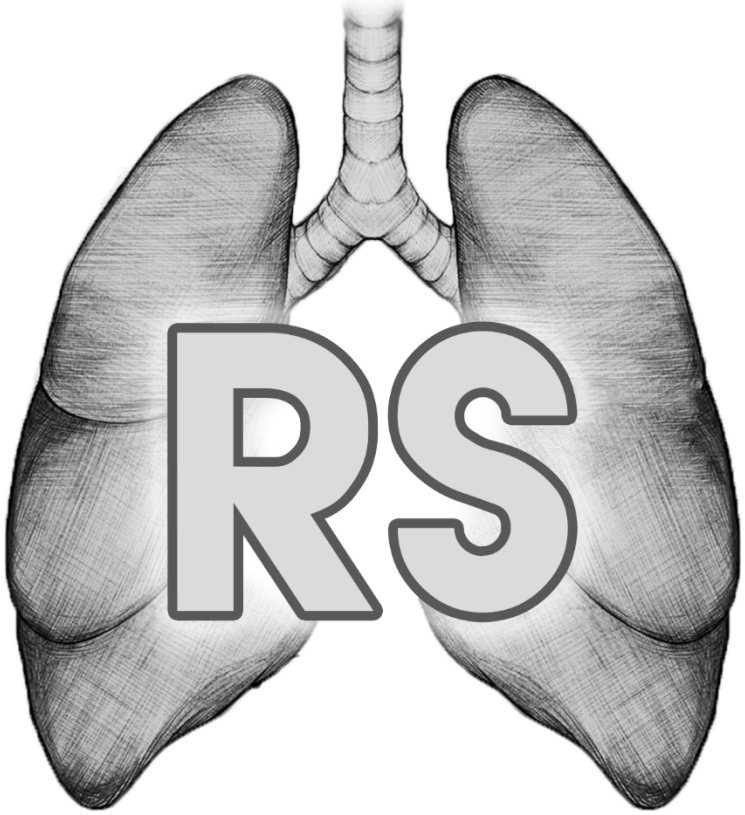

PATHOLOGY

✓ Sheet ○ Slide ○ Handout

Number

7

Subject

Granulomatous diseases and diffuse alveolar hemorrhagic syndromes

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Date: **00/00/2016**

Price:

Topics of the lecture:

- *Granulomatous lung diseases*
- *Diffuse alveolar hemorrhagic syndromes*

❖ **Introduction:**

- Remember that lung diseases are classified into **restrictive** and **obstructive** lung diseases.
- The restrictive diseases are caused by infiltration due to either **fibrosis** or **granulomas**.
- Granulomatous diseases are considered restrictive as they affect the interstitium of the lung thus affecting the compliance of the lung.

❖ Granulomatous lung diseases:

→ They include:

1. **TB.**
2. **Sarcoidosis.**
3. **Allergic pneumonitis.**

→ ***Firstly we will discuss granulomas in general :***

❖ Granulomas: *-in general-*

- To understand the pathogenesis of such diseases, we need to understand what are granulomas and how they are formed:
  - → Firstly, the granulomas are a type of **chronic** inflammation characterized by the accumulation of **macrophages** *–they are the main cells involved-* in addition to the presence of **lymphocytes** *-as a rim around the macrophages-* and rarely plasma cells. Some of the macrophages form giant cells.
  - → Granuloma does **NOT** always mean that there is central necrosis. The idea here is the accumulation of macrophages not the necrosis.
  - → **NOTE:** A multi-nucleated giant cell is formed when few macrophages are fused together and the cytoplasmic boundaries in-between are lost, so there is a huge cytoplasm with several nuclei.

- **The pathogenesis:**
  - → macrophages are activated by a certain antigen and they start to secret interleukins -- mainly **IL-12--** in order to stimulate T helper cells→T helper cells, when activated, will secret IFN-γ → further activation and attraction of the macrophages→macrophages will accumulate at the site of inflammation and the lymphocytes will form the rim around them→ so the ending result is a granulomatous lesion.
  - → Note that in granuloma the **bi-directional activation** plays an important role in its pathogenesis.

Agent>> macrophages>> IL-12>> T cells>> INF gamma…*

→ **The agent in the case of:**

- TB →tuberculosis bacilli
- Sacoidosis → unknown, it may be autoimmune or viral, it is not definitely known.
- Allergic pneumonitis→ more than one agent (could be hay, maple tree…).

- **Types of granuloma:**

- **Caseating granuloma** means a specific type of necrosis in the center of the granuloma that is characterized by presence of cheesy like material because we lost the cells completely even cell boundaries cannot be recognized. And it is seen **only** in TB granuloma.
- **Necrotizing granuloma** means there is center of necrosis which is **not caseating granuloma**. It is seen in rheumatoid arthritis where neutrophils are prominent and there is a beginning of coagulative necrosis.

NOTE: in coagulative necrosis the cell boundaries are still there with highly eosinophilic cytoplasm and loss of the nucleus.

- Non-caseating necrosis can occur in any type of granulomas→ **thus necrotizing granuloma does NOT necessarily mean caseating granuloma**. Although scientifically it is correct to say that caseating granuloma is a necrotizing granuloma but clinically it is not, so:

Once the pathologist report says that there is necrotizing granuloma it means that it is NOT TB and NOT caseating.*

The caseating granuloma occurs only in TB*.

- The mechanism of caseation of the granuloma:
  - → Hypoxia and free radical injury will result in the death of the cells thus necrosis.

1. Sarcoidosis داء الساركويد:

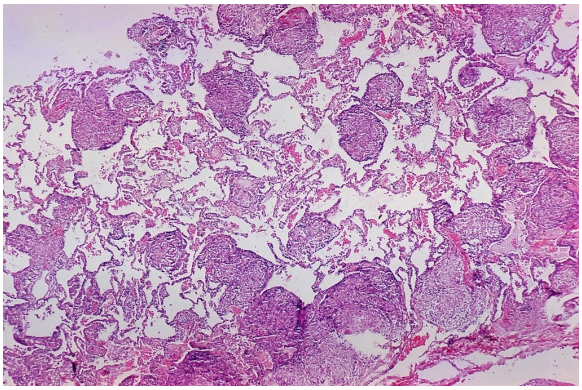
- Granulomatous disease that can affect any organ of the body **(multi-system disease)** of **unknown etiology**. Once it affects the lungs, it will cause restrictive lung disease.
- Affects young adults; younger than 40 years old.
- One of the rare diseases that affects the **non smokers**.
- Certain genetic factors related to sarcoidosis:
  - ► Higher risk in cases of familial clustering of sarcoidosis
  - ► Association with certain human leukocyte antigens (HLA) (class I HLA-A1 and HLA-B8).
- After lung transplantation, recurrence is seen in 75% of cases, which suggests that the patient has an underlying autoimmune or genetic predisposition.

Important Note: TB can cause non-caseating and caseating necrosis. The caseating necrosis is specific for TB.

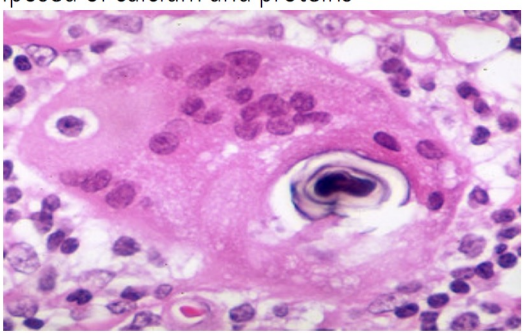
NOTE: macrophages can recognize two injurious agents:
- ► Infection via its toll-like receptors
- ► Cell injury products and crystals via inflammasomes.

➢ **Morphology:**

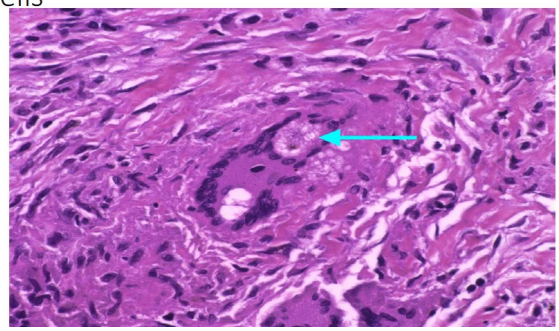
- What is seen in sacoidosis is a lot of granulomas.
- In sarcoidosis, some giant cells have cytoplasmic inclusions that look like stars, called **stellate inclusions** or **Asteroid bodies**.
- Also some calcification is seen within giant cells, forming what is known as **Shaumann bodies**.
- So to diagnose sarcoidosis we see:
  - → ***non-caseating granuloma with certain bodies -Asteroid and Shaumann-***
- However these are **NOT** diagnostic as they are not specific for sarcoidosis; they are seen in many other diseases:
  - → For example, Non-caseating granulomas are seen in many diseases other than sacoidosis, including: TB.
- Thus diagnosis of sacoidosis is **diagnosis by EXCLUSION:**
  - → You need to exclude ALL the other causes including TB, allergic pneumonitis, gout, any foreign body presence, cat scratch disease, leprosy, ……. *-the last two diseases cause skin granulomas not lung granulomas.*
  - → The exclusion depends on the **patient's history**, for example a patient whose job's settings can cause diseases then you have to exclude the occupational diseases -only- to be able to diagnose him/her with sarcoidosis *(not the whole list of diseases you need to look for, you have to be realistic).*



Shaumann bodies: laminated concretions composed of calcium and proteins



Asteroid bodies: stellate inclusion within giant cells



➢ Organ involvement in sarcoidosis:

- Sarcoidosis is a multi-systemic disease which means that a granuloma in any organ can be caused by sarcoidosis. It can affect any organ: lung, skin, kidney, liver, stomach, heart…
- However, **lung** is affected in 90% of the cases.
- **Lymph nodes:**
  - → Any lymph nodes can be involved.
  - → Intrathoracic hilar lymph nodes are affected in around 75% of the cases then Para-tracheal lymph nodes.
  - → The peripheral lymph nodes are also affected in one third of the patients.
  - → So sarcoidosis can cause **lymphadenopathy.**
  - → sarcoidosis is found in most cases incidentally by X-ray where you can see enlarged hilar lymph nodes So when hilar lymph nodes are enlarged the main differential diagnosis is sarcoidosis; however; we should look for other causes as well.

- **Lacrimal glands:**
  - → Are involved in 25% of the cases causing **dryness in the eyes** and blindness but very rarely.

- **Skin involvement**:
  - → appears as two types:

- ► **Erythema nodosum** *- red nodules on the skin -* : occurs in the legs in the **acute** stages of the disease and **no granuloma** is formed at this stage.
- ► **Subcutaneous nodules:** in chronic stages, containing non-caseating granuloma.

- **Hypercalcemia:**
  - → In around 10% of the cases.
  - → The macrophages have **alpha hydroxylase enzyme** that activates **vit.D** and this is believed to be the cause of hypercalcemia. *Some new studies say that there is PTH increments in some patients.*
  - → Calcification that is seen as Shaumann bodies in sarcoidosis may be due to hypercalcemia or the process of inflammation that forms the granuloma.
  - → **NOTE:** two types of calcification occur in the body; metastatic and dystrophic calcifications. Dystrophic calcification is related to necrosis. Hypercalcemia can cause calcification not the opposite.
- **Parotid gland** *-not mentioned during the lecture-*
  - ► Unilateral or bilateral parotitis with painful enlargement of the parotid glands
  - ► Some patients develop xerostomia (dry mouth).
  - ► Combined uveoparotid involvement is designated Mikulicz syndrome.

➢ Clinically:

- Most patients are **asymptomatic** but if there is severe destruction then symptoms of restrictive lung diseases will appear (i.e. cor pulmonale, cyanosis).
- The patient may come with symptoms related to the dryness of the eyes or parotid enlargement.
- **Clinical course is unpredictable:**
  - → some patients recover spontaneously
  - → Others recover after steroidal treatment.
  - → Some will develop permanent lung dysfunction or visual impairment.
  - → 10-15% ends up with pulmonary fibrosis and cor pulmonale.

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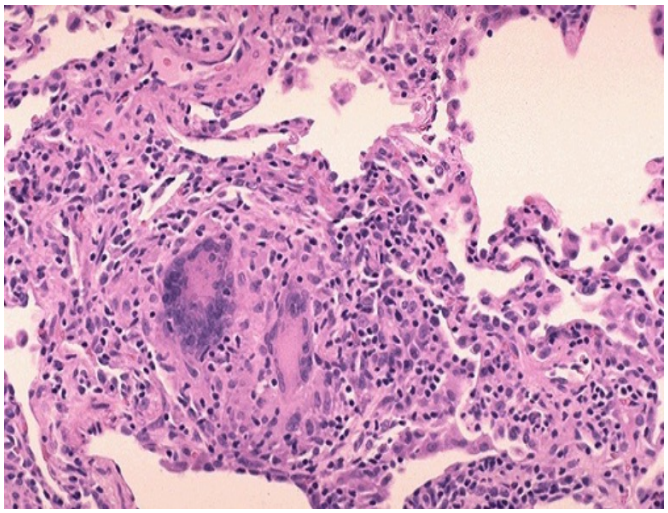
2. Hypersensitivity pneumonitis:

- ❖ Known also as **allergic alveolitis**. As this name implies there is allergic reaction in the alveoli.
- ❖ **NOTE:** In bronchial asthma, the proximal airways are affected but in allergic alveolitis the alveoli are the ones that are affected.
- ❖ It is type 4 hypersensitivity reaction (i.e. cell mediated reaction).
- ❖ Note that all granulomas involve type 4 hypersensitivity reactions (T cell mediated reactions).

- The pathogenesis is the same as all granulomas and the offending agent is usually from **occupational settings** and most commonly is **hay**. Thus farmers are frequently affected by this disease.
- hypersensitivity pneumonitis includes several syndromes. The main ones are:
  - Farmer's lung →by hay.
  - Maple bark disease→ by maples trees (شجر القيقب).
  - Pigeon breeder' Lung→by pigeon's droppings.
- **Chronic exposure** is required to develop these syndromes. *hence they are occupational diseases.*
- The morphology of the granuloma in this disease is the same as sarcoidosis.
- It is important to know the causes of the diseases as it is important in the treatment. For example occupational diseases are **reversible** in their acute stages. The patient is also advised to leave the job; however this is not a practical solution.

History is always important

- Occupational diseases are very common and in each job there is a specific disease that affects its workers, examples:
  - Anesthetists→ cervical spine diseases
  - Pathologist→a musculoskeletal disease characterized by severe pain and restricted movement in the thumb.



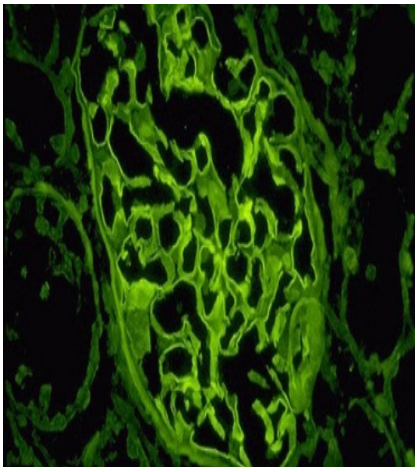
TB will be discussed in the next sheet.

❖ Diffuse alveolar hemorrhagic syndromes:

- Simply these are characterized by diffuse hemorrhage in the alveoli.
- The hemorrhage that occurs in the lung could be secondary to pulmonary hypertension, and bleeding disorders.
- There are also primary diseases that cause bleeding in the lungs and these are causes of death. They are very dangerous as the lungs are filled with blood so no breathing will take place.
- **NOTE:** they are even more dangerous than ARDS.
- Two syndromes will be discussed:

1- Goodpasture syndrome:

- A rare disease that affects the lungs and kidneys. It causes glomerulonephritis and hemorrhagic interstitial pneumonitis.
- It is caused by **auto-antibodies** against collagen type 4, forming immune complexes that accumulate in the lung causing hemorrhage and in the kidney causing glomerulonephritis.
- It is diagnosed by:
  - → presence of blood in the alveoli
  - → From kidney biopsy, immune complexes can be stained by immunofluorescence. And their appearance is characterized by **linearly deposited Igs that line the capillary walls** and this is **specific** for Goodpasture syndrome. *Shown in the right figure*



2- Idiopathic Pulmonary Hemosiderosis:

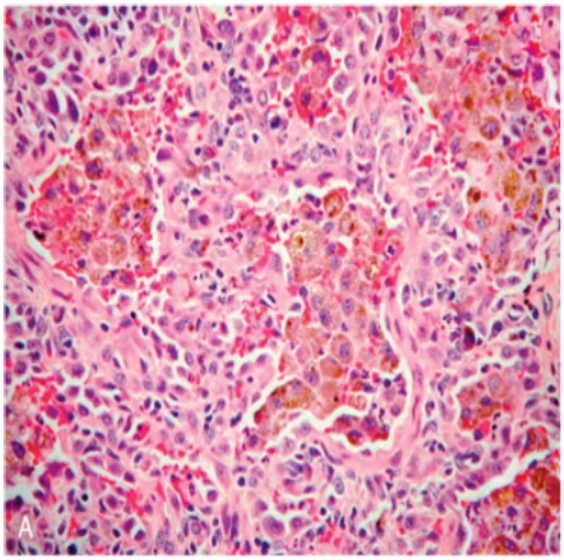
- The cause is not known.
- There is alveolar involvement like the goodpasture syndrome
- However; it differs from the previous syndrome by two things:
  - → **No kidney involvement.**
  - → **No auto-antibodies are found.**

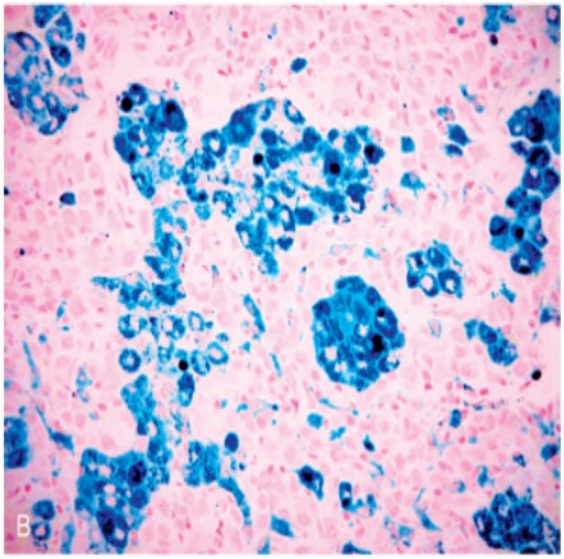
- These patients respond well to steroids and immune suppression suggesting that autoimmune mechanisms are involved but the antigen is not known yet.

- Macrophages appear blue when stained by **perl's stain -iron stain-.** This stain is used to show the hemosiderin that resulted from bleeding.

- *Why to stain hemosiderin:* the blood that diffused to the alveoli will be reabsorbed after a while by macrophages and its remnants will appear as hemosiderin which has a brown color. But brown pigments can appear for many reasons in the lung; it can be caused by melanin, lipofuscin or iron →thus we use perl's stain to make sure that this pigment is hemosiderin and caused by bleeding.

Diffuse alveolar hemorrhage syndrome –perl'sstain





Sorry for any mistakes,

Wish all best of luck~