Hypersensitivity Pneumonitis

Histopathology

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Context.—The classic histopathology of hypersensitivity pneumonitis (HSP) is well known but variations do occur and at times the diagnosis can be difficult. This is particularly true in the chronic stage of the disease.

Objective.—To review the wide variety of histopathologic changes that can be seen in HSP and to offer a practical approach to diagnosis, including the diagnosis of recently described variants of HSP such as the so-called hot tub lung.

Data Sources.—This review draws from the author’s own experience and a concurrent search of national and international literature.

Conclusions.—The diagnosis of HSP can be made with confidence only in light of clinical, serologic, and radiographic data. A particular challenge for pathologists is the recognition of the disease in its chronic stage. In this stage, the identification of poorly formed granulomas in association with (1) a pattern of homogeneous linear fibrosis and (2) irregular fibrosis in a partially peribronchiolar distribution would facilitate the diagnosis.


Little is known about the gross pathologic features of hypersensitivity pneumonitis (HSP) and equally scant information is available on the microscopy of its acute stage. Therefore, this discussion is largely limited to the histopathology of the subacute and chronic stages of the disease.

In the subacute stage, there may be irregular areas of patchy consolidation that tend to be centriacinar in distribution. The chronic stage has been well described and consists of interstitial fibrosis with honeycomb change in areas, which in some cases may be indistinguishable from other causes of pulmonary fibrosis. Lung biopsies are usually obtained from patients with subacute or chronic disease, whereas acute HSP is less often seen in surgical pathology material because the patient may not seek medical attention during this stage or the diagnosis may be made clinically; therefore, there are few descriptions of the acute phase of the disease. The histopathology of acute farmer’s lung has been described as that of acute diffuse alveolar damage with necrosis and an acute inflammatory infiltrate including areas of vasculitis. The histopathology of the subacute and chronic manifestations of HSP is well known and is similar, regardless of the responsible antigen. Some of the differences attributed in the literature to certain antigens may be more related to the stage of the disease than to a specific etiology; nevertheless, these exceptions are mentioned later in this article. In the subacute stage, there is typically an interstitial pneumonitis that tends to be bronchiolocentric (Figure 1), with interstitial lymphoplasmacytic infiltrates, cellular bronchiolitis, and so-called poorly formed (loose) nonnecrotizing granulomas, isolated giant cells (Figure 2) with occasional cholesterol clefts, and Schaumann bodies. In reality these “granulomas” are aggregates of lymphocytes, plasma cells, and macrophages as well as multinucleated giant cells. They are usually small and poorly circumscribed and tend to blend with the surrounding interstitial infiltrate (Figure 3), which helps to distinguish them from granulomas in other granulomatous diseases. Stains for microorganisms (fungi, acid fast organisms) are usually negative (with the possible exception of some cases of hot tub disease). Obliterative bronchiolitis can also be present in some patients (Figure 4), and it is important to keep in mind that, although HSP is essentially an interstitial disease, a small airway obstructive component may also be significant and is seen as bronchiolar involvement by the pathologist. A triad of interstitial pneumonitis, cellular bronchiolitis, and ill-defined granulomas has been described in 80% of the well-documented cases of HSP. Some cases will demonstrate only 1 or 2 of these features, and in these cases, it is particularly important to demonstrate a chronologic relation between exacerbations and exposures to the causal antigen. Lymphoid follicles may be present, but this is not a constant or prominent finding. Occasional areas of organizing pneumonia with Masson bodies are commonly seen (Figure 5). Eosinophils and neutrophils are not a prominent feature in HSP. Certain antigens have been associated with a tissue response; some examples follow. In farmer’s lung, the biopsy may show extensive bronchiolitis obliterans with numerous fibroblastic plugs admixed with chronic inflammatory cells. It is possible to find staining for thermophilic Actinomyces or spores of Cryptostroma corticale within histiocytes or granulomas in maple bark stripper’s disease.
Figure 1. Note dense distinct inflammatory reaction in a peribronchiolar location (hematoxylin-eosin, original magnification ×2).

Figure 2. A poorly formed granuloma made up of large multinucleated cells with cholesterol clefs and a cuffing of a small lymphocytes (hematoxylin-eosin, original magnification ×4).

Figure 3. The granulomas are scattered in the lung parenchyma, at times blending into the surrounding interstitial infiltrate (hematoxylin-eosin, original magnification ×10).

Figure 4. Obliterative bronchiolitis with an intraluminal plug of young connective tissue. Note partial loss of bronchiolar epithelium (hematoxylin-eosin, original magnification ×10).
In some cases of pigeon breeder’s disease, biopsies taken during subacute stages show marked peribronchiolar inflammation and prominent follicular hyperplasia of the bronchial-bronchiolar–associated lymphoid tissue. Patients with pigeon breeder’s disease frequently show collections of foamy macrophages, which may represent small foci of endogenous lipid pneumonia (Figure 6), although it has been suggested that some antigens (such as those seen in pigeon breeder’s disease) may be present in some of these foamy cells.13

Hot tub lung is a granulomatous lung disease that has been associated with exposure to nontuberculous mycobacteria present in hot water aerosols from hot tubs/spas, showers, and indoor swimming pools.14–18 The pathogenesis of hot tub lung has been controversial in the literature, and although some authors regard this entity as a form of HSP, others favor an infectious etiology.14,19 Patients with hot tub lung are usually immunocompetent. The lesions are characterized histopathologically by small granulomas that are bronchiolocentric. Although most are nonnecro-
zizing (Figure 7), occasional necrotizing granulomas may be seen. At times, however, the granulomas will be very poorly formed, consisting of a loose collection of multiply nucleated giant cells and epithelioid histiocytes (Figure 8). These granulomas may be seen in an interstitial location or within airspaces. In some cases, mycobacteria have been demonstrated in the lesions.

Recently, a form of HSP associated with exposure to Cytophaga endotoxin in a nylon plant was described. 29 Workers at a nylon plant developed pulmonary disease with systemic symptoms. Cytophaga, an endotoxin-producing bacteria, was isolated from the plant air-conditioning system. The authors identified precipitins to Cytophaga endotoxin, and several workers underwent lung biopsies that showed the histologic features of HSP. This event shows the possible number and diversity of agents capable of eliciting a clinical and pathologic picture of HSP.

In most forms of HSP if exposure to the inciting antigen is avoided, the granulomatous lesions resolve in 4 to 6 months, but persistent exposure results in progression of the disease to interstitial fibrosis that may resemble a non-specific interstitial pneumonia (NSIP) or usual interstitial pneumonia pattern.

In the chronic stage of HSP, a predominantly fibrotic pattern is seen. In a recent report, 3 the fundamental patterns of fibrosis were observed:

1. A subpleural, patchy pattern of generally paucicellular fibrosis with obliteration of the underlying lung structure and architectural distortion very much resembling that seen in usual interstitial pneumonia. Fibroblastic foci associated with the peripheral fibrosis were present in all cases showing this pattern (Figure 9) and isolated giant cells and/or granulomas were found (Figure 10) (giant cells and granulomas were found in both fibrotic and nonfibrotic areas).

2. A homogeneous linear fibrosis that more or less followed the original underlying architecture and very much resembled fibrotic non-specific interstitial pneumonia.

3. Irregular fibrosis in a partially peribronchiolar distribution.

From this information it is evident that chronic HSP may produce fibrotic reactions that mimic other types of interstitial lung disease, particularly usual interstitial pneumonia. As noted in the first article of this series, the diagnosis of HSP should always be made in combination with clinical and radiologic findings.

Immunofluorescence studies in most forms of HSP are usually noncontributory because by the time most biopsies are obtained (subacute and chronic stages), HSP is predominantly a cell-mediated type of injury; however, some studies have found specific antigens in selected cases. 22-24 Although electron microscopy is not necessary to make the diagnosis of HSP, there are several studies describing the ultrastructural features of HSP. Immune complex deposits are usually not found by electron microscopy, a finding that is consistent with the generally negative findings by immunofluorescence. There is thickening of the alveolar basement membranes, and it is possible to find intra-alveolar clusters of loose connective tissue attached to alveolar walls, which have been called buds. 25 These foci contain a small number of macrophages, fibroblasts, and myofibroblasts and represent the reparative stage of an exudative process. 7

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for HSP includes many diffuse interstitial lung diseases including infections, sarcoidosis, bronchiolitis obliterans, usual interstitial pneumonia, and NSIP. Infections, particularly those resulting from mycobacteria, fungi, and respiratory viruses, should always be ruled out by cultures, special stains, and clinical correlation. Sarcoidosis is usually associated with well-formed granulomas in contrast to the loose, poorly formed granulomas seen in HSP. Sarcoidal granulomas follow the lymphatic routes and the interlobular septa (in a pattern similar to berylliosis). Bronchiolitis obliterans can be caused by other types of lung injury, including the cryptogenic form. Although varying degrees of inflammation can accompany the fibrosis, the lymphoplasmacytic interstitial infiltrate seen in HSP is usually small or nonexistent and granulomas are usually absent in non-HSP-associated cases. The cellular pattern of NSIP can be seen in patients with a history of exposure to organic antigens. The pathologist should keep in mind that NSIP is a histologic pattern, and, although it can be idiopathic, some well-documented cases of HSP have been associated with a biopsy diagnosis of NSIP. 26 Drugs such as mesalazine, methotrexate, and others can also serve as stimuli for reactions that have features of HSP, usually NSIP and granulomas. The differential diagnosis should also include lymphoid interstitial pneumonia in which the lymphocytic infiltrate is very prominent while granulomas are usually inconspicuous. In rare cases, lymphocytic interstitial pneumonia can be a manifestation of HSP.

**References**


18. Rickman OB, Ryu JH, Fidler ME, Kalra S. Hypersensitivity pneumonitis...

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