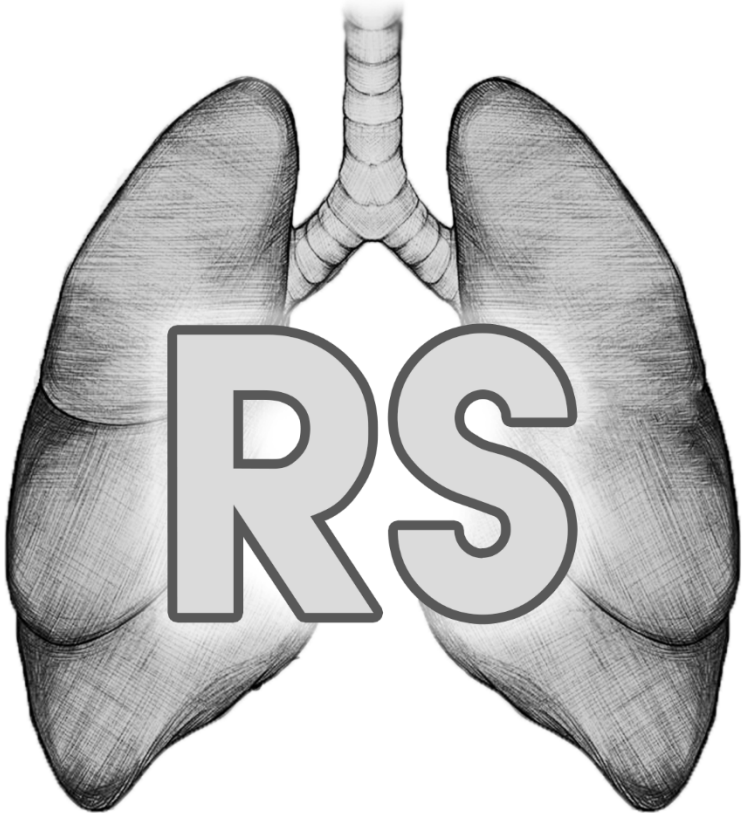

PATHOLOGY

✓Sheet ○Slide ○Handout

Number

5

Subject

Fibrosing Diseases

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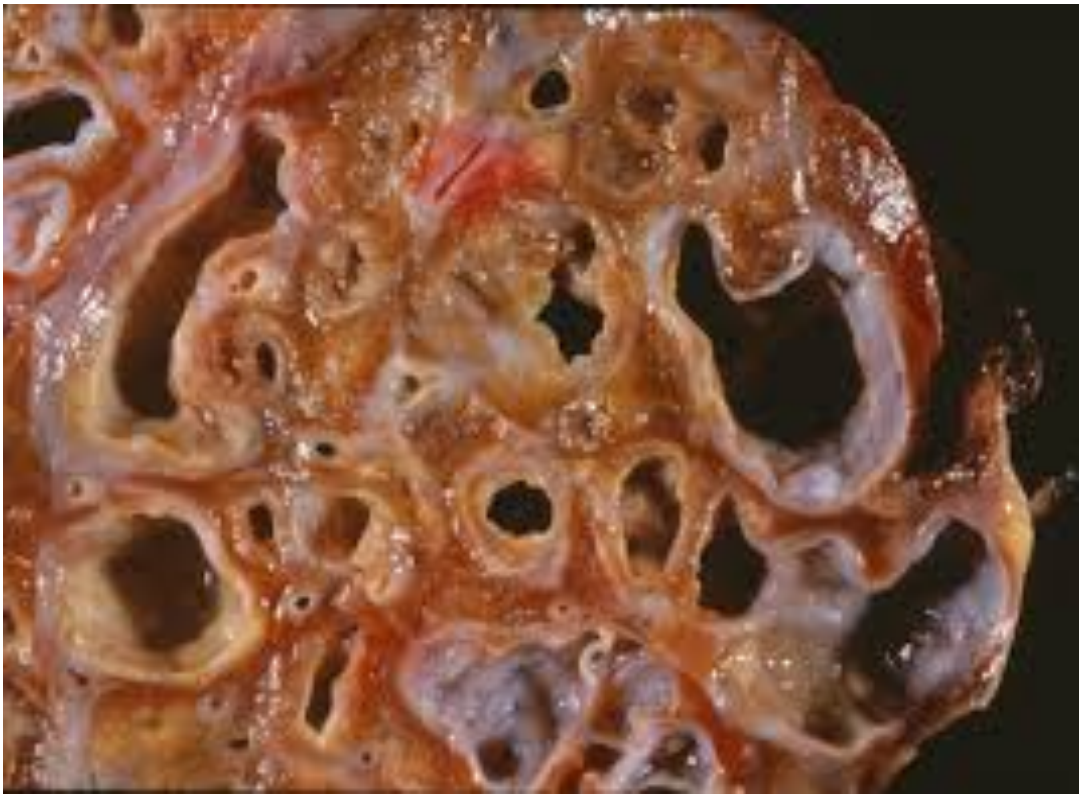
Date: **00/00/2016**

Price:

Note: Before starting with our lecture about Restrictive disease, Dr.Heyam spoke a bit about bronchiectasis and Bronchial asthma

❖ Bronchiectasis:

Bronchiectasis means the permanent dilation of the bronchi and bronchioles. The degree of dilation could be as much as 4 times their usual diameter. Bronchiectasis usually happens bilaterally affecting the lower lobes. If we did an autopsy (post-mortem examination) on a normal lung, we will not be able to follow the course of the bronchi very well because they get smaller and smaller as they branch out within the lung. However, in a bronchiectatic lung, we can follow the bronchi to the periphery of the lung (to the pleura), and we see white fibrosis in the walls of bronchi.



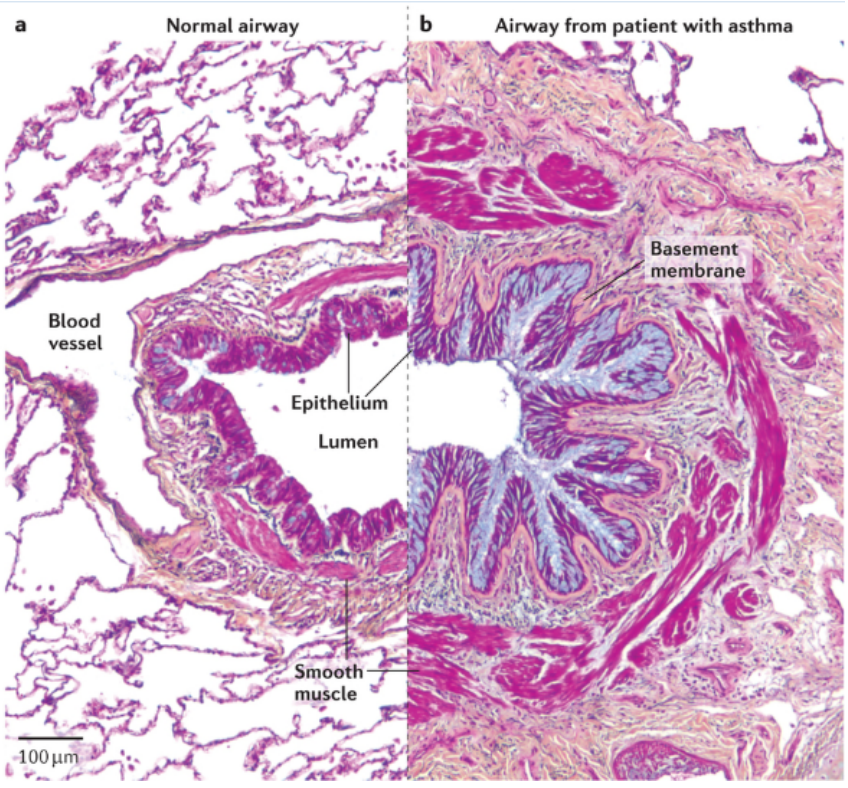
❖ Bronchial asthma:

Atopic asthma happens more in children, it is allergen-induced and patients with atopic asthma have a family history of allergic conditions.
Non-atopic asthma however, occurs at an older age and without a family history.

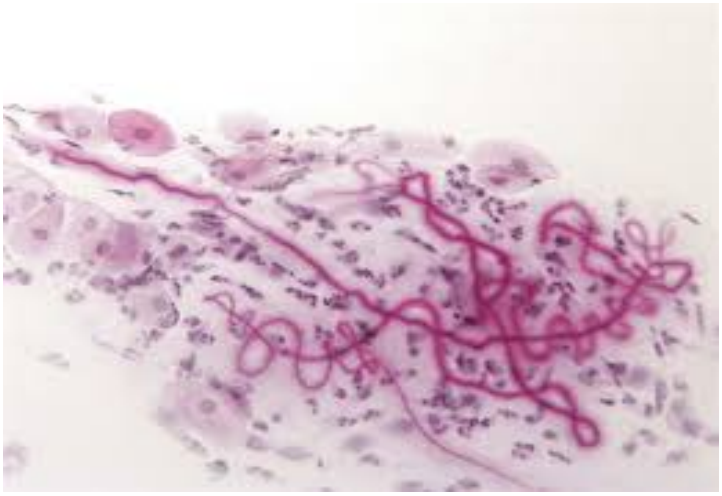
Asthma can also be occupational (related to certain fumes during one's occupation) and it can be drug-induced. The main drug that induced asthma is Aspirin because it increases lipo-oxygenase activity causing bronchoconstriction.

Asthma starts as reversible constriction. However, with each attack (inflammation) structural damage accumulates leading to permanent changes in the bronchus making the constriction irreversible. The presence of these changes is called "Airway Remodeling". Features of airway remodeling are:

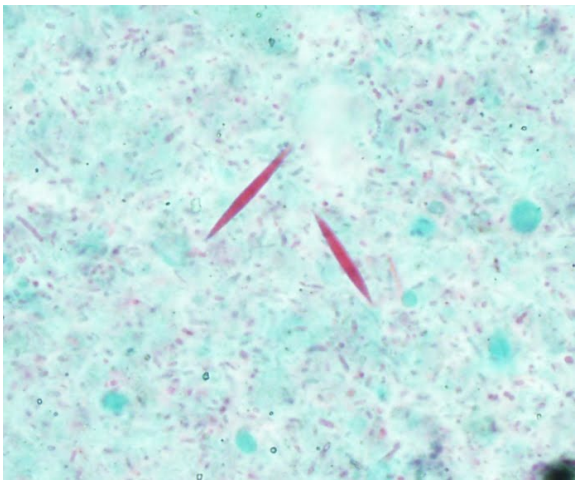
- An increase in the number of Goblet cells
- An abnormally high amount of mucus due to the increased amount of IL-13.
- Increased vascularity in the submucosa.
- Muscle hypertrophy.
- Sub-basement membrane fibrosis.



In the sputum we'll be able to see Curschman's Spirals (Whorls of shed epithelium which the mucus has wrapped around)



we'll also see Charcot-Layden crystals (Crystallized proteins released by Eosinophils)



The main inflammatory cell here is the eosinophil of course, which appears red.

- Now let's start talking about **restrictive lung diseases**

Restrictive lung diseases are characterized by decreased compliance in the lung or the chest wall. Compliance is a measure of the change in volume relative to the change in pressure. So the higher the compliance of the lung the easier its inflation. When compliance decreases, inflation of the lung becomes harder and the forced vital capacity (maximum amount of air that can be expired) also

decreases ,however, the FEV1/FVC ratio remains normal because both the FEV1 and FVC decrease.

Two examples of restrictive lung diseases that we already took are ARDS and neonatal RDS. Those two diseases are acute diseases, today we're more concerned about Chronic Restrictive lung diseases.

Suppose you got a patient and the evidence pointed to restrictive disease (he has a dry cough and dyspnea and his FVC was decreased), what do you do?

- ✓ The first thing you should make sure if that the problem is actually in the lung. This is because the problem might actually be in the chest wall not the lung. Here are some examples that we should know:
  1-Obesity. If the patient was 250 Kg, then it's safe to assume that the cause of the restrictive disease is the obesity itself.

2- Guillain-Barre syndrome. It's an autoimmune disease that affects the peripheral nervous system causing muscle weakness. So if the nerves supplying the breathing muscles are affected, then inspiration would be a lot harder.

3- Mesothelioma. This is a diffuse tumor in the pleura causing it to be stiffer, so even if the lung within the pleura is healthy, the tough pleura would cause restrictive lung disease.

After we've excluded that it might be a problem in the chest wall, we're now sure that it's actually a lung problem. How do lung problems cause restrictive lung disease?

As we said, restrictive lung diseases is when we have decreased compliance, so inflating the alveoli with air becomes a lot harder in restrictive diseases .In a healthy lung , the interstitium is soft and delicate so expanding it is easy . However if the interstitium was invaded by *fibrosis* or *granulomas* then expansion of the alveoli (and the lung) becomes a lot harder. In this lecture, we are concerned with fibrosis not granulomas. Fibrosing diseases are a heterogeneous entity (different etiologies) that have very similar symptoms and different treatments.

- ✓ The next step is to know whether the problem started in the lung (primary) or if there is another disease or factor in the body that caused the lung to have problems (secondary). We have to know this if we want to give the most effective treatment. If it were a primary lung disease then we do not know the cause, all we know is, is that the lung suddenly started having a certain problem, this limits our options of treatment a lot. Whereas if we knew that the cause started somewhere else in the body then we can just fix this problem.

Examples of <u>secondary fibrosing lung diseases</u> that we have to exclude are:

1) It might be an autoimmune disease like Systemic Lupus Erythematous (SLE). This disease affects many body parts and may lead to fibrosis in the lung.
2) Scleroderma. This disease starts as sclerosis in the skin but it might affect other organs like the esophagus or the lung.
3) It might be occupation-related like asbestosis and silicosis.
4) Smoking. Smoking alone is enough to elicit inflammation in the lung and cause fibrosis.
   When we took emphysema, we said that some people may not get any lung diseases, while some may get emphysema and COPD (both obstructive) and some smoker may get fibrosis (restrictive). This depends on many factors like polymorphisms and the responsiveness of the fibroblasts to the toxins in smoke.
5) The fibrosis may come as a consequent of the treatment. Radiotherapy can cause lung fibrosis and so can Bleomycin (chemotherapeutic drug) and Amiodarone (antiarrythmic drug).

   If the disease is not due to any of the above causes, this means that it is a primary fibrosing disease. We'll be taking 3 diseases today, and all of them have the same clinical presentation. Dyspnea, dry cough and if the disease is in advances stage the patient will be very hypoxic and cyanosed.

Idiopathic Pulmonary Fibrosis (aka Cryptogenic Fibrosing Alveolitis)

Cryptogenic and idiopathic both mean the same thing. They mean that the etiology of the disease is unknown. This makes this disease a disease of exclusion. That's why we spoke a lot about all the diseases that we have to exclude before reaching the conclusion that this patient may have this disease.

This disease is very bad news. If you tell a patient that he has IPF, you are essentially telling him that unless he gets a lung transplant (which is very complicated), he's going to die in three years.

Of the three lung diseases we'll be discussing, this is the only one that doesn't respond to treatment. The treatment for the other 2 is Oral Steroids for 6 months. If we concluded that the patient has IPF, we give him oral steroids anyway hoping that we might have misdiagnosed the patient.

IPF affects males more and patients are usually old (above 65 y.o) when they get the disease.
They present with a dry cough and depending on the stage of the disease, become very hypoxemic and cyanotic. Again, even with treatment they die within 3 years.

Pathogenesis of IPF:

What we know for sure is that a certain unknown trigger causes fibrosis. Fibrosis happens after repair which itself happens after injury. The injury in this case is to Pneumocytes. Normally after injury we get a minimal amount of fibrosis. However, in IPF we have exaggerated fibrosis (a lot of bands). Since the most important factor for fibrosis is TGF-β and the most important cell for activating fibrosis is the M2 macrophage (you may remember it from the alternative pathway), we assume that patients with IPF have problems with TGF-β and M2 macrophages. TGF-β also inhibits an anti-fibrosis protein called Caveolin, making the fibrosis even worse.

As doctors worked and wondered about the cause of the disease, they got a clue. They noticed that some people have an inherited susceptibility for the disease. This led to a theory. The theory is that the "unknown trigger", we spoke about, can shorten telomeres. When telomeres get short enough, the pneumocyte goes into senescence and then apoptosis. This theory is also supported by the fact that TGF-β causes telomeres to shorten. So IPF may actually be a cycle. Short telomeres cause apoptosis (which is technically damage) which causes repair and fibrosis and the TGF-β required for the fibrosis causes more telomere shortening. This theory fits with the Morphology of the disease.

Morphology of IPF:

The histological and radiological pattern in IPF is called Usual Interstitial Pneumonia. We see patchy fibrosis within the interstitium and we see various stages of fibrosis. We see both early fibrotic lesions, which contain a lot of fibroblasts, and late fibrotic lesions which contain a lot of collagen fibers without any fibroblasts. The presence of both stages means that it's a continuous process(insidious) .IPF is the only disease (of the three we're talking about in this lecture) which we see both stages of fibrosis together in.

Non-specific interstitial fibrosis:

It's also not a well understood disease, we don't know the etiology for this disease either. However the main things here are:
1) That patients improve when given oral steroids for 6 months
2) Under the microscope we will only see one stage of fibrosis, not both. The lesions will be either all cellular (early) or all fibrotic (late).

Cryptogenic Organizing pneumonia aka Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

Cryptogenic means unknown etiology
Organizing means that we also have fibrosis in this disease
The word pneumonia isn't really in its place here. There is no infection in this disease.

BOOP has a very specific feature under the microscope: we see polypoid plugs of loose organizing connective tissue within the alveolar ducts, alveoli ad often bronchioles.

BOOP patients also improve with steroids and also here we only see one stage of fibrosis (very similar to non-specific interstitial fibrosis).

Differentiating between these 3 lung diseases is very hard when doing a biopsy. Sometimes pathologists only write "Fibrosis in the lung". But why?
Although we said that the different diseases have certain characteristic features (2 stages in IPF, and the polypoid plugs in BOOP), the chance of taking a biopsy from an area which contains one of the characteristic features is low.
For example, if you saw 2 stages of fibrosis then it's IPF for sure, but it can also be IPF if we only saw one stage, meaning that the whole lung does contain both stages simultaneously but the little piece that biopsied does not.