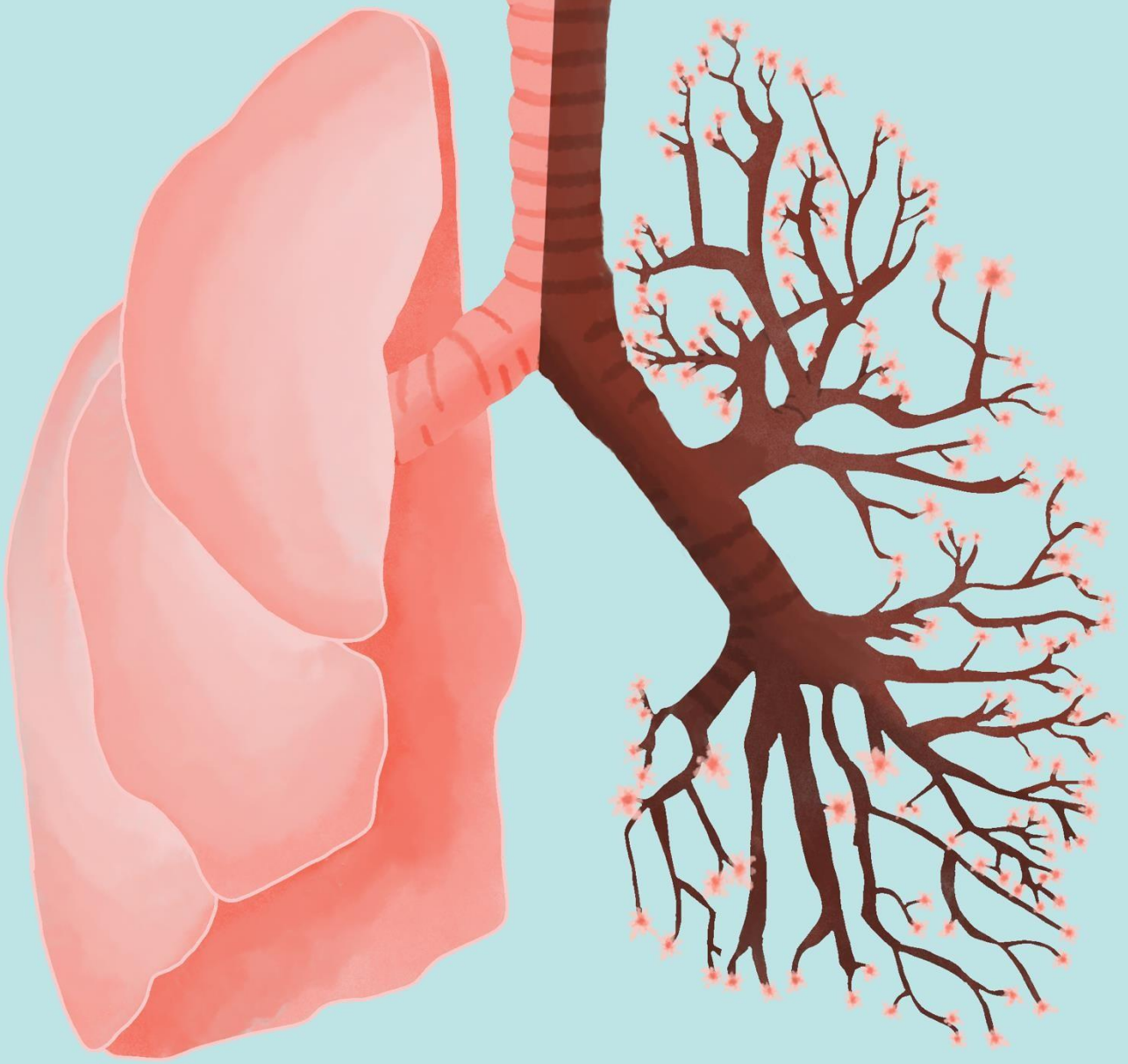
RESPIRATORY SYSTEM
PATHOLOGY



Title: ASTHMA & BRONCHIECTASIS — 3

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Asthma

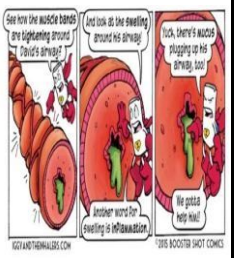
Asthma is a chronic inflammatory disorder of the airways that causes recurrent episodes of **wheezing, dyspnea (shortness of breath), chest tightness and cough**, especially at night and/or early in the morning. Its **hallmarks** are:

1. **Intermittent** (not continuous) and **reversible** (not permanent) airway obstruction [bronchospasm].
2. Chronic bronchial inflammation with **eosinophil** infiltration.
3. Bronchial smooth muscle cell **hypertrophy and hyper-reactivity.**
4. Increased **mucus secretion**.

Major Factors contributing to development of asthma are:

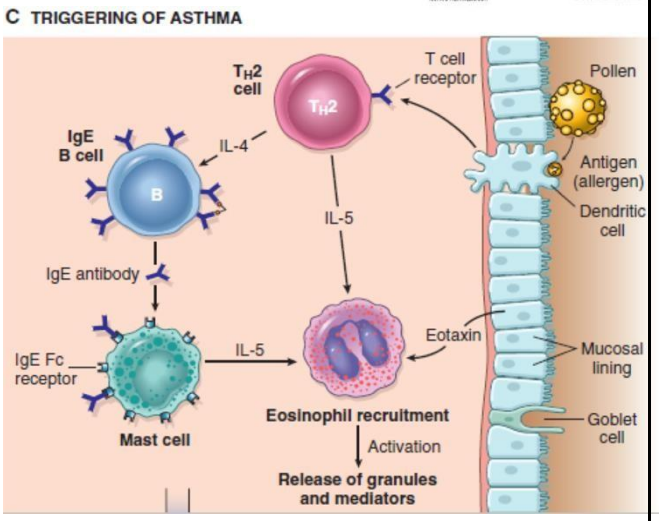
1) Genetic predisposition to type 1 hypersensitivity [atopy].
2) Acute and chronic airway inflammation.
3) Bronchial hyper-responsiveness to a variety of stimuli.

Asthma can be **triggered** by exposure to different stimuli such as:



- Respiratory infections (especially viral ones).
- Airborne irritants such as smoke and fumes.
- Cold air, stress and exercise.

Pathogenesis: This figure shows the initial airway response after exposure to one of the inhaled allergens for the first time. The allergen (antigen) will be recognised by antigen presenting cells (APCs) or dendritic cells in the epithelial lining, resulting in the activation of T helper lymphocytes which start releasing inflammatory mediators. This will lead to the production of IgE as well as recruitment and activation of eosinophils. Examples on mediators and their functions:

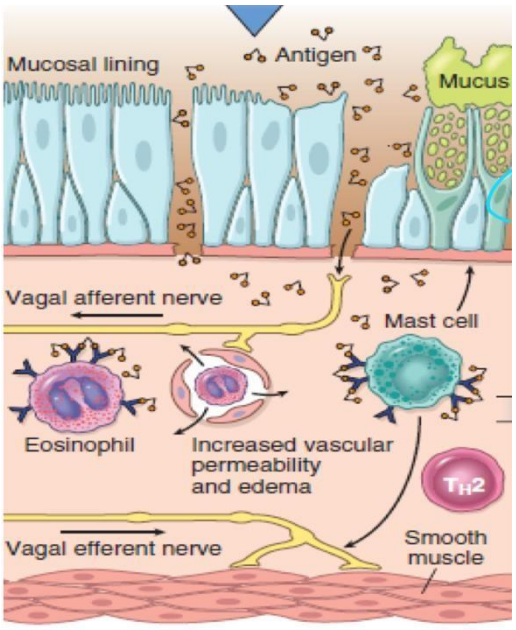


- ❖ IL-4 &IL-13 : Stimulate IgE production.
- ❖ IL-5 : Activation of eosinophils.

❖ IL-13 : Stimulates mucus production.
Now the IgE coats the submucosal mast cells. In case of **re-exposure** to the same allergen, two waves/phases of reactions happen as following:

I. The early-phase reaction, which is dominated by: (immediate phase)

a. **Bronchoconstriction** is triggered by mediators released by mast cells including: histamine, prostaglandins D2, leukotrienes [C4, D4 & E4] and by reflex neural pathways.
b. **Increased mucus production**.
c. **Vasodilation.**

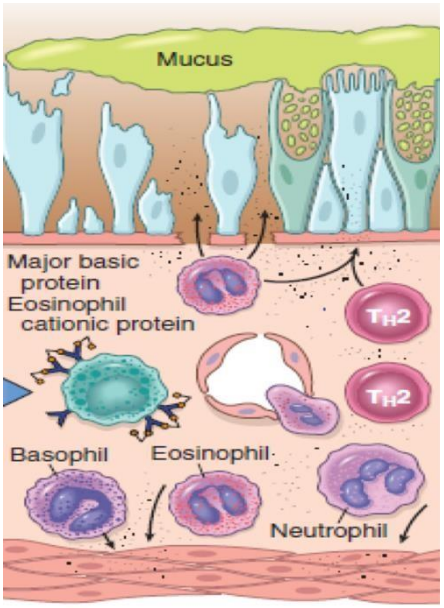


D IMMEDIATE PHASE (MINUTES)

This figure highlights the immediate reaction upon re-exposure to the antigen (this is triggered by Ag-induced cross-linking of IgE bound to Fc receptors on mast cells). Mast cells release previously preformed mediators that directly and via neural reflexes **induce**: bronchospasm, increased vascular permeability, mucus production and recruitment of leukocytes.

II. The late-phase reaction, which is inflammatory in its nature:

Inflammatory mediators stimulate epithelial cells to produce chemokines [eotaxin: Potent chemo-attractant and activator for eosinophils]. This leads to recruitment of T-helper type 2(TH2) lymphocytes, eosinophils and other leukocytes, resulting in the amplification of the inflammatory reaction.



E LATE PHASE (HOURS)

This figure shows leukocytes recruited to the site of reaction including neutrophils, eosinophils, basophils, lymphocytes and monocytes, which all will initiate the late phase reaction. Eosinophils release *major basic proteins* and *eosinophil cationic proteins* that cause damage to the epithelium.

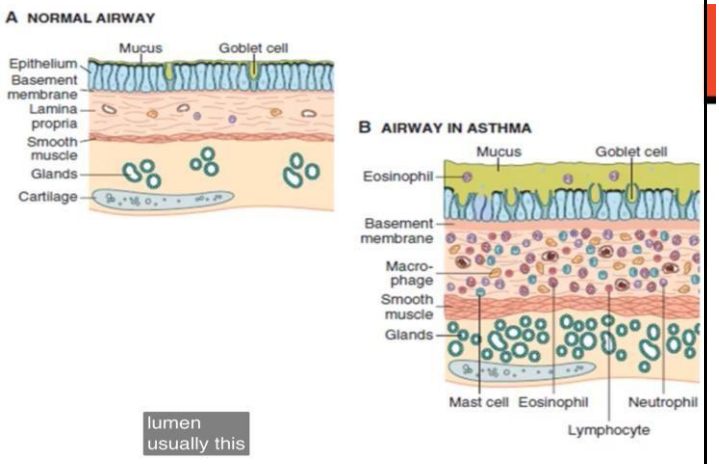
- **Airway Remodeling:** Structural changes in the bronchial wall due to *repeated bouts of inflammation*. These changes include:

a. Thickening of airway wall.
b. Sub-basement membrane fibrosis (Deposition of subepithelial collagen).
c. Hypertrophy and/or hyperplasia of bronchial smooth muscle.

d. An increase in size of the submucosal glands and goblet cell metaplasia of the airway epithelium (hypertrophy of mucus glands) .
e. Increased sub-mucosal vascularity.
f. Metaplasia of the airway epithelium.
g. Distension of lungs **in fatal cases**, caused by trapped air with small areas of atelectasis.

The figures to the right show comparisons between asthmatic and normal people's airways:

Asthmatic airways are marked by:



- **Increased number of mucus secreting goblet cells** in the mucosa.
- **Hypertrophy of submucosal glands**.
- **Accumulation of mucus in the bronchial lumen** (notice the green layer of mucus overlying the surface epithelium in pic B) which is secondary to previously mentioned points.
- **Thickened basement membrane** (beneath the epithelium)
- **Intense chronic inflammation** composed of eosinophils, macrophages and other inflammatory cells).
- **Hypertrophy and hyperplasia of smooth muscles (along with submucosal glands)**.

Types of asthma

1. **Atopic asthma:** Is the most common type. It is a classic example of *type 1 IgE mediated hypersensitivity reaction* (don't forget the mechanism of action mentioned in the previous page). It begins in childhood and a positive family history of atopy and/or asthma is **common**. The attacks are preceded by allergic rhinitis, urticaria (extra: A rash of red whelts on the skin that itch intensely sometimes with dangerous swelling), or eczema. They are triggered by allergens in dust pollen, animal dander (material shed from animal feather or fur), food or by infections.

   There are two tests used to confirm asthma:

   a. **Skin test with allergen (antigen): Immediate wheel and flare reaction.**The skin break test is the **most common** allergy skin **test done**. How is it performed? Tiny drops of the allergen are put on the back→ then a needle is

used to break the skin underneath each drop. Now, in case someone is **allergic**, a red, itchy rash will appear especially at the site of the needle break.

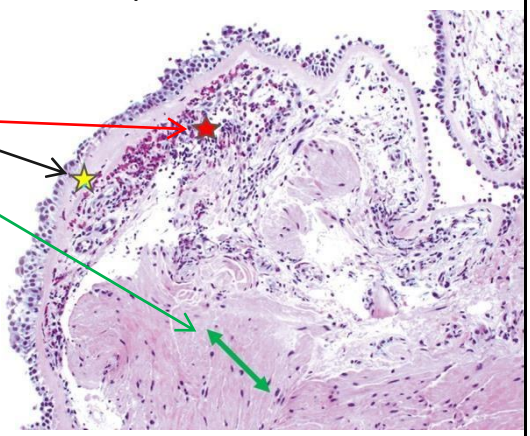
b. **Serum radioallergosorbent tests (RSTs):** A blood test that uses radioimmunoassay to detect specific IgE antibodies which helps determine the substances a subject is allergic to.

2. **Non-atopic asthma:** it shows no evidence of allergen sensitisation, so the skin test is negative. It is **less common** to have a positive family history of asthma, and it is triggered most commonly by: viral infections [rhinovirus and parainfluenza virus] and inhaled air pollutants [sulfur dioxide, ozone and nitrogen dioxide]. Although connections between exposures and non-atopic asthma are not well understood, the ultimate humoral and cellular mediators of airway obstruction are the same for both atopic and non-atopic variants of asthma, thus both are treated in a similar way.

3. **Drug-induced asthma:** Several drugs can provoke asthmatic attacks, however, **aspirin** is considered the most striking example→ Patients present with recurrent rhinitis, nasal polyps, urticaria and bronchospasm. The precise pathogenesis is unknown, but it is likely to involve some abnormality in prostaglandin metabolism from inhibition of cyclooxygenase by aspirin.
{10:0}
4. **Occupational asthma:** This type is triggered by fumes [epoxy resin & plastics] organic and chemical dust [wood, cotton & platinum], gases [toluene] and other chemicals. The attacks usually develop after repeated exposure to the causative antigen. This occurs in: farmers, animal handlers, mattress manufacturers, bakers, food processors, cotton workers & manufacturers of metals.

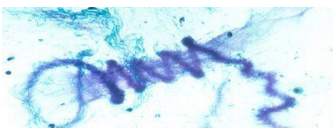
Morphology

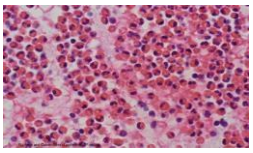
This image shows a bronchial biopsy specimen from an asthmatic patient:



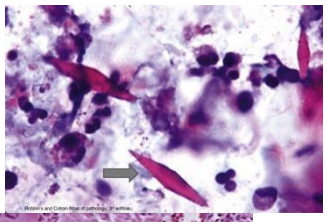
1. Sub-basement membrane fibrosis
2. Eosinophilic inflammation
3. Smooth muscle hyperplasia and hypertrophy

- The most striking finding in asthmatic patients is occlusion of bronchi and bronchioles by thick **mucus plugs**. These plugs contain whorls of shed epithelium called **Curschmann Spirals** found in sputum→

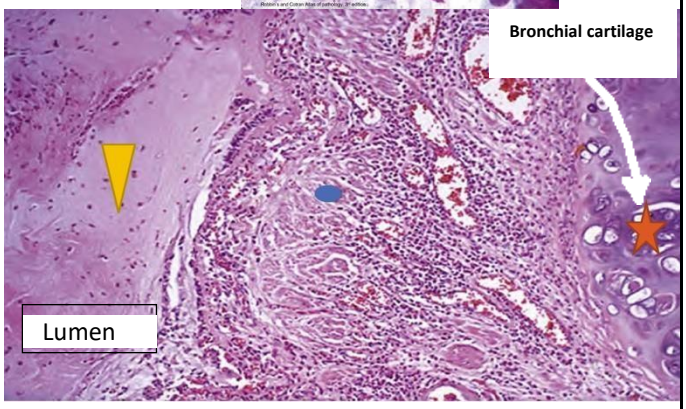




- **Eosinophils** are the characteristic inflammatory cells in asthma→
- **Charcot-Leyden crystals**: Crystalloids made up of the eosinophilic protein **Galectin-10.**
- **Also, don't forget remodeling characteristics mentioned before.**



The image aside shows predominantly expanded **submucosa** (the submucosa lies between the bronchial cartilage [orange star] and the lumen that is stuffed with mucus [the yellow triangle]). It is widened by smooth muscle hypertrophy, edema and inflammatory cells (mainly eosinophils).



Clinical features

1. **Coughing**: Becomes worse at night and early morning.
2. **Wheezing:** Whistling sound especially during expiration. Sometimes it can be heard even without a stethoscope.
3. **Chest tightness:** It feels like something is squeezing or sitting on the chest
4. **Dyspnea** [shortness of breath/inability to breathe properly]

Notes: Asthma is associated mainly with difficulty in expiration. Each asthmatic attack may last from one hour to several hours and goes away either spontaneously or with therapy. The interval between attacks is free from respiratory difficulties. Asthma is reversible except for advanced severe cases.

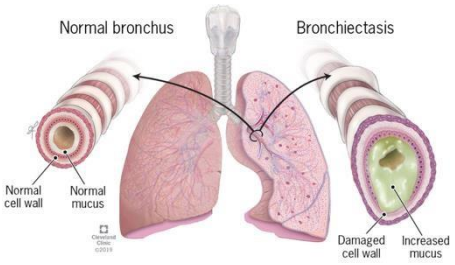
- **Status asthmaticus :** A severe paroxysm that does not respond to therapy and persists for days or weeks. It is associated with **hypercapnia** (increased carbon dioxide in the bloodstream), **acidosis** and severe **hypoxia** which could be fatal.

Management: Standard therapies include :

1. **Anti-inflammatory drugs** [such as glucocorticoids]
2. **Bronchodilators** [such as beta-adrenergic drugs]
3. **Leukotriene inhibitors:** as leukotrienes are potent bronchoconstrictors.
4. Agents that **block specific immune mediators**, such as IL-4 & IL-5, are of modest benefit in some patients but are not broadly efficacious.

Bronchiectasis

- ✓ **Permanent** (irreversible) dilation of **bronchi** and **bronchioles** caused by destruction of smooth muscle and supporting elastic tissue [remember emphysema is permanent dilation of the airways ***distal*** to the terminal bronchioles].
- ✓ It is typically associated with or results from chronic necrotizing infections. Bronchiectasis is not a primary disorder as it always occurs **secondary** to persistent infections or obstructions.



- ✓ It is diagnosed with appropriate **history and radiograph** demonstration of bronchial dilation.
- ✓ Cough and expectoration of copious amounts of purulent sputum

The conditions that most commonly predispose to bronchiectasis include (primary predisposing causes):

1. **Bronchial obstruction:** Caused by tumors, foreign bodies and impaction of mucus (localized to the obstructed lung segment) **or** as a complication of atopic asthma and chronic bronchitis.

2. **Congenital or hereditary conditions :**

A. **Cystic fibrosis:** Affects the lungs and digestive system. In this condition, the body produces thick and sticky mucus that may block the lung and pancreas. The obstruction caused by abnormally viscid mucus and secondary infections cause widespread severe bronchiectasis.

B. **Immunodeficiency states:** The bronchiectasis may be localized or diffused due to recurrent bacterial infections.

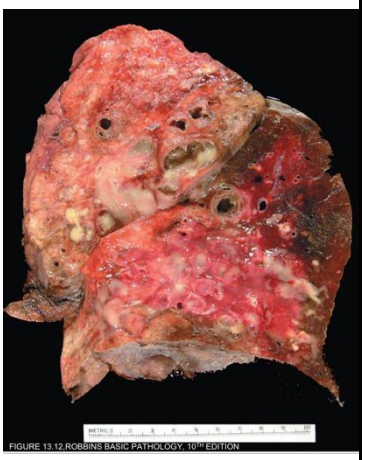
C. **Primary ciliary dyskinesia (immotile cilia syndrome):** It is a rare autosomal recessive disorder caused by inherited abnormalities of cilia that impair the mucociliary clearance of the airway, leading to persistent infections. It is associated with bronchiectasis and sterility in males.

3. **Necrotizing or suppurative pneumonia :** Particularly with virulent organisms such as Staphylococcus aureus or Klebsiella species.

Pathogenesis: Two intertwined processes contribute to bronchiectasis:

1) **Obstruction:** Impairs the clearance of secretions, providing a favorable environment for superimposed infection. This causes inflammatory damage to the bronchial wall and accumulation of exudate, which further distend the airways leading to irreversible dilation.
2) **Persistent necrotizing infection** in the bronchi or bronchioles may lead to poor clearance of secretions. The accumulation of secretions results in obstruction and inflammation associated with peribronchial fibrosis and traction on the bronchi, which also leads to irreversible dilation.

Morphology



- **Macroscopic findings :** Bronchiectasis affects the lower lobes bilaterally, particularly the vertical air passages. It is most severely involved in distal bronchi and bronchioles. The airways may be dilated as much as four times the usual diameter.
  This image shows a gross appearance of a lung of a cystic fibrosis patient with bronchiectasis who had lung resection for transplantation. The bronchi are markedly dilated and filled with purulent mucus.

- **Microscopic findings :** The histologic findings vary according to activity and chronicity of the disease. In full-blown active cases, there is an intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles due to severe inflammation. The **lining epithelium desquamate** and causes **extensive ulceration**. Typically mixed flora is cultured from the sputum including: **staphylococcus, streptococcus, pneumococcus, enteric organizers and aerobic bacteria.**

When healing occurs:

- **The lining epithelium may regenerate completely however the injury cannot be fully reversed.**
- **Abnormal dilation and scarring.**
- **Chronic cases may involve fibrosis of bronchial and bronchiolar walls as well as peribronchiolar fibrosis.**
- **In some cases necrosis destroys the bronchial and bronchiolar walls producing an abscess cavity.**

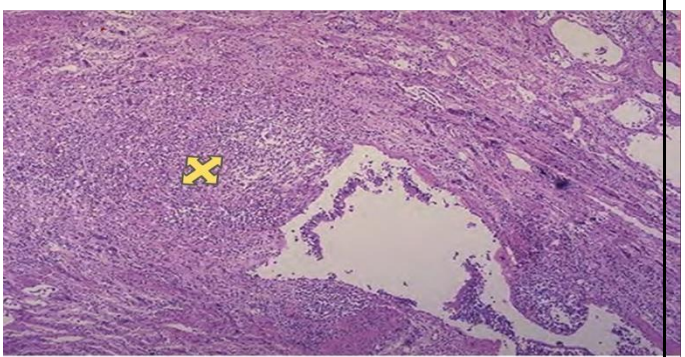


Figure 5-34 **Bronchiectasis, microscopic** dilated bronchus in which the mucosa and bronchial wall are not seen clearly because of the necrotizing inflammation with tissue destruction.
Robbin's and Cotran Atlas of pathology, 3rd edition

This image shows bronchiectasis. Necrotizing

inflammation in the center has dilated the bronchus to the degree that you cannot see the mucosal lining because it is mostly desquamated.

Clinical features

1. **Severe persistent cough and expectoration with mucopurulent sputum** (which is typically yellow or green in color) and contains: WBCs, cellular debris, dead tissue and mucus. Copious amounts of purulent sputum can also be seen in cases of lung abscess. Other symptoms include: dyspnea, rhinosinusitis, and hemoptysis.
2. **Symptoms are usually episodic and precipitated by upper respiratory tract infections URTI.**
3. **Severe widespread bronchiectasis presents with significant ventilatory defects.** This can be associated with **hypoxemia, hypercapnia, pulmonary hypertension and cor pulmonale.** However, with current treatment, outcomes have been improved and severe complications such as brain abscesses and cor pulmonale have become less frequent.

The following table summarizes the main features of chronic obstructive pulmonary diseases [important, the doctor compared between diseases' features, you can refer to the video as a revision]

Table 13.1 Disorders Associated With Airflow Obstruction: The Spectrum of Chronic Obstructive Pulmonary Disease

Clinical Entity	Anatomic Site	Major Pathologic Changes	Etiology	Signs/Symptoms
Chronic bronchitis	Bronchus	Mucous gland hypertrophy and hyperplasia, hypersecretion	Tobacco smoke, air pollutants	Cough, sputum production
Bronchiectasis	Bronchus	Airway dilation and scarring	Persistent or severe infections	Cough, purulent sputum, fever
Asthma	Bronchus	Smooth muscle hypertrophy and hyperplasia, excessive mucus, inflammation	Immunologic or undefined causes	Episodic wheezing, cough, dyspnea
Emphysema	Acinus	Air space enlargement, wall destruction	Tobacco smoke	Dyspnea
Small airway disease, bronchiolitis*	Bronchiole	Inflammatory scarring, partial obliteration of bronchioles	Tobacco smoke, air pollutants	Cough, dyspnea

*Can be present in all forms of obstructive lung disease or by itself.

✓ Clinical case

A 45-year-old gentleman smoked two packs of cigarettes per day for 20 yrs. For the past 4 years, he has had a chronic cough with copious mucoid expectoration. During the past year, he has had multiple respiratory tract infections. He has also developed difficulty breathing, tightness of the chest, and audible wheezing. His breathing difficulty is relieved by inhalation of a β-adrenergic agonist and disappears after the chest infection has resolved. Which of the following pathologic conditions is most likely responsible for his clinical condition?

A) α1-Antitrypsin deficiency with panlobular emphysema

B) Centrilobular emphysema with cor pulmonale

C) Chronic asthmatic bronchitis

D) Cystic fibrosis with bronchiectasis

"ليس الخير أن يكثر مالك وولدك، ولكن الخير أن يعظم حلمك ويكثر علمك "

- علي بن أبي طالب رضي الله عنه