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Material

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❑BRONCHIAL ASTHMA

Asthma is a disease of airways that is characterised by increased responsiveness of the tracheobronchial tree to a variety of stimuli resulting in widespread spasmodic narrowing of the air passages which may be relieved spontaneously or by therapy. Asthma is an episodic disease manifested clinically by paroxysms of dyspnoea, cough and

wheezing. However, a severe and unremitting form of the disease termed status asthmaticus may prove fatal. Bronchial asthma is common and prevalent worldwide; in the United States about 4% of population is reported to suffer from this disease. It occurs at all ages but nearly 50% of cases develop it before the age of 10 years. In adults, both sexes are affected equally but in children there is 2:1 malefemale ratio. ETIOPATHOGENESIS AND TYPES. Based on the stimuli initiating bronchial asthma, two broad etiologic types are traditionally described: extrinsic (allergic, atopic) and intrinsic (idiosyncratic, non-atopic) asthma. A third type is a mixed pattern in which the features do not fit clearly into either of the two main types. The contrasting features of the two main types are summed up in Table 17.6. 1. Extrinsic (atopic, allergic) asthma. This is the most common type of asthma. It usually begins in childhood or in early adult life. Most patients of this type of asthma have personal and/or family history of preceding allergic diseases such as rhinitis, urticaria or infantile eczema. Hypersensitivity to various extrinsic antigenic substances or 'allergens' is usually present in these cases. Most of these allergens cause ill-effects by inhalation e.g. house dust, pollens, animal danders, moulds etc. Occupational asthma stimulated by fumes, gases and organic and chemical dusts is a variant of extrinsic asthma. There are increased levels of IgE in the serum and positive skin test with the specific offending inhaled antigen representing an IgE-mediated type I hypersensitivity reaction which includes an 'acute immediate response' and a 'late phase reaction': Acute immediate response is initiated by IgE-sensitised mast cells (tissue

counterparts of circulating basophils) on the mucosal surface. Mast cells on degranulation release mediators like histamine, leukotrienes, prostaglandins, platelet activating factor and chemotactic factors for eosinophils and neutrophils. The net effects of these mediators are bronchoconstriction, oedema, mucus hypersecretion and accumulation of eosinophils and neutrophils. Late phase reaction follows the acute immediate response and is responsible for the prolonged manifestations of asthma. It is caused by excessive mobilisation of blood leucocytes that include basophils besides eosinophils andContrasting Features of the Two Major Types of Asthma. Feature Extrinsic Asthma Intrinsic Asthma

1. Age at onset In childhood In adult 2. Personal/family history Commonly present Absent 3. Preceding allergic illness (atopy) Present (e.g. rhinitis, urticaria, eczema) Absent 4. Allergens Present (dust, pollens, danders etc) None 5. Drug hypersensitivity None Present (usually to aspirin) 6. Serum IgE levels Elevated Normal 7. Associated chronic bronchitis, nasal polyps Absent Present 8. Emphysema Unusual Common

neutrophils. These result in further release of mediators which accentuate the above-mentioned effects. In addition, inflammatory injury is caused by neutrophils and by major basic protein (MBP) of eosinophils. 2. Intrinsic (idiosyncratic, non-atopic) asthma. This type of asthma develops later in adult life with negative personal or family history of allergy, negative skin test and normal serum levels of IgE. Most of these patients develop typical symptom-complex after an upper respiratory tract infection by viruses. Associated nasal polypi and chronic bronchitis are commonly present. There are no recognisable allergens but about 10% of patients become hypersensitive to drugs, most notably to small doses of aspirin (aspirin-sensitive asthma). 3. Mixed type. Many patients do not clearly fit into either of the above two categories and have mixed features of both. Those patients who develop asthma in early life have strong allergic component,

while those who develop the disease late tend to be non-allergic. Either type of asthma can be precipitated by cold, exercise and emotional stress.

MORPHOLOGIC FEATURES. The pathologic changes are similar in both major types of asthma. The pathologic material examined is generally autopsy of lungs in patients dying of status asthmaticus but the changes are expected to be similar in non-fatal cases. Grossly, the lungs are overdistended due to over-inflation. The cut surface shows characteristic occlusion of the bronchi and bronchioles by viscid mucus plugs. Microscopically, the following changes are observed (Fig. 17.21): 1. The mucus plugs contain normal or degenerated respiratory epithelium forming twisted strips called Curschmann's spirals. 2. The sputum usually contains numerous eosinophils and diamond-shaped crystals derived from eosinophils called Charcot-Leyden crystals. 3. The bronchial wall shows thickened basement membrane of the bronchial epithelium, submucosaloedema and inflammatory infiltrate consisting of lymphocytes and plasma cells with prominence of eosinophils. There is hypertrophy of submucosal glands as well as of the bronchial smooth muscle. 4. Changes of bronchitis and emphysema may supervene, especially in intrinsic asthma.

CLINICAL FEATURES. Asthmatic patients suffer from episodes of acute exacerbations interspersed with symptomfree periods. Characteristic clinical features are paroxysms of dyspnoea, cough and wheezing. Most attacks typically last for a few minutes to hours. When attacks occur continuously it may result in more serious condition called status asthmaticus. The clinical diagnosis is supported by demonstration of circulation eosinophilia and sputum demonstration of Curschmann's spirals and Charcot-Leyden crystals. More chronic cases may develop cor pulmonale.

EMPHYSEMA The WHO has defined pulmonary emphysema as combination of permanent dilatation of air spaces distal to the terminal bronchioles and the destruction of the walls of dilated air spaces. Thus, emphysema is defined morphologically, while chronic bronchitis is defined clinically. Since the two

conditions coexist frequently and show considerable overlap in their clinical features, it is usual to label patients as ‘predominant emphysema’ and ‘predominant bronchitis’. CLASSIFICATION. As mentioned in the beginning of this chapter, a lobule is composed of about 5 acini distal to a terminal bronchiole and that an acinus consists of 3 to 5 generations of respiratory bronchioles and a variable number of alveolar ducts and alveolar sacs (page 461). As per WHO definition of pulmonary emphysema, it is classified according to the portion of the acinus involved, into 5 types: centriacinar, panacinar (panlobular), para-septal (distal acinar), irregular (para-cicatricial) and mixed (unclassified) emphysema. A number of other conditions to which the term ‘emphysema’ is loosely applied are, in fact, examples of ‘overinflation’. A classification based on these principles is outlined in Table 17.4.

Classification of ‘True Emphysema’ and ‘Overinflation’.

A. TRUE EMPHYSEMA 1. Centriacinar (centrilobular) emphysema 2. Panacinar (panlobular) emphysema 3. Paraseptal (distal acinar) emphysema 4. Irregular (para-cicatricial) emphysema 5. Mixed (unclassified) emphysema

B. OVERINFLATION 1. Compensatory overinflation (compensatory emphysema) 2. Senile hyperinflation (aging lung, senile emphysema) 3. Obstructive overinflation (infantile lobar emphysema) 4. Unilateral translucent lung (unilateral emphysema) 5. Interstitial emphysema (surgical emphysema)

ETIOPATHOGENESIS. The commonest form of COPD is the combination of chronic bronchitis and pulmonary emphysema. Chronic bronchitis, however, does not always lead to emphysema nor all cases of emphysema have changes of chronic bronchitis. The association of the two conditions is principally linked to the common etiologic factors— most importantly tobacco smoke and air pollutants. Other less significant contributory factors are occupational exposure, infection and somewhat poorly-understood familial and genetic influences. All these factors have already been discussed above. However, pathogenesis of the most significant event in emphysema, the destruction of the alveolar walls, is not linked to bronchial changes but is closely related to deficiency of serum alpha-1-antitrypsin (α1-protease inhibitor) commonly termed protease-antiprotease hypothesis detailed below. Protease-antiprotease hypothesis. Alpha-1-antitrypsin

(α1-AT), also called α1-protease inhibitor (α-1-Pi), is a glycoprotein that forms the normal constituent of the α1globulin fraction of the plasma proteins on serum electrophoresis. The single gene locus that codes for α-1-AT is located on the long arm of chromosome 15. It is normally synthesised in the liver and is distributed in the circulating blood, tissue fluids and macrophages. The normal function of α1-AT is to inhibit proteases and hence its name α1protease inhibitor. The proteases (mainly elastases) are derived from neutrophils. Neutrophil elastase has the capability of digesting lung parenchyma but is inhibited from doing so by anti-elastase effect of α1-AT. There are several known alleles of α1-AT which have an autosomal codominant inheritance pattern and are classified as normal (PiMM), deficient (PiZZ), null type (Pi null null) having no detectable level, and dysfunctional (PiSS) type having about half the normal level.

The most common abnormal phenotype in classic α1-AT deficiency is homozygous state PiZZ resulting from a single amino acid substitution Glu→Lys which causes spontaneous polymerisation of α1-AT and inhibits its release from the liver. The remaining material of α1-AT in the liver causes hepatic cirrhosis. Clinically significant deficiency is also associated with homozygous Pi null null and heterozygous Pi nullZ. The heterozygote pattern of PiMZ has intermediate levels which is not sufficient to produce clinical deficiency, but heterozygote individuals who smoke heavily have higher risk of developing emphysema. The α1-AT deficiency develops in adults and causes pulmonary emphysema in smokers as well as in nonsmokers, though the smokers become symptomatic about 15 years earlier than non-smokers. The other organ showing effects of α1-AT deficiency is the liver which may develop obstructive jaundice early in infancy, and cirrhosis and hepatoma late in adulthood (Chapter 22). The mechanism of alveolar wall destruction in emphysema by elastolytic action is based on the imbalance between proteases (chiefly elastase) and anti-proteases (chiefly anti-elastase): By decreased anti-elastase activity i.e. deficiency of α-1 antitrypsin. By increased activity of elastase i.e. increased neutrophilic infiltration in the lungs causing excessive elaboration of neutrophil elastase. There are enough evidences to suggest that smoking promotes emphysema by both decreasing the amount of antielastase as well as by increasing the elastolytic protease in the lungs. These are as under: 1. Oxidant in cigarette smoke has inhibitory influence on α-1-antitrypsin, thus lowering the level of anti-elastase activity.

Contrasting Salient Features of ‘Predominant Bronchitis’ and ‘Predominant Emphysema’. Feature Predominant Bronchitis Predominant Emphysema

1. Age at diagnosis About 50 years About 60 years

2. Underlying pathology Hypertrophy of mucus-producing Inflammatory narrowing of bronchioles and cells destruction of septal walls

3. Dyspnoea Late, mild Early, severe

4. Cough Before dyspnoea starts After dyspnoea starts

5. Sputum Copious, purulent Scanty, mucoid, less frequent

6. Bronchial infections More frequent Less frequent

7. Respiratory insufficiency Repeated Terminal

8. Cyanosis Common (‘blue-bloaters’) Rare (‘pink-puffers’)

9. Lung capacity Normal Increased (barrel-chest) 10. Blood gas values ↓ pO2, ↓ pCO2, no compensatory pO2 and pCO2 usually within normal limits due hyperventilation to compensatory hyperventilation

11. Cor pulmonale Frequent Rare and terminal

12. Chest X-ray Large heart, prominent vessels Small heart, hyperinflated lungs

2. Smokers have up to ten times more phagocytes and neutrophils in their lungs than nonsmokers; thus they have very high elastase activity. Pathogenesis of emphysema by protease-antiprotease mechanism is diagrammatically illustrated in Fig. 17.17. PATHOLOGIC FEATURES. Emphysema can be diagnosed with certainty only by gross and histologic examination of sections of whole lung. The lungs should be perfused with formalin under pressure in inflated state to grade the severity of emphysema with naked eye.

Grossly, the lungs are voluminous, pale with little blood. The edges of the lungs are rounded. Mild cases show dilatation of air spaces visible with hand lens. Advanced cases show subpleural bullae and blebs bulging outwards from the surface of the lungs with rib markings between them. The bullae are air-filled cyst-like or bubble-like structures, larger than 1 cm in diameter (Fig. 17.18). They

are formed by the rupture of adjacent air spaces while blebs are the result of rupture of alveoli directly into the subpleural interstitial tissue and are the common cause of spontaneous pneumothorax. Microscopically, depending upon the type of emphysema, there is dilatation of air spaces and destruction of septal walls of part of acinus involved i.e. respiratory bronchioles, alveolar ducts and alveolar sacs. Changes of bronchitis may be present. Bullae and blebs when present show fibrosis and chronic inflammation of the walls.

CLINICAL FEATURES. Cases of 'predominant emphysema' develop clinical features after about one-third of the pulmonary parenchyma is damaged which occurs most severely in panacinar emphysema. The age at the time of diagnosis is often a decade later (about 60 years) than the age for predominant bronchitis (about 50 years). Though there is considerable overlap between the clinical features of chronic bronchitis and emphysema, the following features generally characterise 'predominant emphysema' (Table 17.5): 1. There is long history of slowly increasing severe exertional dyspnoea. 2. Patient is quite distressed with obvious use of accessory muscles of respiration.

3. Chest is barrel-shaped and hyperresonant. 4. Cough occurs late after dyspnoea starts and is associated with scanty mucoid sputum. 5. Recurrent respiratory infections are not frequent. 6. Patients are called 'pink puffers' as they remain well oxygenated and have tachypnoea. 7. Weight loss is common. 8. Features of right heart failure (cor pulmonale) and hypercapneic respiratory failure are the usual terminal events. 9. Chest X-ray shows small heart with hyperinflated lungs. After these general comments about morphologic and clinical features of emphysema, the specific pathologic changes in individual types of 'emphysema' and 'overinflation' as classified in Table 17.4 are described below.

Morphology of Individual Types of Emphysema

1. CENTRIACINAR (CENTRILOBULAR) EMPHYSEMA. Centriacinar or centrilobular emphysema is one of the common types. It is characterised by initial involvement of respiratory bronchioles i.e. the central or proximal part of the acinus (Fig. 17.19,B). This is the type of emphysema that usually coexists with chronic bronchitis and occurs predominantly in smokers and in coal miners' pneumoconiosis

2. PANACINAR (PANLOBULAR) EMPHYSEMA. Panacinar or panlobular emphysema is the other common type. In this type, all portions of the acinus are affected but not of the entire lung (Fig. 17.19,C). Panacinar emphysema is most often associated with α1-antitrypsin deficiency in middle-aged smokers and is the one that produces the most characteristic anatomical changes in the lung in emphysema.

Grossly, in contrast to centriacinar emphysema, the panacinar emphysema involves lower zone of lungs more frequently and more severely than the upper zone. The involvement may be confined to a few lobules, or may be more widespread affecting a lobe or part of a lobe of the lung. The lungs are enlarged and overinflated.

.ACUTE RENAL FAILURE. As already described above, acute renal failure (ARF) is characterised by rapid decline in renal function. ARF has many causes including glomerular disease, principally rapidly progressive GN and acute diffuse proliferative GN.

IV.CHRONIC RENAL FAILURE. Glomerular causes of chronic renal failure (CRF) have already been described. These cases have advanced renal impairment progressing over years and is detected by significant proteinuria, haematuria, hypertension and azotaemia. Such patients generally have small contracted kidneys due to chronic glomerulonephritis.

Ischemic heart disease

Ischaemic heart disease (IHD) is defined as acute or chronic form of cardiac disability arising from imbalance between the myocardial supply and demand for oxygenated blood.

ETIOPATHOGENESIS IHD is invariably caused by disease affecting the coronary arteries, the most prevalent being atherosclerosis accounting for more than 90% cases, while other causes are responsible for less than 10% cases of IHD. Therefore, it is convenient to consider the etiology of IHD under three broad headings: i) coronary atherosclerosis; ii) superadded changes in coronary atherosclerosis; and iii) non-atherosclerotic causes.

I. Coronary Atherosclerosis Coronary atherosclerosis resulting in ‘fixed’ obstruction is the major cause of IHD in more than 90% cases. The general aspects of atherosclerosis as regards its etiology, pathogenesis and the morphologic features of atherosclerotic lesions have already been dealt with at length in the preceding Chapter 15. Here, a brief account of the specific features in pathology of lesions in atherosclerotic coronary artery disease in particular are presented. 1. Distribution. Atherosclerotic lesions in coronary arteries are distributed in one or more of the three major coronary arterial trunks, the highest incidence being in the anterior descending branch of the left coronary, followed in decreasing frequency, by the right coronary artery and still less in circumflex branch of the left coronary. About onethird of cases have single-vessel disease, most often left anterior descending arterial involvement; another one-third have twovessel disease, and the remainder have three major vessel disease. 2. Location. Almost all adults show atherosclerotic plaques scattered throughout the coronary arterial system. However, significant stenotic lesions that may produce chronic myocardial ischaemia show more than 75% (three-fourth) reduction in the cross-sectional area of a coronary artery or its branch. The area of severest involvement is about 3 to 4 cm from the coronary ostia, more often at or near the bifurcation of the arteries, suggesting the role of haemodynamic forces in atherogenesis. 3. Fixed atherosclerotic plaques. The atherosclerotic plaques in the coronaries are more often eccentrically located bulging into the lumen from one side (Fig. 16.13). Occa

sionally, there may be concentric thickening of the wall of the artery. Atherosclerosis produces gradual luminal narrowing that may eventually lead to ‘fixed’ coronary obstruction. The general features of atheromas of coronary arteries are similar to those affecting elsewhere in the body and may develop similar complications like calcification, coronary thrombosis, ulceration, haemorrhage, rupture and aneurysm formation.

II. Superadded Changes in Coronary Atherosclerosis The attacks of acute coronary syndromes, which include acute myocardial infarction, unstable angina and sudden ischaemic death, are precipitated by certain changes superimposed on a pre-existing fixed coronary atheromatous plaque. These changes are as under: 1. Acute changes in chronic atheromatous plaque. Though chronic fixed obstructions

are the most frequent cause of IHD, acute coronary episodes are often precipitated by sudden changes in chronic plaques such as plaque haemorrhage, fissuring, or ulceration that results in thrombosis and embolisation of atheromatous debris. Acute plaque changes are brought about by factors such as sudden coronary artery spasm, tachycardia, intraplaque haemorrhage and hypercholesterolaemia. 2. Coronary artery thrombosis. Transmural acute myocardial infarction is often precipitated by partial or complete coronary thrombosis. The initiation of thrombus occurs due to surface ulceration of fixed chronic atheromatous plaque, ultimately causing complete luminal occlusion. The lipid core of plaque, in particular, is highly thrombogenic. Small fragments of thrombotic material are then dislodged which are embolised to terminal coronary branches and cause microinfarcts of the myocardium.