Lecture One

COPD Part 1

Pathology and pathogenesis of ***Bronchial Asthma***

432 ***Pathology*** *Team*

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Respiratory Block

NOTE: female-side notes are written in purple.

Pathology and pathogenesis of: Bronchial Asthma

Lecture Objectives:

At the end of this lecture the student should be capable of:

- *Understanding asthma an episodic, reversible bronchoconstriction caused by increased responsiveness of the trachea bronchial tree to various stimuli.*
- *Knowing that asthma is divided into two basic types: extrinsic or atopic allergic and intrinsic asthma.*
- *Understanding the morphological changes seen in cases of severe asthma.*

Introduction to respiratory diseases

The respiratory system is one of the body's most susceptible systems to diseases, and these disease range from mild, to moderate and even severe fatal diseases.

Clinical presentation:

The patient complaining about his respiratory system usually presents with two main symptoms:

1- **Cough:**
   a. Productive cough → with sputum
   b. Dry cough → with**out** sputum

2- **Dyspnea:**

Dyspnea is the difficulty in breathing, it can be caused by:

   a. Cardiac problem
   b. Respiratory problem

NOTE: There are other symptoms which are specific for each respiratory disease; we will come on them later on.

Categories of respiratory diseases:

When the physician decides that his patient is suffering from a respiratory disease, he has to put him under one of these categories depending on his **signs**, **symptoms** and **laboratory** investigation:

1- **Obstructive diseases** (causes obstruction to the air flow)**.**
2- **Restrictive diseases** (lung cannot expand).
3- **Infectious diseases** (inflammatory diseases).
4- **Tumors.**
5- **Congenital anomalies.**

Obstructive diseases

A- Bronchial asthma

Inflammation of airways → TYPE I hypersensitivity

Asthma is an **inflammatory chronic obstructive pulmonary disease** characterized by **intermittent**, **episodic** and **reversible** bronchospasm, due to increased sensitivity to various stimuli:

1- **Reversible:** Can be cured with bronchodilators and corticosteroids.
2- **Intermittent** ...يظهر ثم يختفي ثم يظهر ثم يختفي وهكذا
3- **Episodic**: يأتي على شكل نوبات وليس بشكل دائم مستم 24 ساعة
4- **Bronchospasm**: spasm of the bronchial smooth muscles causes an obstruction to the air flow, thus asthma is categorized as an **Obstructive Lung Disease.**

REMEMBER:

1-The parts affected by the spasm are the smooth muscles.
2-Asthma primarily targets the bronchi and terminal bronchioles.

Types of bronchial asthma:

There are many types of asthma, but the most common ones are:

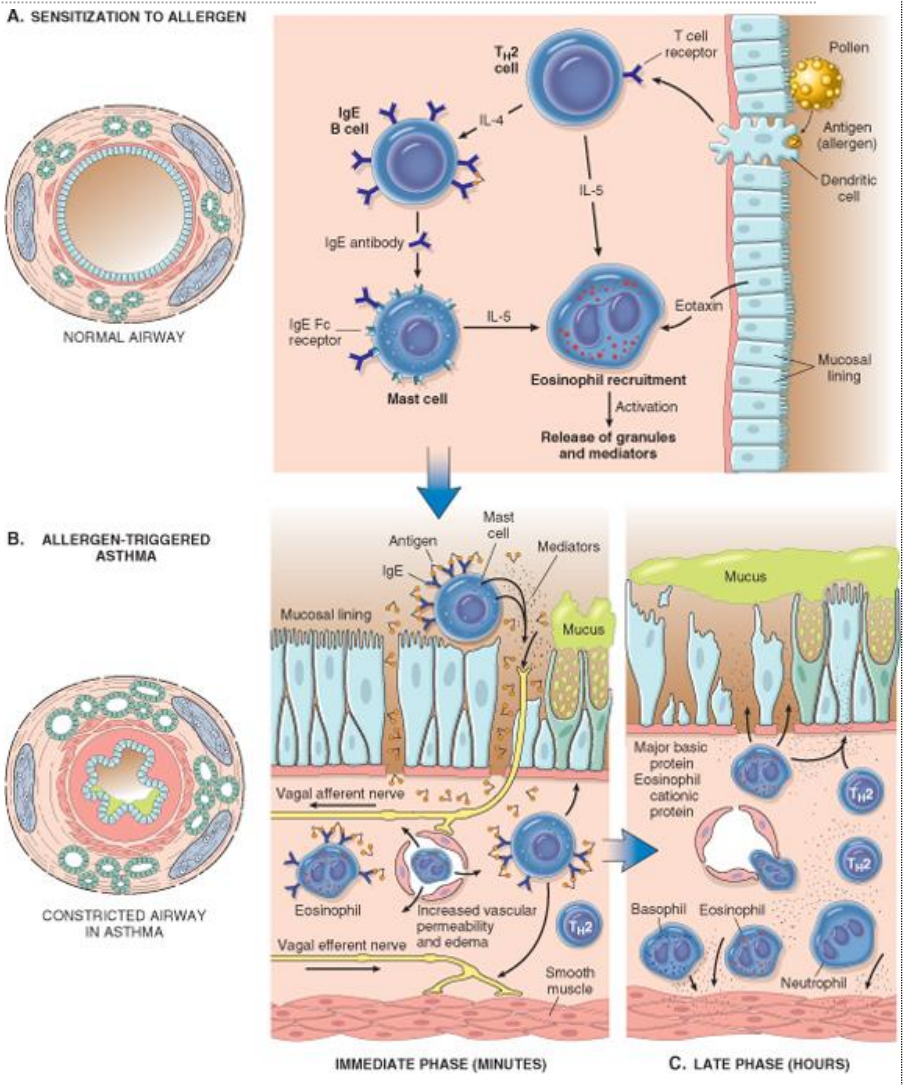
1- **Extrinsic\Atopic\Allergic (immune triggered) asthma:**
Is mediated by a **type I hypersensitivity response** involving **IgE** bound to **mast cells**. The disease begins in **childhood** and usually in patients with a **family history of allergy** (eczema, allergic rhinitis, allergic conjunctivitis…). **Serum IgE is increased**, **positive** prick test, skin test with antigen results in wheel and flare reaction (redness and edema in the skin).

2- **Intrinsic\Non-Atopic (non-immune triggered) asthma:**
Includes asthma associated with **chronic bronchitis** as well as other asthma variants such as **exercise -or cold- induced asthma**. It usually begins in **adult life** and is **not associated** with a **history of allergy.** Serum IgE levels are **normal**, **negative** prick test.

3- **Drug induced** :

Caused by drug intake ex. Aspirin, β blockers…

4- **Occupational:** fumes, dusts and gases.



Pathogenesis:

PHASE I (exposure):

Sensitization to allergen. Inhaled allergens (antigens) elicit a T_H2-dominated response resulting in specific IgE production and eosinophil recruitment (priming or sensitization).

NOTE that there is no allergic reaction

T_H2 releases 3 lymphokines:

1- **IL-4:** activates IgE production.
2- **IL-5:** activates eosinophils.
3- **IL-13:** increases mucous secretion.

PHASE II (re-exposure, early phase): Allergen-triggered asthma. On re-exposure to antigen (Ag):

1- The immediate reaction is triggered by Ag-induced cross-linking of IgE bound to IgE receptors on mast cells in the respiratory airways.
2- Mast cells release chemical mediators that open tight junctions between epithelial cells.
3- Antigen can then enter the mucosa to activate mucosal mast cells and eosinophils, which in turn release additional mediators.
4- Collectively, either directly or through stimulating Vagus nerve, the mediators induce bronchospasm, increased vascular permeability, and mucus production, besides recruiting additional mediator-releasing cells from the blood.

PHASE III (re-exposure, late phase): Late phase (hours). The arrival of stimulated leukocytes (neutrophils, eosinophils, basophils, and T_H2 cells) to the mucosa and sub-mucosa signals the initiation of the late phase of asthma and their arrival is along with the release of several chemical mediators from leukocytes, endothelium, and epithelial cells. **Factors, particularly from eosinophils (e.g., major basic protein, eosinophil cationic protein), also cause damage to the epithelium..**

Summary

PHASE I (exposure)

Inhaling the antigen (first time) → TH2 lymphocytes activation →lymphokines secretion →Mast cells activation + B lymphocytes produce IgE antibodies specific for the antigen →IgE coats the mast cells

PHASE II (re-exposure, early phase)

Inhaling the antigen (second time) → antigen attaches to FC segment of the specific IgE → Mast cells degranulation and release of chemical mediators → chemical mediators open tight junctions between epithelial cells→ Antigen can then enter the mucosa to activate mucosal mast cells and eosinophils → Chemical mediators produced by mucosal mast cells and eosinophils act on smooth muscles (directly-indirectly by stimulating vagal nerve) → **Bronchospasm**

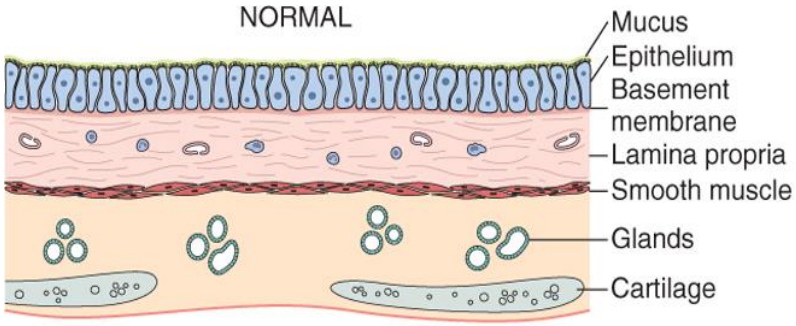
PHASE III (re-exposure, late phase)

There is accumulation of neutrophils, macrophages and T lymphocytes→ Stimulation of eosinophils →accumulation of eosinophils and mucous in the bronchus →Further tightening of the lumen →Eosinophils secrete (major basic protein) which in addition to the mucous and the other mediators can cause destruction of the lining wall if left without treatment for a long period of time

Comparison of a normal bronchiole with a bronchiole of an asthmatic patient

Note:

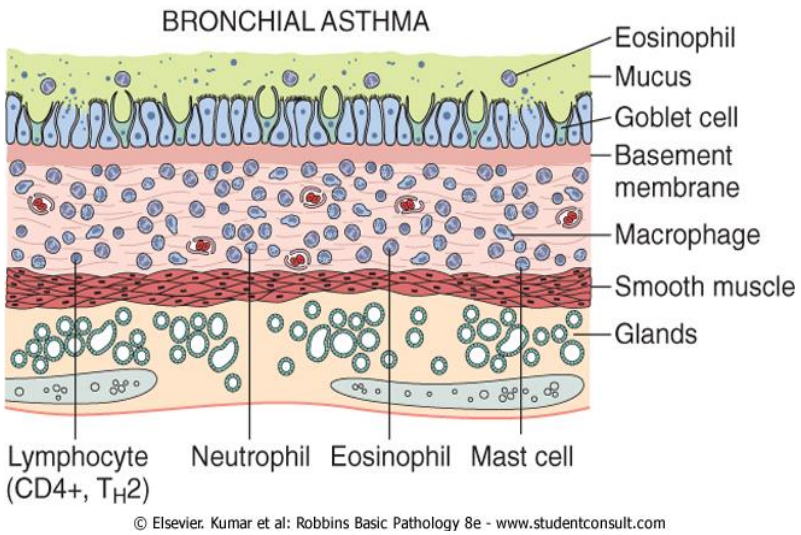
1- The **accumulation of mucus** in the bronchial lumen forming **mucous plugs**, resulting from **an increase in the number of mucus-secreting goblet cells** in the mucosa and hypertrophy of submucosal mucous glands.



2- In addition, there is intense chronic inflammation caused by recruitment of eosinophils, macrophages, T_H2 cells and other inflammatory cells.

3- Basement membrane underlying the mucosal epithelium is thickened.

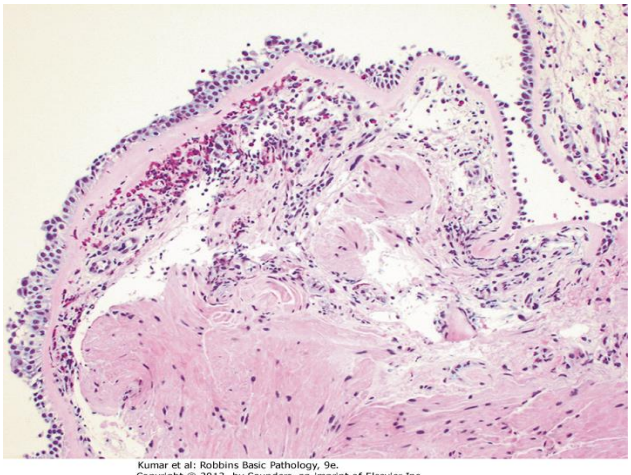
There is hypertrophy and hyperplasia of smooth muscle cells. Due to the frequent contractions of the muscles.



NOTE: Bronchial asthma may also lead to **status asthmaticus** which is a **prolonged** attack of bronchial asthma that can last for **days** and responds **poorly** to therapy.

The patient usually has hypoxemia and acidosis.

Death can result from **status asthmaticus**, and for this reason this condition is regarded as **an acute medical emergency.**



(Bronchial biopsy specimen from an asthmatic patient showing sub-basement membrane fibrosis, eosinophilic inflammation, and smooth muscle hyperplasia)

SUMMARY:

The major etiologic factors of asthma are genetic predisposition to type I hypersensitivity (atopy\allergy), acute and chronic airway inflammation, and bronchial hyper responsiveness to a variety of stimuli. **The inflammation involves many cell types and numerous inflammatory mediators, but the role of type 2 helper T (T_H2) cells may be critical to the pathogenesis of asthma.**

Clinical features:

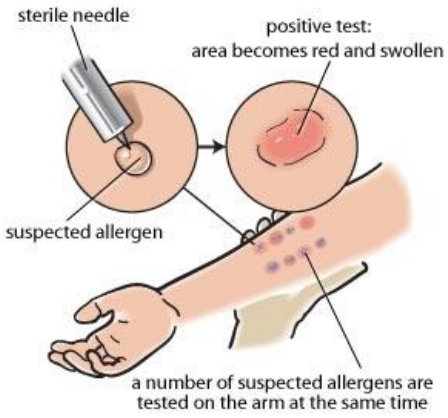
The patient is usually present with:

1- **Wheezing:** Due to the bronchospasm and mucous , the lumen becomes contracted and tightened, thus the air flowing inside the contracted lumen produce a whistle like sound.
2- **Dyspnea** (shortness of breath)
3- **Cough:** The patient may or may not complain of cough which could be productive or not (dry).

These symptoms usually presented at night or at early mornings.

Clinical examination:

1- **Prick test:** The physician tries to know the type of antigen that caused the allergic response →



2- **RAST test:** We look for the antibody that is produced against a certain allergen.

3- **Spirometry:** Examining the **FEV_1** which is usually reduced according to the severety of the disease. If the patient is given a bronchodilator and his FEV_1 is improved, it is a strong sign for asthma.

4- **Sputum:** It is very important to take a specimen from the sputum from patients with respiratory problems, to make sure there is no infection and no malignancy. The person taking the specimen has to avoid bad sputum (which is only saliva) to get accurate results.

A good specimen should be: Sputum coming from the *bronchial tree*, which can be recognized by alveolar macrophages and coloumnar cells.

Sputum specimen is a type of CYTOLOGY.

There are **three** important findings in asthma patients' sputum:

1- **Curshmann's spirals:** Which are mucous plugs arranged in spirals.
2- **Charcot-Leyden crystals:** Which are proteinatious needle shaped substances seen in sputum of bronchial astma patients.
3- **Eosinophils.**

Other mediator produced in asthma:

- Prostaglandins D2, E2, F2 (induce bronchospasm and vasodilatation).
- Histamine (induce bronchospasm and increase vascular permeability).
- Platelet-activating factor (cause aggregation of platelets and release of histamine).
- Acetylcholine: released from intrapulmonary motor nerves, resulting in airway smooth muscle constriction by direct stimulation of muscarinic receptors.
- Mast cell tryptase (inactivate normal bronchodilator).

Complications of asthma:

1- **Status asthmaticus.**
2- **Secondary infection**: bronchitis, emphysema, pneumonia…
3- **Cor pulmonale:** heart faliure secondary to a chronic respiratory disease.
4- **Respiratory failure.**

Summary:

· **Asthma** is characterized by reversible bronchoconstriction caused by airway hyper responsiveness to a variety of stimuli.

· **Atopic asthma** is caused by a **TH2** and **IgE**-mediated immunologic reaction to environmental allergens (Type I hypersensitivity) and is characterized by acute-phase (immediate) and late-phase reactions. The **TH2** cytokines **IL-4**, **IL-5**, and **IL-13** are important mediators.

· **Triggers** for non-atopic asthma are **less clear** but include viral infections and inhaled air pollutants, which can also trigger atopic asthma.

· **Eosinophils** are key inflammatory cells found in almost all subtypes of asthma; eosinophil products such as major basic protein are responsible for **airway damage**.

· **Airway remodeling** (sub-basement membrane thickening and hypertrophy of bronchial glands and smooth muscles) adds an irreversible component to the obstructive disease.