narrowing, all of which contribute to airflow obstruction. Mucus plugs and inflammatory exudates can occlude the small airways, leading to increased resistance to airflow.

Recently, demonstration of profound decreases in small airway numbers and cross-sectional area in lungs of individuals with COPD has provided important evidence that loss of the small airways occurs with sufficient severity to result in the spirometrically detectable expiratory airflow limitation that characterizes COPD. Indeed, there is evidence that small airway loss may precede emphysema development in COPD.

Immune-mediated abnormalities are also seen at the level of the small airways in COPD. Lymphoid follicles may form around these airways in response to ongoing antigenic stimulation and bacterial infection, with a prominence of B cells and CD8+ T cells in more advanced COPD. Emphysema is associated with airflow obstruction of the small airways caused by destruction of the alveoli tethered to the airways, which normally provide a force opposing airway closure. These myriad changes at the small airway level contribute significantly to the physiologic abnormalities and altered local immune response in COPD.

Clinical Presentation

COPD related to chronic tobacco exposure is characterized by slowly progressive dyspnea that is first noticed during exertion but progresses over years until it is evident with minimal exertion (e.g., when dressing) or even at rest. Affected individuals complain of exercise intolerance and fatigue, and the disease eventually may lead to weight loss, depression, and anxiety as a result of increased work of breathing. Chronic cough can be present and is productive or dry, depending on the degree of mucus metaplasia (e.g., chronic bronchitis). In general, emphysema caused by chronic cigarette smoking is almost never observed in patients before 40 years of age. If it is, consideration should be given to genetic disorders such as α_1-antitrypsin deficiency.

During the early stages of COPD, the physical examination may be normal. Normal examination results and the absence of symptoms often delay diagnosis. Inspection of the thorax and palpation may fail to reveal findings. As the disease progresses, the lungs may become hyperresonant to percussion, and auscultation may show diminished breath sounds with rhonchi or wheezes. The chest wall may begin to remodel, giving the patient the appearance of a "barrel chest." During the late stages of COPD, patients show evidence of increased work of breathing with use of accessory muscles, pursed-lip breathing, and weight loss. Skeletal muscle wasting may also become evident. Despite their respiratory insufficiency, some patients are able to sustain relatively normal oxygen levels in blood until very late in the disease, leading to the classic clinical presentation of the "pink puffer." Other patients tend to retain carbon dioxide and diminish their work of breathing, resulting in chronic respiratory acidosis and, in extreme cases, polycythemia and cyanosis; this is the prototypical "blue bloater" phenotype. There is also an overlap of COPD with other respiratory disorders, such as obstructive sleep apnea, that may contribute to carbon dioxide retention.

Although COPD results in chronic, progressive dyspnea, periodic acute exacerbations are also characteristic. A rapidly worsening of pulmonary function and an increased burden of respiratory symptoms such as dyspnea, cough, and sputum production characterize COPD exacerbations. Acute exacerbations are associated with various triggers, most importantly viral or bacterial respiratory infections, air pollution or other environmental factors, pulmonary embolism, and cardiac failure. Exacerbations are more common with increasing severity of COPD, with increasing age, and during the winter months. Exacerbations vary widely in severity. Severe exacerbations may lead to hospitalization, acute respiratory failure, and death. After an exacerbation, it may take weeks for the patient to return to a baseline level of function. Patients with frequent exacerbations of COPD experience an accelerated rate of decline in FEV_1. Patients who have experienced a COPD exacerbation are more likely to experience future exacerbations, suggesting that exacerbation is an important event in the natural history of COPD. On occasion, an exacerbation of COPD leading to acute respiratory failure is the first event leading to the diagnosis of COPD in an individual patient.

COPD is associated with a number of comorbid conditions, such as atherosclerotic heart disease, lung cancer, osteoporosis, and depression. These comorbidities may be related to smoking, to the chronic systemic inflammation present in patients with COPD, to the impaired quality of life resulting from COPD, or to treatments (e.g., corticosteroids) administered during the course of COPD. Monitoring for and appropriate management of these coexisting disorders is an important part of the ongoing assessment of patients with COPD.

As COPD progresses, the lung volumes increase (hyperinflation) and the diaphragms flatten, rendering inspiratory excursions inefficient. Tidal volume decreases and respiratory rate increases in an effort to decrease the work of breathing. In advanced disease, the cardiovascular system becomes affected as a result of the loss of vasculature in destroyed alveolar walls and vasoconstriction and vascular remodeling due to chronic hypoxia. With a limited area for blood flow, pulmonary vascular resistance is increased, leading to increased right ventricular afterload and development of pulmonary hypertension. This accelerates the development of right ventricular failure, which is referred to as cor pulmonale in the setting of lung disease. Right heart gallop, distended neck veins, hepatojugular reflux, and leg edema characterize cor pulmonale.

Diagnosis and Differential Diagnosis

Diagnosis

Pulmonary function tests, especially spirometry, are essential for the diagnosis of COPD. A reduced FEV_1/FVC ratio (<0.70) on spirometry performed after administration of a bronchodilator is diagnostic of COPD. Although some degree of reversibility of the obstruction may be detected with bronchodilators, and airway hyperreactivity can be unveiled by bronchoprovocation challenges if performed, the obstructive defect is not entirely reversible in COPD. This characteristic and the consistent and progressive nature of the expiratory flow limitation represent key features that help distinguish COPD from asthma, a major differential diagnostic consideration. The severity of disease and prognosis can be estimated by the FEV_1: