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Genetic and Selected Nongenetic Disorders of the Respiratory Tract

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TRACHEOBRONCHOMEGALY

The typical pathologic features of tracheobronchomegaly (*i.e.*, Mounier-Kuhn syndrome) are dilatation of the trachea and major bronchi. There is frequently saccular bulging of the intercartilaginous septa, but bronchial dilatation alone occurs rarely. A transverse tracheal diameter greater than 2.5 cm or right and left main bronchial diameters greater than 2.3 and 2.0 cm, respectively, may suggest the diagnosis in adults. The clinical features are loud, nonproductive cough and recurrent bronchitis or pneumonitis, with symptoms often beginning in childhood. The condition appears to be an autosomal recessive disease.[1,2]

TRACHEOBRONCHOPATHIA OSTEOPLASTICA

Tracheobronchopathia osteoplastica is more common than Mounier-Kuhn syndrome. The pathologic features are cartilaginous and bony deposits in the membranes between the cartilage rings of the lower trachea and frequently of the major bronchi; only the bronchi can be involved. The pars membranacea of the airway is not involved. Clinical features include cough, hoarseness, dyspnea, and hemoptysis.[3] This disorder must be differentiated from endotracheal or endobronchial chondroma, which is usually a solitary lesion (see Chap. 73).

FOCAL MUSCULAR HYPERPLASIA OF THE TRACHEA

Focal muscular hyperplasia of the trachea is rare, and apparently nothing is known of the pathogenesis of this condition.[4]

CONGENITAL PULMONARY LYMPHANGIECTASIA

Congenital pulmonary lymphangiectasia, with enlarged dilated lymphatics in the interlobular septa of the lung (Color Fig. 9-1), must be differentiated microscopically from endolymphatic air, a regular finding in infants with pulmonary interstitial emphysema with hyaline membrane disease or other conditions of excessive inspiratory pressure. The lungs in pulmonary lymphangiectasia are typically enlarged and firm. The lesion is commonly associated with obstructed total anomalous pulmonary venous return (TAPVR) and is unusually frequent in the Ivemark asplenia syndrome (see Chap. 7). It has been proposed that the reduced pulmonary compliance of the process provides a major limitation to successful surgical treatment of obstructed TAPVR.[5]

IDIOPATHIC PULMONARY MICROLITHIASIS

Idiopathic pulmonary microlithiasis can be congenital, and a significant fraction of patients with the disease are diagnosed in childhood. The lesion consists of laminated concretions predominantly composed of calcium carbonate in alveolar lumens, sometimes in alveolar septa and bronchiolar walls, and rarely in extrapulmonary loci such as the testis and sympathetic chain. Although most often identified in chest radiographs obtained for other reasons that show a diffuse fine pulmonary infiltration of the middle lung fields with relative sparing of bases and apices of the lungs, the disorder leads to slowly progressive pulmonary and cardiac failure, with death usually in or after the fourth decade.[6]

PULMONARY LYMPHANGIOMYOMATOSIS

Pulmonary lymphangiomyomatosis, also called pulmonary muscular hyperplasia or muscular pulmonary cirrhosis, is restricted to females between puberty and menopause and causes rapidly progressive pulmonary failure. Death usually occurs after 5 to 10 years. The irregular laminar or nodular proliferation of smooth muscle seen in the lungs can also affect the thoracic duct and mediastinal and retroperitoneal lymph nodes. Chylothorax may be a feature in addition to respiratory difficulty, pneumothorax, and hemoptysis. The radiologic picture can be that of honeycomb lung. The process is similar to that of the pulmonary lesion of tuberous sclerosis, an autosomal dominant genetic disorder, and the apparent restriction of the condition to females is unexplained.[7–12]

PRIMARY PULMONARY HYPERTENSION

The pathogenesis of primary pulmonary hypertension, which shows a female preponderance and can be familial, is obscure. The muscular thickening of pulmonary arteries and arterioles caused by pulmonary venous hypertension can be similar, and adequate study of lung biopsies to ensure the patient does not have pulmonary venoocclusive disease rather than primary pulmonary hypertension is essential (see Chap. 23).[5] Some patients have changes in other organs that suggest collagen disease, and appropriate studies to rule out mixed connective disease, which may cause pulmonary hypertension, are indicated.

SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax can occur in Marfan syndrome, which can also cause marked emphysema, especially of the upper lung fields, in infancy.[5,13] However, spontaneous pneumothorax can occur as a primary disease and can have a familial pattern of occurrence. Further study of connective tissue, especially collagen chemistry, in spontaneous pneumothorax could be informative.

CYSTIC FIBROSIS OF THE PANCREAS

Cystic fibrosis of the pancreas (CFP) is the most common genetic disorder causing death in childhood in populations of European origin, but it is uncommon in populations of African origin and rare in Asians. The respiratory tract lesion of bronchiolar obstruction by abnormally viscous mucus is rarely clinically significant before 3 months of age, but it leads to purulent infection of the air passages, usually by strains of *Pseudomonas aeruginosa* or by *Staphylococcus aureus*. The inflammatory process leads to slowly progressive bronchiolectasis and bronchiectasis, which usually first become apparent in the upper lobes. Pulmonary fibrosis from regurgitation of exudate into the lung parenchyma and from organization of exudate in ulcerated, smaller air passages may occur in the late stages. Lung abscess can occur, and middle lobe syndrome, probably caused by bronchial compression by enlarged, massively plasma cell-laden, hilar lymph nodes, is not uncommon.

Squamous metaplasia of airway epithelium as a result of vitamin A deficiency because of malabsorption has become uncommon. Males with CFP are almost invariably aspermic because of atresia of the vasa deferentia and abnormalities of the epididymides and seminal vesicles; these lesions have been observed in infants at 3 days of age. Male patients with CFP and their clinically unaffected male siblings have an increased frequency of inguinal hernia or hydrocele. The product of the *CFTR* gene, located on chromosome 7, called the cystic fibrosis transmembrane conductance regulator, is a component of a cell membrane chloride pore; several different mutations of the gene are known. Some clinically normal males with bilateral congenital absence of the vasa deferentia are compound heterozygotes for one of the more frequent mutations of the *CFTR* gene (*i.e.*, AF508 mutation) and for a rare mutation (see Chap. 11).[14–16]

YOUNG SYNDROME

The diagnostic features of Young syndrome are obstructive azoospermia, typically with palpable cystic changes of the epididymis; chronic sinusitis; bronchitis with elevated production of secretions; or bronchiectasis. No other features of CFP are present. A few patients with the syndrome fathered children when young, but they became aspermic and sterile later in life.[17] The extent to which these patients are compound heterozygotes for mutations or other abnormalities of the CFP gene requires further study. Cystic obstructive lesions of the epididymis have been reported in older men with adult polycystic disease of kidneys and liver, a dominant disorder for which gene testing is available (see Chap. 11).

IMMOTILE CILIA SYNDROME

The group of conditions called immotile cilia syndrome has been mentioned as Kartagener syndrome in the discussion of disorders of abnormal visceral situs (see Chap. 7). Nasal, sinus, and respiratory tract infections from defective ciliary epithelial toilette are major clinical features. Electron microscopic study of the cilia in nasal or tracheal mucosal biopsies have shown several ultrastructural abnormalities in these patients, some perhaps secondary (see Chap. 11).[14,17]

FIBROCYSTIC PULMONARY DYSPLASIA AND OTHER GENETIC DISORDERS WITH PULMONARY FIBROSIS

Tachypnea and cyanosis are clinical features of the autosomal dominant disorder fibrocystic pulmonary dysplasia (FCPD).[18–20] Clinical onset may be in childhood, and early-onset carcinoma of the lung is a feature of this disease.[21] Apparently dominant pulmonary fibrosis with relatively rapid onset and progression to pulmonary failure in men in middle life may be a different disorder.

Pulmonary fibrosis also is a frequent feature of several autoimmune disorders and immunodeficiency conditions in childhood, most often ataxia-telangiectasia.[22–24] It can also occur in

von Recklinghausen neurofibromatosis and in the syndrome of familial lymphedema, pleural effusions, and yellow nails.[25–29]

Diaz and colleagues observed that an increase in the number of pulmonary mast cells was often associated with a syndrome of interstitial pneumonitis progressing to pulmonary fibrosis and pulmonary insufficiency. Whether the mastocytosis is a feature of the fibrotic process or is causative through secretion of vasoactive and other factors is unknown.

## PULMONARY EMPHYSEMA OF α_1-ANTITRYPSIN DEFICIENCY

Pulmonary emphysema of α_1-antitrypsin deficiency is an autosomal codominant disorder and a significant cause of pulmonary emphysema, with clinical onset typically occurring after 20 years of age (see Chap. 26). Clinical features of the disease in children consist of episodes of transient neonatal cholestatic jaundice with hepatic cirrhosis presenting in the second decade. The mechanism of the progressive emphysema is considered to be deficient control of elastase activity in the lungs, resulting in destruction of alveolar tissue. The ease of determining the *PI* gene, which codes for the protease inhibitor, makes neonatal screening simple. Human-derived and recombinant DNA preparations of α_1-antitrypsin are available, and effective synthetic elastase inhibitors may soon be developed.[30]

PULMONARY ALVEOLAR SEPTAL AND STROMAL CALCINOSIS

Pulmonary alveolar septal and stromal calcinosis, the clinical picture of which is confusingly subtle, can rapidly progress to pulmonary insufficiency in children with chronic renal insufficiency (Color Fig. 9-2). It is perhaps most strikingly associated with renal hypodysplasia in male infants, but it can have a relatively abrupt appearance after renal transplantation or in pediatric patients with end-stage renal disease.[31, 32] Several children with acute lymphatic leukemia and death from pulmonary alveolar calcinosis have been reported.[33]

PRIMARY AND SECONDARY PULMONARY HEMOSIDEROSIS

The cause of primary or idiopathic pulmonary hemosiderosis (IPH) in children is not determined but may be an autoimmune effect (Fig. 9-1). The clinical features are those of episodic respiratory distress with laboratory findings of hemolytic anemia. Cutz described a marked increase in the number of mast cells in the lungs of patients with IPH (Color Fig. 9-3).[34] Pulmonary hemosiderosis often affects patients with pulmonary venous hypertension, and in the past, it was associated with the mitral stenosis of rheumatic fever. Pulmonary siderosis from aspiration of blood
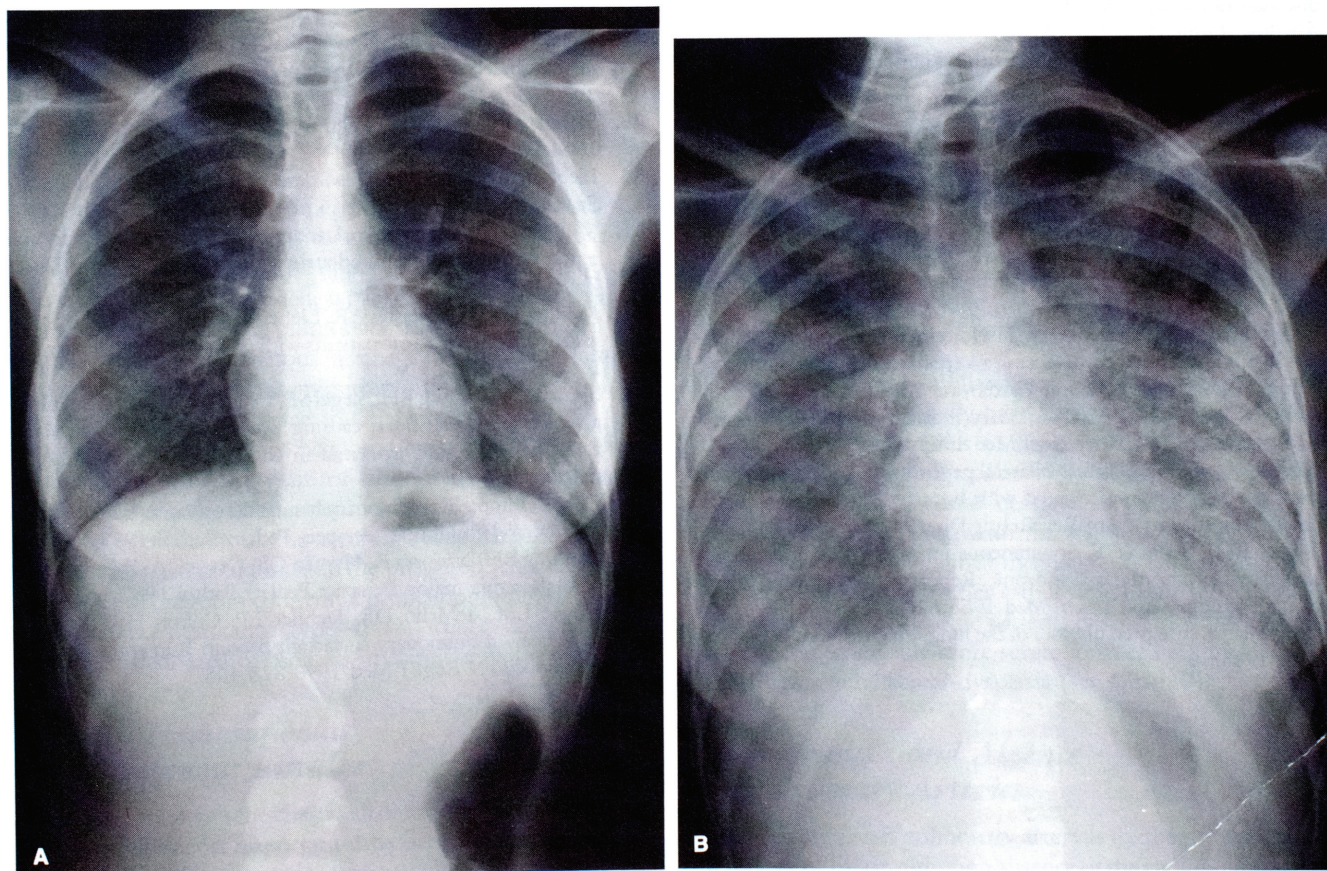
FIGURE 9-1. Chest x-ray film of a 10-year-old girl (**A**) before and (**B**) after the onset of primary pulmonary hemosiderosis that presented as a flulike illness followed by respiratory difficulties. (Contributed by the editor.)

from angiomas of the pharynx or upper airway is rare. The major cause of pulmonary hemosiderosis in childhood is thalassemia major, which causes a massive accumulation of hemosiderin-laden macrophages in the alveoli with ferrugination of connective tissue and blood vessel walls (Color Fig. 9-4). The reduction of pulmonary compliance by the stromal ferrugination and the increase in pulmonary mass that must be moved with respiration have been proposed as explanations of the physiologic effects of pulmonary hemosiderosis in thalassemia (see Chap. 11).[35]

PULMONARY SURFACTANT PROTEIN B DEFICIENCY

This recently described condition causes severe postnatal respiratory difficulty and early death. The pathologic findings in the lungs resemble those of alveolar proteinosis.[36]

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