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Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases

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Summary Usual interstitial pneumonia is an almost uniformly fatal form of fibrosing interstitial lung disease. It is the most common idiopathic interstitial pneumonia, and currently, there is no effective therapy. Lung biopsy is often needed for diagnosis, and pathologists must be able to recognize its features and distinguish it from other interstitial lung diseases that have a better prognosis and a more favorable response to therapy. This review is an attempt to clarify the diagnostic pathologic features of usual interstitial pneumonia and to provide guidelines for its distinction from other interstitial lung diseases that enter the differential diagnosis.

1. Introduction

Usual interstitial pneumonia (UIP) is the most common idiopathic interstitial pneumonia and the one with the worst prognosis [1,2]. Median survival is only 2 to 3 years, and there is no effective therapy. Implementation of increasing numbers of clinical trials testing the value of novel treatment strategies has placed greater demands on pathologists for ever more precise and correct diagnoses. The single most important task for the pathologist, therefore, when evaluating biopsies containing interstitial pneumonia is to correctly diagnose UIP and separate it from other interstitial pneumonias that have a better prognosis and response to therapy. Interpretation of pathologic findings can be difficult because these diseases are characterized by a mixture of inflammation and fibrosis, and diagnosis depends more on qualitative differences rather than specific pathognomonic features. Another part of the problem is that current classification schemes are complex and difficult to follow. There is uncertainty about the role of clinical input, with one popular classification advocating a combined "clinical-radiologic-pathologic (CRP) diagnosis" and suggesting that pathologists describe histologic "patterns" rather than make diagnoses [1]. Furthermore, diagnostic discrepancies among pathologists have been highlighted in several articles [3-6], and the implication is that pathology is no longer the gold standard of diagnosis [7-9]. This review is an attempt to address these controversies and in doing so provide the pathologist with a straightforward and practical approach to diagnosing the chronic interstitial pneumonias. Specific diagnostic features of UIP are reviewed, and commonly encountered problem areas in differential diagnosis are addressed individually.

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1.1. Diagnostic criteria for UIP

UIP is a chronic interstitial fibrosing process that destroys lung parenchyma and eventuates in respiratory failure. There are 3 main histologic criteria for diagnosis as outlined in Table 1 [10]. First, at low magnification, the lung is affected in a nonuniform, *patchwork pattern*, which is characterized by alternating zones of abnormal and normal lung side by side without transition zones, much like the patchwork pattern of a quilt (Fig. 1). The process has a striking heterogeneous appearance, often with small islands of residual normal or nearly normal lung interspersed among extensively scarred parenchyma. Second, there is evidence of architectural distortion that is usually characterized by a combination of areas of honeycomb change and scars that replace normal alveoli, although in early or poorly sampled cases, only small scars may be visible (Fig. 2). Honeycomb areas are characterized by enlarged airspaces lined by bronchiolar epithelium and often filled by mucin and variable numbers of inflammatory cells. They are surrounded by dense collagen and variable amounts of inflammation. Honeycomb change is usually located in peribronchiolar parenchyma, and there may be overlap with so-called peribronchiolar metaplasia. Scars are characterized by irregular, thick areas of collagen deposition that obliterate alveoli (in contrast to collagen deposition that thickens alveolar septa but does not destroy them). Third, small areas of active fibrosis (fibroblast foci) are present in the background of collagen deposition, and they reflect the temporal heterogeneity of the process. That is, fibroblast foci indicate current ongoing disease, whereas the collagen-type fibrosis, scarring, and honeycomb change indicate disease that has occurred in the distant past. Fibroblast foci are composed of small dome-shaped collections of spindle-shaped fibroblasts and myofibroblasts within myxoid stroma (Figs. 1 and 2). They are present in the interstitium, and their surface is covered by hyperplastic alveolar lining cells. Because of their myxoid stroma, they are easily recognizable at low magnification.

Inflammation may be present in UIP, but is usually minimal and overshadowed by the fibrosis and scarring. An exception can occur in and around honeycomb areas where chronic inflammation, lymphoid aggregates with germinal centers, and even acute inflammation may be prominent and likely are related to poor clearance from the areas of scarred lung.

Table 1 Diagnostic criteria for UIP

I. Patchwork pattern of parenchymal involvement (nonuniformity, spatial heterogeneity)
II. Architectural distortion (honeycomb change and/or scars)
III. Temporal heterogeneity (fibroblast foci and collagen deposition)

1.2. The role of clinical input for diagnosis

The single most useful piece of information for pathologists is the appearance of the lungs on high-resolution computed tomography (HRCT) scan. In histologically difficult cases, for example, the presence of bibasilar honeycomb change is an important clue suggesting UIP and militating against non-UIP fibrosing processes. The combination of bibasilar reticular opacities and subpleural honeycomb change on HRCT, in fact, is considered diagnostic of UIP by itself, thus obviating the need for biopsy [2,6,9]. This pathognomonic radiographic finding is present in only one half or less of patients with UIP, however, and diagnosis in patients with "atypical" radiographic features is dependent solely on pathologic interpretation. The presence of ground glass opacities on HRCT is a frequent but nonspecific finding in interstitial pneumonias. Although it usually indicates an inflammatory rather than a fibrotic process, cases of UIP with superimposed acute injury can have this appearance, and diagnosis in such cases, again, depends on the pathologic interpretation. Certain other interstitial lung diseases such as Langerhans cell histiocytosis (LCH) and lymphangiomyomatosis, for example, have fairly specific HRCT changes. As with the interstitial pneumonias, biopsy is often performed only in those cases lacking diagnostic HRCT findings, and diagnosis, thus, rests on the histologic findings alone.

Other than the HRCT findings in some patients, the clinical presentation is usually not discriminatory because most individuals with interstitial lung disease of any type complain of progressive dyspnea and chronic cough and have restrictive abnormalities on pulmonary function testing. The situation is further complicated in that increasingly sensitive diagnostic tools have expanded the range of possible clinical phenotypes. For example, it was emphasized in an international consensus statement in 2000 that most affected patients are older than 50 years and have had respiratory symptoms for more than 6 months [11], but more recent experience indicates that UIP can occur in younger patients [12], the disease can present acutely [13-15], and some patients may be asymptomatic or have subclinical disease [14-16]. Accurate and confident histologic diagnosis is essential, therefore, in the face of potentially "discordant" clinical findings.

Although a combined "CRP diagnosis" is recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement on the idiopathic interstitial pneumonias [1], and a multidisciplinary approach is advocated by others [8,9], the fact is that clinical input is often of limited value in separating these diseases. This conclusion is supported by studies of Flaherty et al [3,8] that examined the effect of sequentially adding clinical, radiologic, and pathologic information to the evaluation of patients with suspected idiopathic interstitial pneumonia. Combining clinical information with HRCT results had minimal impact on clinical diagnoses, whereas knowledge of