PATHOPHYSIOLOGY

The pathophysiology of HP has not been characterized in depth on an immunologic level, although it has been established that HP is an immune-mediated condition that occurs in response to inhaled antigens that are small enough to deposit in distal airways and alveoli. From a lymphocyte perspective, HP has been categorized as a condition with a T_H1 inflammatory pattern. However, emerging evidence suggests that T_H17 lymphocyte subsets may be involved in the pathogenesis of the disease as well. Although the presence of precipitating IgG antibodies against specific antigens in HP suggests a prominent role for adaptive immunity in the pathophysiology of HP, innate immune mechanisms may also make an important contribution. This is highlighted by the observation that Toll-like receptors and downstream signaling proteins such as MyD88 are activated in HP. Although no clear genetic basis for HP has been established, in specific cohorts, polymorphisms in genes involved in antigen processing and presentation, including TAP1 and major histocompatibility complex type II, have been observed.

CLINICAL PRESENTATION

Given the heterogeneity among patients, variability in offending antigens, and differences in the intensity and duration of exposure to antigen, the presentation of HP is accordingly variable. Although these categories are not fully satisfactory in capturing this variability, HP has been traditionally categorized as having *acute, subacute, and chronic* forms. Acute HP usually manifests itself 4–8 h following exposure to the inciting antigen, often intense in nature. Systemic symptoms, including fevers, chills, and malaise, are prominent and are accompanied by dyspnea. Symptoms resolve within hours to days if no further exposure to the offending antigen occurs. In subacute HP resulting from ongoing antigen exposure, the onset of respiratory and systemic symptoms is typically more gradual over the course of weeks. A similar presentation may occur as a culmination of intermittent episodes of acute HP. Although respiratory impairment may be quite severe, antigen avoidance generally results in resolution of the symptoms, although with a slower time course, on the order of weeks to months, than that seen with acute HP. Chronic HP can present with an even more gradual onset of symptoms than subacute HP, with progressive dyspnea, cough, fatigue, weight loss, and clubbing of the digits. The insidious onset of symptoms and frequent lack of an anteceding episode of acute HP make diagnosing chronic HP a challenge. Unlike with the other forms of HP, there can be an irreversible component to the respiratory impairment that is not responsive to removal of the responsible antigen from the patient's environment. The disease progression to hypoxemic respiratory failure can mirror that seen in idiopathic pulmonary fibrosis (IPF). Fibrotic lung disease is a potential feature of chronic HP due to exposure to bird antigens, whereas an emphysematous phenotype may be seen in farmer's lung.

The categories of acute, subacute, and chronic HP are not completely sufficient in classifying HP. The HP Study Group found on cluster analysis that a cohort of HP patients is best described in bipartite fashion, with one group featuring recurrent systemic signs and symptoms and the other featuring more severe respiratory findings.

Concordant with the variability in the presentation of HP is the observed variability in outcome. HP that has not progressed to chronic lung disease has a more favorable outcome with likely resolution if antigen avoidance can be achieved. However, chronic HP resulting in lung fibrosis has a poorer prognosis, with patients with chronic pigeon breeder's lung having demonstrated a similar mortality as seen in IPF.

DIAGNOSIS

Although there is no set of universally accepted criteria for arriving at a diagnosis of HP, diagnosis depends foremost on establishing a history of exposure to an offending antigen that correlates with respiratory and systemic symptoms. A careful occupational and home exposure history should be taken and may be supplemented if necessary by a clinician visit to the work or home environment. Specific inquiries will be influenced by geography and the occupation of the patient. When HP is suspected by history, the additional workup is aimed at establishing an immunologic and physiologic response to inhalational antigen exposure with chest imaging, pulmonary function testing, serologic studies, bronchoscopy, and, on occasion, lung biopsy.

Chest Imaging Chest x-ray findings in HP are nonspecific and can even lack any discernible abnormalities. In cases of acute and subacute HP, findings may be transient and can include ill-defined micronodular opacities or hazy ground-glass airspace opacities. Findings on chest x-ray will often resolve with removal from the offending antigen, although the time course of resolution may vary. With chronic HP, the abnormalities seen on the chest radiograph are frequently more fibrotic in nature and may be difficult to distinguish from IPF.

With the wide availability of high-resolution computed tomography (HRCT), this modality has become a common component in the diagnostic workup for HP. Although the HRCT may be normal in acute forms of HP, this may be due to lack of temporal correlation between exposure to the offending antigen and obtaining the imaging. Additionally, because of the transient nature of acute HP, HRCT is not always performed. In subacute forms of the disease, ground-glass airspace opacities are characteristic, as is the presence of centrilobular nodules. Expiratory images may show areas of air trapping that are likely caused by involvement of the small airways **(Fig. 310-1)**. Reticular changes and traction bronchiectasis can be observed in chronic HP. Subpleural honeycombing similar to that seen in IPF may be present in advanced cases, although unlike in IPF, the lung bases are frequently spared.

Pulmonary Function Testing (PFT) Either restrictive or obstructive PFTs can be present in HP, so the pattern of PFT change is not useful in establishing the diagnosis of HP. However, obtaining PFTs is of use in characterizing the physiologic impairment of an individual patient and in gauging the response to antigen avoidance and/or corticosteroid therapy. Diffusion capacity for carbon monoxide may be significantly impaired, particularly in cases of chronic HP with fibrotic pulmonary parenchymal changes.

Serum Precipitins Assaying for precipitating IgG antibodies against specific antigens can be a useful adjunct in the diagnosis of HP. However, the presence of an immunologic response alone is not sufficient for establishing the diagnosis, because many asymptomatic individuals with high levels of exposure to antigen may display serum precipitins, as has been observed in farmers and in pigeon breeders. It should also be noted that panels that test for several specific serum

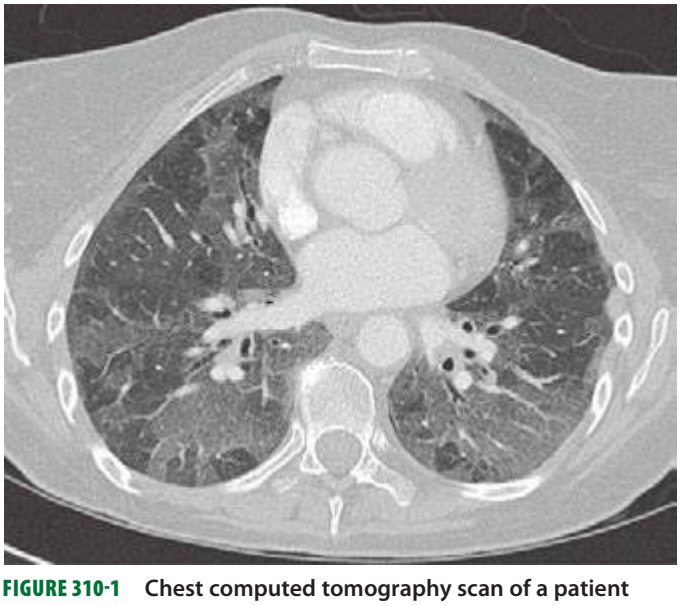

FIGURE 310-1 Chest computed tomography scan of a patient with subacute hypersensitivity pneumonitis in which scattered regions of ground-glass infiltrates in a mosaic pattern consistent with air trapping are seen bilaterally. This patient had bird fancier's lung. *(Courtesy of TJ Gross; with permission.)*