactions** patients usually present with fever, cough, dyspnea and constitutional signs and symptoms arising 4 to 8 hours after exposure to large amounts of the allergen for short duration.
  - Within the 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 or exposure to small amounts of the antigen for prolonged period of time from the environment results in irreversible chronic disease
  - **Chronic disease** is characterized by insidious onset of progressive cough, dyspnea, malaise and weight loss. Pulmonary function tests (**PFT) show restrictive pattern.**



➔ **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

	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

Differential diagnosis of granulomatous disease [18][19]

	Risk factors	Clinical presentation	Biopsy	Other laboratory findings
Sarcoidosis	• African American women in the US	• Dry cough • Erythema nodosum • Lupus pernio • Uveitis	• Non-caseating granulomas • Giant cells	• ↑ CD4/CD8 ratio in bronchoalveolar lavage • ↑ ACE levels in blood
Tuberculosis (TB)	• Immunocompromised individuals • Previous TB and/or recent TB exposure	• Fever, weight loss, and night sweats • Productive cough that does not respond to conventional antibiotic therapy • Hemoptysis	• Caseating granulomas • Langhans giant cells, epithelioid macrophages, and lymphocytes • Acid-fast M. tuberculosis	• M. tuberculosis or its DNA
Hodgkin lymphoma	• History of infectious mononucleosis	• Pel-Ebstein fever • Alcohol-induced pain • Pruritus	• Non-caseating granulomas • Reed-Sternberg cells • Inflammatory cell infiltrate (e.g., eosinophils, fibroblasts, plasma cells)	• Single or combined cytopenias (i.e., anemia, leukopenia, and/or thrombocytopenia)
Non-Hodgkin lymphoma	• Infections (e.g., EBV infection or Helicobacter pylori) • Cell damage (caused by toxic substances, immunosuppressive drugs, cytostatic therapy, radiation)	• Indolent lymph node enlargement • Splenomegaly • Evidence of bone marrow suppression (i.e., pallor, infections) • Possible large abdominal mass (in Burkitt lymphoma)	• Non-caseating granulomas without Reed-Sternberg cells • B-lymphocytes or T-lymphocytes • Inflammatory cell infiltrate	• Single or combined cytopenias

Pneumoconiosis	• Exposure to mineral dust (e.g., silica)	• Often, patients are asymptomatic and the physical examination is unremarkable.
		• In symptomatic patients
		  ◦ Progressive exertional dyspnea
		  ◦ Chronic cough (possibly with sputum)
		  ◦ Auscultatory findings (e.g., rales, crackles)
		  ◦ Signs of respiratory failure (e.g., digital clubbing)
			• Non-caseating granulomas
			• Silica/asbestos bodies
				• Positive beryllium lymphocyte proliferation test (BeLPT)

Granulomatosis with polyangiitis	• Caucasian individuals aged 65–74 years	• Chronic rhinitis/sinusitis with thick purulent/bloody discharge • Treatment-resistant pneumonia • Glomerulonephritis	• Non-caseating granulomas	• Positive cytoplasmic ANCA
Histoplasmosis [20]	• AIDS • Exposure to bird or bat excrement	• Pulmonary (e.g., dry cough, oral ulcers) or extrapulmonary (e.g., splenomegaly) manifestations	• Caseating granulomas • Identification of H. capsulatum yeast with silver stain	• Positive polysaccharide urine and serum antigen test

From AMBOSS

For addition

Treatment

- **Isolated pulmonary sarcoidosis**: In most cases, no treatment is required. The disease is often asymptomatic, non-progressive, and has a high rate of spontaneous remission.
- **Symptomatic or extrapulmonary sarcoidosis** [13]
  - First line: glucocorticoids
  - Second line: alternative immunosuppressive therapy (e.g., methotrexate or azathioprine), possibly in combination with glucocorticoids
  - Antimalarial drugs (e.g., chloroquine, hydroxychloroquine)
  - Last resort in severe pulmonary disease: lung transplantation
  - NSAIDs are always indicated for symptom relief.