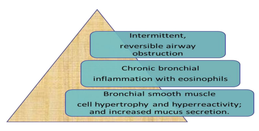
Mahmoud Al Qusairi

Obstructive Diseases

Chronic Bronchitis :

- Chronic bronchitis is defined based on clinical features.
- Definition.
  -A clinical condition characterized by a persistent productive cough for at least three consecutive months in at least two consecutive years (WHO)
  - It is common among cigarette smokers and urban dwellers.
- Forms of clinical bronchitis
  - 1- Simple chronic bronchitis :Patients have a productive cough with mucoid sputum, but airflow is not obstructed.
  - 2- Asthmatic bronchitis :Patients may demonstrate hyper-responsive airways with intermittent bronchospasm and wheezing
  - 3- Chronic obstructive bronchitis :
    - Including heavy smokers who develop frank chronic outflow obstruction, usually with associated emphysema.
- Pathogenesis
  - ❑Hypersecretion of mucus, beginning in the large airways as major bronchi.
  - ❑In advanced disease, even small bronchioles are involved.
  - ❑The environmental irritants induce hypertrophy of mucus glands in the bronchi & goblet cell metaplasia, which leads to a marked increase in mucus-secreting goblet cells in the bronchi & bronchioles.
  - ❑In addition to inflammation with infiltration of lymphocytes, macrophages & neutrophils.
  - ❑Eosinophils are NOT seen in chronic bronchitis.
  - ❑Microbial infection is often present but has a secondary role chiefly by maintaining the inflammation.
- Whereas the defining mucus hypersecretion is primarily a reflection of the involvement of large bronchi, the airflow obstruction in chronic bronchitis results from:
  1- So called small-airways disease induced by goblet-cell metaplasia with mucus-plugging of the bronchiolar lumen, inflammation, and fibrosis.
  2- Co-existent emphysema.
- Clinical features and course
  - - Cough with the production of excessive mucoid or mucopurulent sputum
    - Some patients may develop COPD with outflow obstruction; this is accompanied by hypercapnia,
      hypoxemia & in severe cases, cyanosis.
    - -For unknown reasons, they tend to be obese. called blue bloater
- Morphology
  - Grossly
    - ❖The mucosal lining of larger airways is usually hyperemic & swollen by edema and covered by a layer of mucopurulent secretion.
    - ❖The smaller bronchi & bronchioles may also be filled with similar secretions.
  - Histologically
    - ❖The larger bronchi: goblet cell metaplasia of bronchial epithelium and hyperplasia of submucosal mucus-secreting glands.
      The magnitude of the increase in size is assessed by the ratio of the thickness of the submucosal gland layer to that of the bronchial wall from the epithelial layer down to the cartilage.
      The ratio is called the Reid index, which normally is 0.4 .
      - Variable inflammatory cells, largely mononuclear cells but sometimes with neutrophils, are present in the bronchial mucosa.
      - Chronic bronchiolitis is inflammation of small bronchioles, showing goblet cell metaplasia, mucus plugging inflammation & fibrosis.
      - In severe cases narrowing and obstruction with complete obliteration of the lumen due to fibrosis called bronchiolitis Obliterans.
      - Squamous metaplasia [?] DYSPLASIA

Asthma

- Definition :
  -Is a chronic inflammatory disorder of the airways that causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night & / or early in the morning.
  - It is characterized by increased responsiveness of the tracheobronchial tree. - So simply, it is a reversible recurrent airway obstruction.
- Clinical features
  - This clinical picture is caused by repeated immediate hypersensitivity and late-phase reactions in the lung that give rise to the triad of :
  - 

  - ❑Attacks of severe dyspnea, with wheezing & cough.
  - ❑Progressive over-inflation of the lungs & air is trapped distal to the bronchi, which are obstructed.
  - ❑The attack lasts from minutes to hours, then gradually subsides spontaneously, or with therapy with intervals between attacks that are free from symptoms
  - ❑Occasionally, severe paroxysms occur that do not respond to therapy & persist for days (called Status asthmaticus), associated with hypercapnia, acidosis & severe hypoxia, and may be fatal.
- Types:
  Asthma is a heterogeneous disease triggered by a variety of agents.
  - Atopic asthma
    - The most common type.
    - Usually begins in childhood.
    - Due to IgE & TH2 lymphocytes -mediated immune response to environmental antigens (e.g. dust, pollen) in genetically predisposed individuals.
    - Often associated with a personal or family history of allergic diseases (Rhinitis, eczema)
    - A skin test is positive
  - Non-atopic asthma
    - Patients do not have evidence of allergen sensitization. - Usually develops later in life.
    - No history of allergies.
    - Normal IgE levels.
    - Skin test results usually are negative.
    - Respiratory infections due to viruses and inhaled air pollutants are common triggers.
  - Drug-induced asthma
    - Aspirin is the most common example.
      Occupational asthma:
    - Occupational asthma may be triggered by fumes and organic and chemical dusts. - Asthma attacks usually develop after repeated exposure to the inciting antigen(s).
- Pathogenesis
  - The major contributing factors in asthma are genetic predisposition to type I hypersensitivity (atopy), acute and chronic airway inflammation, and bronchial hyperresponsiveness to a variety of stimuli.
    ❖Genetic Susceptibility to atopic asthma is multigenic:
    - Polymorphisms in the ADAM33 gene may be linked to increased proliferation of bronchial smooth muscle cells and fibroblasts, contributing to bronchial hyperreactivity and subepithelial fibrosis.
  - Pathogenesis of atopic asthma
    - 1- Stage of sensitization:
      Exposure to the inhaled antigen will lead to activation of Helper T lymphocytes (TH2) that will release:
      (1) IL-4 and IL-13 that stimulate plasma cells to produce IgE
      (2) IL-5 is chemotactic to & activating eosinophils, which produce major basic protein or eosinophil cationic protein; both are toxic to epithelial cells
      (3) IL-13 stimulates mucus production from goblet cells and the submucosal glands.
    - 2- Early (immediate) phase reaction :
      - Starts within minutes after repeated exposure to the same antigen characterized by vasodilation, increased vascular permeability, and edema fluid in bronchial mucosa with smooth muscle spasm causing bronchoconstriction and increased mucus production.
      ·The reaction will be triggered by the effect of IgE antibodies on mast cells in the airways, leading to the release of their granules (Histamine, Leukotrienes & prostaglandins).
      ·Stimulation of subepithelial vagal (parasympathetic) receptors provokes bronchoconstriction.
    - 3-Late phase reaction :
      - Inflammatory in nature.
      - Inflammatory mediators stimulate epithelial cells to produce chemokines that promote the recruitment of TH2 cells, eosinophils, and other leukocytes, thus amplifying an inflammatory reaction that is initiated by resident immune cells.
      - This phase is characterized by inflammation, tissue destruction, mucosal ulceration, smooth muscle spasm
    - 4- Airway outflow remodeling :
      -The structural changes in the bronchial wall occurring as a late secondary change in asthma after repeated bouts of inflammation, including:
      -Deposition of collagen in the subepithelial basement membrane
      - Hypertrophy of mucus glands.
      -Hypertrophy of bronchial smooth muscle and fibroblasts.
- Morphology
  - Grossly
    - -In fatal cases with status asthmaticus or cases of prolonged chronic asthma, the lungs look over- distended because of the overinflation, and there may also be some areas of atelectasis.
      -The most striking gross finding is occlusion of the bronchi & bronchioles by thick mucus plugs.
  - Histologically
    - The sputum of the patient and the bronchial tissue show the mucus plugs containing whorls of shed necrotic epithelial cells called (Curschmann's spiral).
    - Also seen are numerous eosinophils & charcot-leyden crystals, which are made up of eosinophilic protein.
    - Features of airway remodeling include:
      ❑ Thickening of the airway wall.
      ❑ Sub-basement membrane fibrosis.
      ❑ Increased submucosal vascularity
      ❑ An increase in the size of the submucosal glands and goblet cell metaplasia of the airway epithelium
      ❑ Hypertrophy and/or hyperplasia of the bronchial smooth muscle

Emphysema

- Defined based on morphologic and radiologic features.
- Abnormal permanent enlargement of the air spaces distal to the terminal bronchioles (in the acinus), associated with the destruction of the wall of acini but without obvious fibrosis.
- Types of emphysema:
  - 1. Centriacinar (centrilobular) Emphysema:
    - The central or the proximal part of the acini, formed by the respiratory bronchioles, are affected, while the distal alveoli are spared.
    - The lesions are more common & severe in the upper lobes
    - Most commonly due to cigarette smoking, often in association with chronic bronchitis
  - 2. Panacinar (Panlobular) Emphysema :
    - The acini are uniformly enlarged from the level of the respiratory bronchioles to the terminal blind alveoli.
    - It tends to occur in the lower lung zones.
    - - Occurs in alpha- 1 anti-trypsin deficiency.
  - 3. Distal acinar (Paraseptal) emphysema:
    - The proximal portion of the acinus is normal, but the distal part is primarily involved.
    - -More severe in the upper half of the lungs.
    - The emphysema is more striking adjacent to the pleura and along the lobular connective tissue septa.
    - It occurs adjacent to areas of fibrosis or atelectasis.
  - 4.Irregular Emphysema
    - The acinus is irregularly involved; it is associated with scarring in healed inflammatory diseases.
    - - Although clinically Asymptomatic, it is the most common form of emphysema.
- Pathogenesis
  - Two Pathways are involved :
    1- PROTEASE -ANTIPROTEASE imbalance. 2- OXIDANT – ANTIOXIDANT imbalance
    - Such imbalances almost always coexist
  - Complex interactions between inflammatory mediators and inappropriate activation of repair mechanisms may result in tissue destruction without fibrosis.
  - α 1- antitrypsin is a major inhibitor of protease, particularly elastase, which is secreted by neutrophils during inflammation.
  - Exposure to toxic agents such as tobacco induces ongoing inflammation with infiltration of neutrophils, macrophages & lymphocytes in lung tissue
  - Elastases, cytokines & oxidants are released by these cells, causing epithelial injury, and unless inhibited by antitrypsin, anti-elastase, and antioxidants, the cycle of inflammation & proteolysis of ECM continues.
  - Decrease in these protective mechanisms produce damage.
    - Decrease in antiprotease activity may be : i- Genetic: α 1- antitrypsin deficiency ii- Acquired: Smoking
    - More than 80% of patients with congenital α 1- antitrypsin deficiency develop symptomatic panacinar emphysema.
    - A secondary consequence of oxidative injury caused by smoking is the inactivation of a native anti- protease, resulting in functional α 1- antitrypsin deficiency even in normal individuals.
    - Tobacco smoke contains abundant ROS (free radicals), which deplete anti-oxidant mechanisms
    - Activated neutrophils add to the pool of ROS in the alveoli
- How does obstruction occur?
  - Small airways are normally held open by the elastic recoil of the lung parenchyma, and the loss of elastic tissue in the walls of alveoli that surround respiratory bronchioles reduces radial traction and thus causes the respiratory bronchioles to collapse during expiration functional airflow obstruction despite the absence of mechanical obstruction.
- Clinical Features :
  - Dyspnea (progressive
  - Weight loss (thin).
  - Without concomitant chronic bronchitis usually presents with a barrel chest, dyspnea, and prolonged expiration, sitting forward in a hunched-over position.
  - Hyperventilation
  - The blood gases stay normal very until late in the disease due to hyperventilation, and there is adequate oxygenation of the blood.
  - Patients are called Pink-puffers.
- Morphology of Emphysema:
  - Grossly:
    - The diagnosis & classification of E . depend on the macroscopical appearance of the lung.
    - In pan-acinar E. the lungs are pale voluminous hyperinflated and obscure the heart.
    - In centriacinar E. the features are less impressive, the lung look deeper pink than in pan-acinar E., and less voluminous.
  - Bullous emphysema :
    - Any form of emphysema that produces large subpleural blebs or bullae i.e. air spaces larger than 1cm., when rupture leads to pneumothorax
  - Histologically :
    - ❑Thinning & destruction of alveolar walls; with advanced disease, the adjacent alveoli create large air spaces.
    - ❑Terminal & respiratory bronchioles may be deformed
    - ❑Alveolar capillaries are diminished.
    - ❑Bronchiolar inflammation and submucosal fibrosis are consistently present in advanced disease

Bronchiectasis

- Definition :
  -Is a permanent dilatation of bronchi & bronchioles, caused by the destruction of muscle & elastic supporting tissue, resulting from or associated with chronic, necrotizing infections.
  - It is a secondary sequel to persistent infections or obstruction.
- Etiology
  - 1. Bronchial Obstruction:
    Localized (F.B. or Tumor) Generalized (asthma, bronchitis)
  - 2. Congenital & hereditary conditions :
    ❑Cystic fibrosis: obstruction by abnormally viscid mucus and secondary infections
    ❑Immunodeficiency: recurrent bacterial infections.
    ❑Primary ciliary dyskinesia (also called the immotile cilia syndrome): It is caused by inherited abnormalities of cilia that impair mucociliary clearance of the airways, leading to infections.
  - 3. Post-necrotizing suppurative inflammation (staphylococcus aureus, TB).
- Pathogenesis
  - Two processes are involved:
    ❖Bronchial obstruction. <—>❖Chronic persistent infections. Either may be the initiator: - Obstruction caused by a foreign body impairs the clearance of secretions, providing a favorable substrate for infection. The resultant inflammatory damage to the bronchial wall and the accumulating exudate further distends the airways, leading to irreversible dilation.
    - Conversely, persistent necrotizing infection in the bronchi or bronchioles may lead to poor clearance of secretions, obstruction, and inflammation with peribronchial fibrosis and traction on the bronchi, culminating again in full-blown bronchiectasis.
- Clinical features
  - -Sever persistent cough with expectoration of mucopurulent fowl-smelling sputum
    -Frank hemoptysis may occur.
    -Clubbing of fingers.
    -In severe bronchiectasis: hypoxemia, hypercapnia, pulmonary hypertension, and cor pulmonale. -Septic emboli may arise from lung abscess and may lead to brain abscess.
- Morphology
  - Grossly
    - Localized or diffuse.
    - -Bronchi of the lower lobes of both lungs are frequently involved by bronchiectasis; they become markedly dilated.
    - -Their Lumina is filled with dirty purulent exudates when removed a reddish ulcerated mucosa is seen.
    - -More severe in the distal bronchial tree.
  - Microscopically
    - ❑Vary with the severity and duration of the disease.
    - ❑In active full-blown disease, intense acute & chronic inflammatory exudates within the wall of the
      bronchi & bronchioles are seen, and desquamation of lining epithelium causes extensive ulceration.
    - ❑Typically, mixed flora is cultured from the sputum.
    - ❑When healing occurs, the lining epithelium may regenerate completely; however, the injury usually cannot be repaired, and abnormal dilation and scarring persist.
    - ❑In more chronic cases, fibrosis of the bronchial and bronchiolar walls and peribronchiolar fibrosis develop