**Respiratory diseases د. سرى سلمان عجام**

***Emphysema : -***

Definition: is characterized by irreversible enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls without obvious fibrosis.

Incidence.

COPD is a major public health problem. It is the fourth leading cause of morbidity and mortality in the United States

Types of emphysema:-

Emphysema is classified according to its anatomic distribution within the lobule. Recall that the lobule is a cluster of acini, the terminal respiratory units

***there are four major types: (1) centriacinar, (2) panacinar, (3) paraseptal, and (4) irregular. Of these, only the first two cause clinically significant airflow obstruction . Centriacinar emphysema is far more common than the panacinar form, constituting more than 95% of cases.***

1- centriacinar ( centrlobular) emphysema:

In which the central and proximal part of acinus are affected ( formed by respiratory bronchioles )

The lesions are more sever and common in upper lobes particularly in apical airspaces or segments . emphysematous spaces often contain large amounts of black pigment In sever centriacinar emphysema , the distal acinus also becomes involved.

This type of emphysema is most commonly seen as a consequence of cigarette smoking and often in association with chronic bronchitis.

2- panacinar emphysema :

In this type of emphysema, the acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli

The prefix “pan” refers to the entire acinus but not to the entire lung. In contrast to centriacinar emphysema, panacinar emphysema tends to occur more commonly in the lower zones and in the anterior margins of the lung, and it is usually most severe at the bases

It tends to occur more commonly in the lower lung zones and is the type of emphysema that occurs in α1-antitrypsin deficiency.

3- Distal Acinar ( paraseptal) Emphysema

In this form, the proximal portion of the acinus is normal but the distal part is dominantly involved.

The emphysema is more striking adjacent to the pleural margin of the lobules. It occurs adjacent to areas of fibrosis, scarring, or atelectasis and is usually more severe in the upper half of the lung .

The characteristic findings are of multiple, continuous, enlarged airspaces from less than 0.5 cm to more than 2.0 cm in diameter, sometimes forming cystlike structures. This type of emphysema probably underlies many of the cases of spontaneous pneumothorax in young adults.

4-Airspace Enlargement with Fibrosis (Irregular Emphysema)

Irregular emphysema, so named because the acinus is irregularly involved, is almost invariably associated with scarring. Thus, it may be the most common form of emphysema, because careful search of most lungs at autopsy shows one or more scars from a healed inflammatory process. In most instances, these foci of irregular emphysema are asymptomatic and clinically insignificant

**Clinical Features:**

1- Dyspnea is usually the first symptom. In patient with no "bronchitic" component , barrel-chest is a prominent feature . Because of dyspnea , there is adequate oxygenation of Hb . and patient called ( pink puffers ).

2- in patient with underlying bronchitis , there are cough and wheezing with purulent sputum with loss of dyspnea lead to 🡪 hypoxia 🡪 patient called blue bloaters

3- weight loss is common and may be so sever as to suggest a hidden malignancy and the patient may die from:

1- respiratory failure

2- right sided heart failure.

**Pathogenesis :**

Emphysema arising as a consequence of two critical imbalances : protease -antiprotease and oxidant – antioxidant imbalances.

The protease- antiprotease imbalance is the underlying cause of pulmonary emphysema in patient with genetic deficiency of α1 – antitrypsin

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α1 – antitrypsin normally present in serum , tissue fluids and macrophages is a major inhibitor of protease (elastase) secreted by neutrophils during inflammation, α1-antitrypsin is encoded by codominantly expressed genes on the proteinase inhibitor *(Pi)* locus on chromosome 14. The *Pi* locus is extremely polymorphic, with many different alleles. Most common is the normal *(M)* allele and the corresponding phenotype. Approximately 0.012% of the US population is homozygous for the *Z* allele, associated with markedly decreased serum levels of α1antitrypsin. More than 80% of these individuals develop symptomatic panacinar emphysema, which occurs at an earlier age and with greater severity if the individual smokes. The following sequence is postulated:

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| --- | --- | --- |
|  | **1.** | Neutrophils (the principal source of cellular proteases) are normally sequestered in peripheral capillaries, including those in the lung, and a few gain access to the alveolar spaces. |
|  | **2.** | Any stimulus that increases either the number of leukocytes (neutrophils and macrophages) in the lung or the release of their protease-containing granules increases proteolytic activity. |
|  | **3.** | With low levels of serum α1-antitrypsin, elastic tissue destruction is unchecked and emphysema results. |

*In smoking:*

1- the direct chemoattractant effect of nicotine and effect of reactive oxygen species in smoke These activate the transcription factor NF-κB, which switches on genes that encode TNF and chemokines, including IL-8. These, in turn, attract and activate neutrophils. .

2-With accumulation of neutrophils which release their protease ( elastase ) leading to tissue damage because of oxidative injury of smoking that lead to inactivation of α1 – antitrypsin

3- smoking also enhances elastic activity in macrophage which is not inhibited by α1 – antitrypsin

4- the abundant reactive oxygen species will deplete the antioxidants tat are normally present in the lung to keep oxidative damage to a minimum thereby inciting tissue damage.

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.

In addition the air way obstruction can be caused by

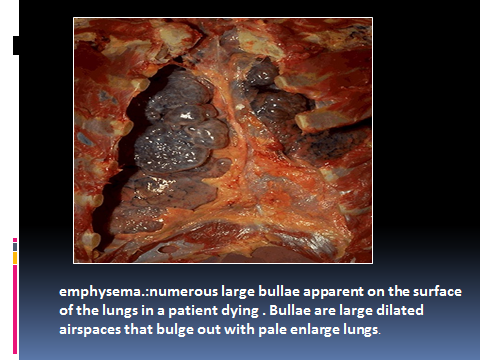
* goblet cell hyperplasia & mucus plug
* inflammatory edema
* muscle hypertrophy

**Morphology:**

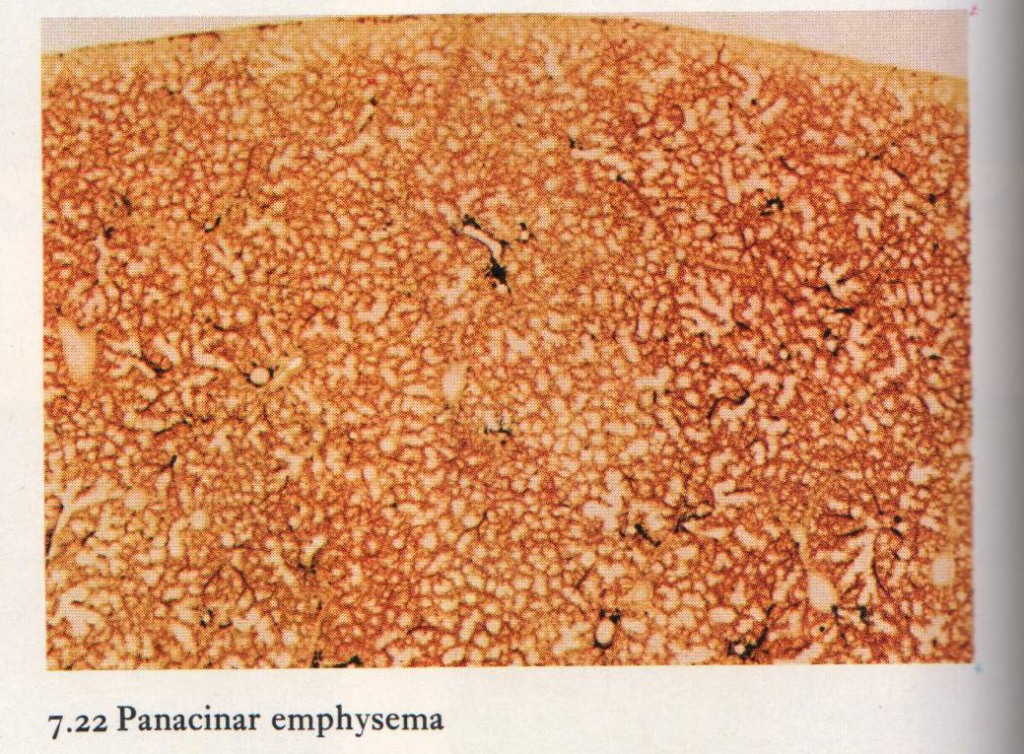
**Grossly** : the lung in panacinar emphysema when well developed , appears pale, voluminous , and obscure the heart when anterior chest wall removed at autopsy.

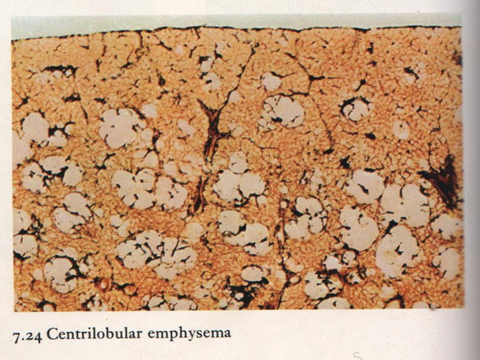
In centriacinar emphysema , the lungs are deeper pink and less voluminous .

In extreme cases, emphysematous bullae may be visible .









**Microscopically** :

1- there is thinning and destruction of alveolar walls. with advanced disease , adjacent alveoli become confluent creating large airspaces.

2- terminal bronchi and bronchioles may be deformed because of loss of septa that help tether those structure in parenchyma .

There is also fibrosis of bronchioles with evidence of bronchitis and bronchiolitis .

Inflammatory changes in small airways were described earlier

**Treatment** options include bronchodilators, steroids, bullectomy, and, in selected patients, lung volume reduction surgery and lung transplantation. Substitution therapy with α1-AT is being evaluated

**Chronic bronchitis :**

Definition : - is persistent productive cough for at least 3 consecutive months in at least 2 consecutive years , in the absence of any other identifiable cause.

It is common in cigarette smokers and people who expose to air pollutants , such as sulfur dioxide and nitrogen dioxide .

When persistent for years, it may (1) progress to COPD, (2) lead to cor pulmonale and heart failure, or (3) cause atypical metaplasia and dysplasia of the respiratory epithelium, providing a rich soil for cancerous transformation

**Clinical features :**

1- prominent cough and production of sputum may persist without ventilator dysfunction and some patients may progress to chronic obstructive disease with hypoxemia and cyanosis .

2- chronic bronchitis is complicated by recurrent infection , pulmonary hypertension and cardiac failure .

**Pathogenesis :**

The primary or initiating factor in the genesis of chronic bronchitis seems to be long-standing irritation by inhaled substances such as *tobacco smoke* (90% of patients are smokers), and dust from grain, cotton, and silica. The earliest feature of chronic bronchitis is *hypersecretion of mucus* in the large airways, associated with hypertrophy of the submucosal glands in the trachea and bronchi.[24] Proteases released from neutrophils, such as neutrophil elastase and cathepsin, and matrix metalloproteinases, stimulate this mucus hypersecretion. As chronic bronchitis persists, there is also *a marked increase in goblet cells of small airways—small bronchi and bronchioles*—leading to excessive mucus production that contributes to airway obstruction. It is thought that both the submucosal gland hypertrophy and the increase in goblet cells are protective metaplastic reactions against tobacco smoke or other pollutants (e.g., sulfur dioxide and nitrogen dioxide).

The role of *infection* seems to be secondary. It is not responsible for the initiation of chronic bronchitis but is probably significant in maintaining it and may be critical in producing acute exacerbations. Cigarette smoke predisposes to infection in more than one way.

1-It interferes with ciliary action of the respiratory epithelium, it may cause direct damage to airway epithelium,

2- it inhibits the ability of bronchial and alveolar leukocytes to clear bacteria.

Viral infections can also cause exacerbations of chronic bronchitis.

**Morphollogy : -**

**Grossly** : the mucosal lining of larger airways is usually hyperemic and swollen and edema fluid . It is often covered by a layer if mucopurulent sputum.

**Microscopically:**

1- trachea and larger bronchi:

1. the **major change is in the size of the mucous gland (hyperplasia)**. This increase can be assessed by the ratio of the thickness of the mucous gland layer to the thickness of the wall between the epithelium and the cartilage (**Reid index**). The Reid index (normally 0.4) is increased in chronic bronchitis, usually in proportion to the severity and duration of the disease.
2. Increase umber of goblet cells in lining epithelium with concomitant loss of ciliated epithelial cells .
3. Squamous metaplasia frequently develops followed by dysplastic changes. A sequence of events that may lead to evolution of bronchogenic carcinoma.
4. A variable density of inflammatory cells largely mononuclear but sometimes admixed with neutrophils is frequently present in the bronchial mucosa , the tissue neutrophilia increases during bronchitic exacerbations. Unlike asthma , eosinophils don not constitute prominent component except in patient with asthmatic bronchitis.

2- bronchioles:

1. Goblet cell metaplasia
2. Inflammation
3. Fibrosis

Smooth muscle hyperplasia. . D

***Bronchiectasis :–***

Definition: is the permanent dilation of bronchi and bronchioles caused by destruction of muscle and supporting elastic tissue resulting from or associated with chronic necrotizing infections. It is not a primary disease but rather is secondary to persisting infection or obstruction caused by variety of conditions.

The condition that most commonly predispose to bronchiectasis include the following:

***1- Bronchial obstruction:*** Common causes are tumors, foreign bodies, and occasionally impaction of mucus. Under these conditions, the bronchiectasis is localized to the obstructed lung segment. Bronchiectasis can also complicate atopic asthma

***2- congenital or hereditary conditions***:

**A-cystic fibrosis** the primary defect in ion transport leads to defective mucociliary action, and accumulation of thick viscid secretions that obstruct the airways. This leads to a marked susceptibility to bacterial infections, which further damage the airways. With repeated infections there is widespread damage to airway walls, with destruction of supporting smooth muscle and elastic tissue, fibrosis, and further dilatation of bronchi. The smaller bronchioles become progressively obliterated as a result of fibrosis (bronchiolitis obliterans).

**B-** **In immunodeficiency states,** particularly immunoglobulin deficiencies, bronchiectasis is prone to develop because of an increased susceptibility to repeated bacterial infections

**C- Kartagener syndrome**, an autosomal recessive disorder, is frequently associated with bronchiectasis. Structural abnormalities of the cilia impair mucociliary clearance, leading to persistent pulmonary infections.

(Kartagener syndrome ) ( bronchiectasis, sinusitis, dextrocardia and male sterility)

***3- Postinfectious conditions***, including necrotizing pneumonia caused by bacteria (Mycobacterium tuberculosis, Staphylococcus aureus, Haemophilus influenzae, Pseudomonas), viruses (adenovirus, influenza virus, human immunodeficiency virus [HIV]), and fungi (Aspergillus species)

***Etiology and Pathogenesis.***

Obstruction and infection are the major conditions associated with bronchiectasis, and it is likely that both are necessary for the development of full-fledged lesions, although either may come first. After bronchial obstruction, normal clearing mechanisms are impaired, there is pooling of secretions distal to the obstruction, and there is inflammation of the airway. Conversely, severe infections of the bronchi lead to inflammation, often with necrosis, fibrosis, and eventually dilation of airway .

**Clinical features**

1- persistent cough with expectoration of mucopurulent sputum. The sputum may contain flecks of blood; frank hemoptysis can occur.

2- clubbing of fingers.

3- hypoxemia , hypercapnia m pulmonary hypertension and core pulmonale.

4- metastatic brain abscesses and reactive amyloidosis are less frequent complications.

**Morphology :-**

**Grossly** :- bronchiectatic involvement of lungs usually affects the lower lobes bilaterally , particularly those air passages that are more vertical. The most sever involvement is found in the more distal bronchi and bronchioles. The airways may be dilated to as much as 4 times their usual diameter.

**Microscopically :**

The histologic findings vary with the activity and chronicity of the disease. In the full-blown picture of disease, an intense acute and chronic inflammatory exudate within the walls of the bronchi and bronchioles and the desquamation of lining epithelium cause extensive areas of ulceration.

Fibrosis of bronchial and bronchiolar walls develop in more chronic cases.

When healing occurs , the lining epithelium may regenerate completely , however so much injury has occurred that abnormal dilation and scarring has occurred.

Necrosis destroys the bronchial and bronchiolar walls and forms lung abscess.

