PATHOLOGY TEAM

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BRONCHIAL ASTHMA- PATHOLOGY

Introduction NORMAL ANATOMY

The air conducting passages consist of :
the nasal cavities, paranasal sinuses,
nasopharynx, oropharynx, hypopharynx (epiglottis·· and larynx), and tracheobronchial tree. At the carina, the trachea branches into the mainstem bronchi which branch into lobar bronchi which branchinto segmental bronchi which supply the intralobar bronchopulmonary segments. Further branching produces subsegmental bronchi, bronchioles, terminal bronchioles
Respiratory bronchioles, alveolar ducts and alveolar sacs. The pulmonary arteries follow the
airways while the pulmonary veins run through the connective tissue septa. Lymphatic channels are present along the bronchovascular structures but are also found in the pleura and connectivetissue septa.

Note :
1- The respiratory zone start from the respiratory bronchioles.
2-The gas exchange don't occur in the terminal bronchioles
3-The distal airspaces are kept open by elastic tension in alveolar walls.

Introduction to Histology

With the exception of the oropharynx and portions of the nasopharynx and hypopharynx (which are lined by squamous epithelium), the upper respiratory tract and the large airways are lined by pseudostratified ciliated columnar
. epithelium interspersed with mucus-secreting **goblet** cells and neuroendocrine cells. Mucus-secreting glands. lie beneath the epithelial surface and the. cartilaginous plates help to maintain patency. .Cartilage, submucosal glands and goblet cells are lost at the level of the bronchioles which are lined by ciliated cuboidal epithelium and Clara cells (which secrete a non-mucoid watery substance that contains lysozyme and immunoglobulins). The majority of the alveolar surface lsiinedby the Type I p neumocytes which are interspersed with the surfactant3 producing Type II (cuboidal! granular) pneumocytes. The interstitium contains collagen, elastin, mast cells, occasional inflammatory cells and connective tissue cells (primarily smooth muscle and fibroblasts). Alveolar macrophages that are derived from blood monocytes are loosely attached to the alveolar wall or lie free

within the alveolar space.

Introduction: Physiology

- FEV1: volume of air blown out forcibly in 1 second. A function of large airways. Dependent on body size.
- Vital capacity (VC): total volume of expired air. (TV+IRV+ERV)
- Tco (transfer factor): absorption of carbon monoxide in 1 breath (gas exchange)

Note : *Normal FEV1= about 80%*

Functional Classification of Lung Disease

-Diffuse pulmonary diseases are divided into:

- Obstructive lung disease: decreased FEV1 and FEV1/VC
- Restrictive lung disease: decreased FEV1. Normal FEV1/VC. Decreased Tco.

Note :

Obstruction : A blocking or clogging of a tube or vessel **,main problem occur in the air way (usually narrowest)**

Restriction : reduce in the expansion of the lung due to :

Accumulation of abnormal cells or substances & the main problem will be (Dyspnea**)**

Respiratory diseases :

1- **COPD.**

2- **Restrictive lung disease.**
3- **Inflammatory lung disease.**
4- **Tumor in the lung .**

Name of Disorders	Pathologic findings
Bronchial asthma	Bronchial smooth muscle hypertrophy. Hyperplasia of bronchial submucosal glands and goblet cells. Airways plugged by viscid mucus containing Curschmann spirals, eosinophils and Charcot-leyden crystals.
Chronic bronchitis	Hyperplasia of bronchial submucosal glands leading to increased Reid index: ratio of the thickness of the gland layer to that of the bronchial wall.
Pulmonary, emphysema	Abnormal dilation of air spaces with destruction of alveolar walls. Reduced lung elasticity.
Bronchiectasis	Abnormally dilated bronchi which are' filled with rnucusand neutrophils. . Inflamamtion and necrosis of bronchial walls and alveolar fibrosis.

Main Categories of (diffuse) Obstructive Disease (COPD) :

- Asthma
- Chronic obstructive pulmonary/airway/lung disease(COPD/COAD/COLD).They are of two types:
  - Chronic bronchitis
  - Emphysema
- Bronchiectasis

Common symptoms:

- Dyspnea: difficulty with breathing
- Cough.

- Wheezing.
- Hemoptysis.

Note:

1- Wheezing : To breathe with difficulty, producing a hoarse whistling sound.
2- Hemoptysis : Coughing with blood .

BRONCHIAL ASTHMA

- Is a chronic relapsing inflammatory disorder characterized by hyper-reactive airways .BA is type of chronic obstructive airway disease. It is an episodic, reversible broncho constriction caused by increased responsiveness of the tracheobronchial tree to various stimuli.
- It is characterized by :

1. hyper-irratibility of the airways causing bronchial constriction.
2. edema and inflammation in response to various substances.
3. *triad of:*
    - *intermittent and reversible airway obstruction*
    - *chronic bronchial inflammation with eosinophils*
    - * *bronchial smooth muscle cell hypertrophy and hyper-reactivity*

*Note : مع صعوبة خروج الهواء والتنفس يكون شغل عضلات الشعيبات الهوائيه اكثر ،،وهذه الزياده تسبب تضخم وفرط نشاط

- It has been divided into two basic types:
    - Extrinsic asthma.
    - Intrinsic asthma.
- Sometimes extrinsic and intrinsic can co-exist in the same patient.

- Atopic : A state that makes persons more likely to develop allergic reactions of any type, including the inflammation and airway narrowing typical of asthma
- Extrinsic :About 70%
- Intrinsic : About 30% (actually unknown cause, but associated with jogging, overweight, and certain drugs like aspirin)

Extrinsic (atopic, allergic) Asthma 70%	**Intrinsic (non-atopic)Asthma 30%**
• **Initiated by type 1 hypersensivity Reaction .** • **response involving IgE bound to mast cells** • **induced by exposure to extrinsic antigen/allergens e.g. food, pollen, dust, etc.** • **Subtypes include:** ○ **Atopic (allergic)asthma.** ○ **Occupational asthma.** ○ **Allergic bronchopulmonary aspergillosis.** • **Develop early in life**	• **Initiated by diverse, non-immune mechanisms e.g. infections, drugs like aspirin, pollutants, inhaled chemical irritants, cold, stress and exercise.** • **No personal or family history of allergic reaction.** • **Develop later in life**

Extrinsic BA

- It is also known as allergic, immune mediated, atopic or reaginic asthma.

- In extrinsic (allergic) BA bronchospasm is induced by inhaled antigens, usually in children with a personal or family history of allergic disease (e.g., eczema, urticaria, or hay fever).
- Symptoms are brought about by type I [immunoglobulin E(IgE) mediated] hypersensitivity reactions to inhaled allergens. Serum levels of IgE usually are elevated.
- Atopic (allergic) asthma is the most common form, begins in childhood
- Other allergic manifestation: allergic rhinitis, urticaria, eczema.
- Skin test with antigen result in an immediate wheel and flare reaction
- Other family member is also affected
- Serum IgE and eosinophil are increased
- immune related, TH2 subset of CD4+ T cells

Non-Atopic Asthma/Intrinsic /idiosyncratic BA

- Intrinsic asthma is a disease of adults in which bronchial hyper reactivity was precipitated by a variety of factors unrelated to immune mechanisms.
- Also known as non-immune mediated asthma.
- It has an unknown basis.
- Symptoms are precipitated by non allergic factors such as inhaled irritants or infection.
- Triggered by respiratory tract infection including viruses and inhaled air pollutants e.g. sulfur dioxide, ozone.
- Positive family history is uncommon.
- Serum IgE – normal.
- No other associated allergies.
- Skin test – negative.
- Hyperirritability of bronchial tree.
- Subtypes:
  -Drug-induced asthma.
  -Occupational asthma

Pathogenesis of Bronchial Asthma

- The pathophysiology of asthma is complex and involves the following components:
- Chronic airway inflammation
- Intermittent airflow obstruction. Airflow obstruction can be caused by a variety of changes including : acute bronchoconstriction, airway edema, chronic mucous plug formation, and airway remodeling
- Bronchial hyper-responsiveness causes exaggerated bronchoconstriction. The degree of airway hyper-responsiveness generally correlates with the clinical severity of asthma.
- Some of the principal cells identified in airway inflammation include : mast cells, eosinophils, epithelial cells, macrophages, and activated T lymphocytes.
- T lymphocytes play an important role in the regulation of airway inflammation through the release of numerous cytokines
- The mechanisms have been best studied in atopic asthma

Note:

Pathogenesis:

Trigger Factor → TH_2 cell → these cytokines

1- IL-3 & IL- 4 (act on B- cell to produce IgE which is on mast cell surface).
2- IL- 5 (increase eosinophil).

Pathogenesis of Bronchial Asthma using Atopic Asthma as a model

Is a classic example of type 1 IgE-mediated hypersensitivity reaction.

IgE-mediated reaction to inhaled allergens elicits:

- acute response (within minutes)
- a late phase reaction (after 4-8 hours)
- Pathogenesis of Bronchial Asthma using Atopic Asthma as a model

Acute-phase response

- Begin 30 to 60 minutes after inhalation of antigen.
- It is the IgE mediated acute bronchoconstriction on exposure to aeroallergens.
- After exposure to an inciting factor (e.g. allergens, drugs, cold, exercise), inflammatory mediators are released by activated macrophages, mast cells, eosinophil, and basophils and they induce bronchoconstriction, increased vascular permeability, and mucous secretion.
- Inflammation of the bronchial walls also may injure the epithelium, stimulating nerve endings and initiating neural reflexes that further aggravate and propagate the bronchospasm

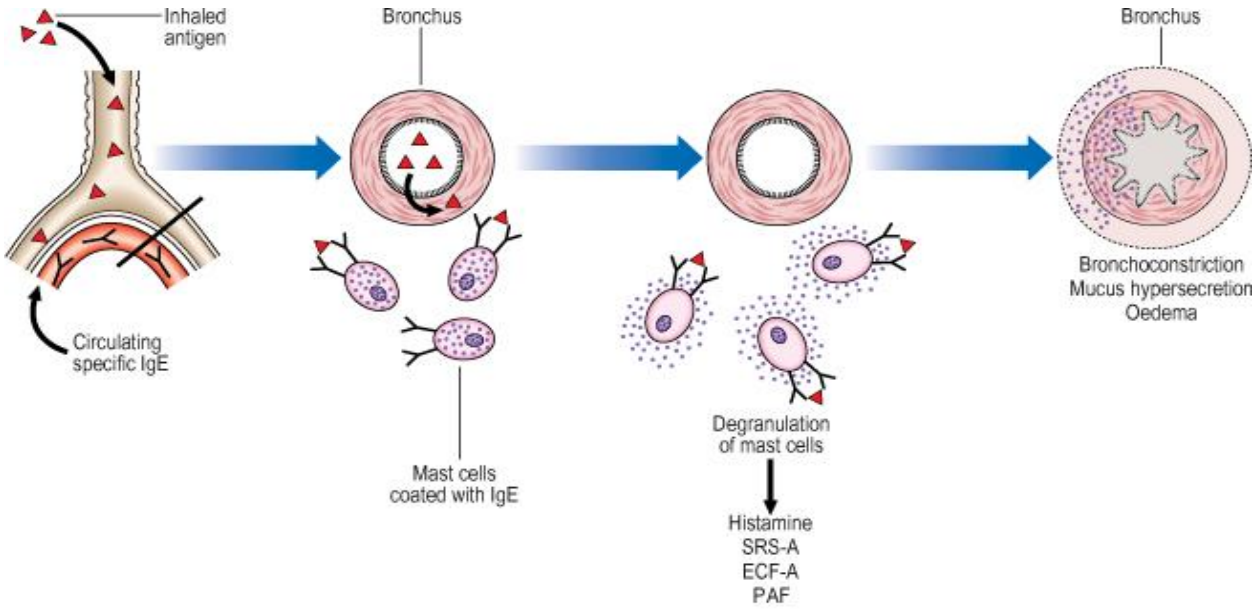
بعد ما يستنشق الشخص الماده المتحسس منها يقوم الجسم بالدفاع وافراز كميه من انفلمنتري مديتور لتنشيط الميكروفيج،الازينوفلسز.. هذه العمليه كنوع من الدفاع فتقوم بتضيق القصيبات الهوائيه عن طريق زياده نفوذيه الاوعيه الدمويه وبالتالي يزيد السائل المخاطي الذي يضيق بدوره القصيبات الهوائيه..

التهاب جدار القصبات الهوائيه ايضا يؤدي الى جرح الطبقه المبطنه وبذلك يؤدي الى تحفيز نهايات الاعصاب التي تقوم بردود فعل التي تزيد وتفاقم من انقباض القصبه الهوائيه..

- Mediator produced are :
  -Leukotrienes C4, D4 & E4 (induce bronchospasm, vascular permeability & mucous production)
  -Prostaglandins D2, E2, F2 (induce bronchospasm and vasodilatation)
  -Histamine (induces bronchospasm and increased vascular permeability)

-Platelet-activating factor (cause aggregation of platelets and release of histamine)
-Mast cell tryptase (inactivate normal bronchodilator).

- The inflammatory mediators lead to
    - smooth muscle contraction, bronchospasm



    - mucous secretion, and
    - Increased vascular permeability and edema.

- Each of these effects is a potent and reversible cause of airway obstruction.
- In addition IL-5 causes increased production of eosinophils in the bone marrow. Chemotactic factors like leukotriene B4 and neutrophil and eosinophil chemotactic factors attract neutrophils, eosinophils, and platelets to the bronchial wall. In turn, eosinophils further aggravates bronchoconstriction and edema.
- **Pathology of asthma:**
- Airway inflammation with mucosal oedema

- Mucus plugging

Late phase reaction

- It is the airway edema which occurs 6-24 hours following an allergen challenge. It is also referred to as the late asthmatic response.
- The arrival of leukocytes at the site of mast cell degranulation lead to release of more mediators to activate more mast cells
- There is epithelial cell damage. Eosinophils produce major basic protein, eosinophilic cationic protein and eosinophil peroxidase (toxic to epithelial cells). Discharge of eosinophil granules that contain eosinophil cationicprotein and major basic protein into the bronchial lumen further impairs mucociliary function and damages epithelial cells.
- Moreover, leukotriene B4 and PAF recruit more eosinophils and other effector cells, and so continue the vicious circle that prolongs and amplifies the asthmatic attack. These amplify and sustain injury without additional antigen.

Pathomorphology

- The pathologic findings are similar in both types:

  A) the bronchi have thickened walls with narrowed lumina and generally are filled with plugs of mucus in acute attack. They undergo constrictive spasms with edema of the bronchial wall and release of viscid mucus.

  B) The subepithelial basement membrane is markedly hypertrophic and there may be infiltrations of eosinophils. Charcot-Leyden crystals and curschmann's spirals are found within the sputum and emanate from the eosinophils.

- Grossly: - lung over distended (over inflation), occlusion of bronchi and bronchioles by thick mucous.

- Histologic finding:

- Thick basement membrane.
- Edema and inflammatory infiltrate in bronchial wall.
- Chronic mucous plug formation consists of an exudate of serum proteins and cell debris that may take weeks to resolve
- mucous contain Curschmann spirals, eosinophil and Charcot-Leyden crystals.
- Submucosal glands increased.
- Hypertrophy of the bronchial wall muscle.

Clinical Course

- The clinical manifestations vary from occasional wheezing to paroxysms of dyspnea and respiratory distress.
- In a classic asthmatic attack – there is dyspnea, cough, difficult expiration, progressive hyperinflation of lung and mucous plug in bronchi. This may resolve spontaneously or with treatment.
- Status asthmaticus – severe cyanosis and persistent dyspnea, may be fatal.

Complications of bronchial asthma

- Airway remodeling in association with structural changes due to long-standing inflammation
- Superimposed infection i.e. pneumonia
- Chronic bronchitis (i.e. Asthmatic bronchitis: chronic bronchitis with superimposed asthma)
- Emphysema, pneumothorax and pneumomediastinum
- bronchiectasis
- respiratory failure requiring intubation in severe exacerbations i.e. status asthmaticus
- In some cases corpulmonale and heart failure develop.

STATUS ASTHMATICUS

- It is the most severe form of asthma. It refers to severe bronchoconstriction that does not respond to the drugs that usually abort the acute attack. There is severe acute paroxysm of respiratory distress.
- This situation is potentially serious and requires hospitalization. Patients in status asthmaticus have hypoxemia and often hypercapnia. ##
- In particularly severe episodes the ventilatory functions may be so impaired so as to cause severe cyanosis and even death.##
- كلها بسبب ضيق القصيبات الهوائيه وقلة تبادل الغازات ##
- It may persists for days and even weeks.

Prognosis of bronchial asthma

- Approximately half the children diagnosed with asthma in childhood outgrow their disease by late adolescence or early adulthood and require no further treatment.
- Patients with poorly controlled asthma develop long-term changes over time (i.e., with airway remodeling). This can lead to chronic symptoms and a significant irreversible component to their disease.
- Many patients who develop asthma at an older age also tend to have chronic symptoms.

Deterrence/Prevention of bronchial asthma

- control of factors contributing to asthma severity. Exposure to irritants or allergens has been shown to increase asthma symptoms and cause exacerbations.

- Clinicians should evaluate patients with persistent asthma for allergen exposures and sensitivity to seasonal allergens. Skin testing results should be used to assess sensitivity to common indoor allergens.
- All patients with asthma should be advised to avoid exposure to allergens to which they are sensitive.

Summary

Asthma: Dyspnea and wheezing

Types	1. Extrinsic asthma: Type 1 Hypersensitivity reaction, IgE, childhood, family Hx of allergy. 2. Intrinsic asthma: associated e bronchial asthma, aspirin, exercise, cold induced. No Hx of allergy
Morphology	• Hypertrophy of bronchial smooth muscle & hyperplasia of goblet cells e eosinophils • Mucous plug e Curschmann spirals & Charcot-Leyden crystals.
Complication	• Superimposed infection • Chronic bronchitis • Pulmonary emphysema • Status asthmaticus