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Cross sectional imaging of pulmonary fibrosis translating pathology into radiology

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ABSTRACT

There are three major pathologic patterns of pulmonary fibrosis; usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP) and airway-centered fibrosis (ACF). These pathologic patterns correspond with radiographic patterns of UIP, NSIP, and chronic hypersensitivity pneumonitis (CHP). Previous studies have demonstrated that the radiologic diagnosis is correct approximately 50% of the time for these fibrotic lung diseases. Understanding the microscopic pathologic patterns that are recapitulated at a macroscopic level in the high resolution CT scan is key to radiologists' ability to correctly diagnose pulmonary fibrosis and thus improve patient outcomes with early diagnosis and avoidance of biopsy. We investigate the similarities between the pathology and radiology features of UIP, NSIP, and ACF.

1. Introduction

There are dozens of radiologic patterns of pulmonary fibrosis but the three most common fibrotic pulmonary diseases, usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP) and chronic hypersensitivity pneumonitis (CrHP) have been confirmed with many registries including the Mount Sinai ILD registry [1, 2]. In 2008, Silva showed the characteristic CT features of CrHP, UIP, and NSIP which allowed confident distinction between these entities in approximately 50% of patients [3]. UIP is the radiologic and pathologic pattern seen in the clinical disease of idiopathic pulmonary fibrosis (IPF), a relentlessly progressive idiopathic fibrotic lung disease with a poor prognosis. The American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT) published consensus diagnostic criteria for IPF in 2011 and clearly defined the criteria for the confident radiographic diagnosis of UIP pattern. These criteria include sub-pleural, basilar predominant fibrosis with reticulations and honeycombing and absence of features suggesting an alternative diagnosis such as air trapping and nodules [4].

In 2013 the American Thoracic Society/European Respiratory Society published an update of the Multidisciplinary Classification of Idiopathic Interstitial Pneumonias (IIPs) and created four categories which include chronic fibrosing IIPs (UIP and NSIP); acute or subacute IIPs; smoking related IIPs; and rare IIPs [5]. The chronic fibrosing IIPs are most common and with their overlapping imaging features can cause radiologic diagnostic dilemma. CrHP is not considered an IIP but it is frequently misdiagnosed as IPF. Morell reported that, 20 of the 46 patients with initially diagnosis of IPF had a subsequent diagnosis of chronic hypersensitivity pneumonitis [6]. Since early and correct diagnosis improves outcomes for patients with pulmonary fibrosis it follows that differentiating the three most common fibrotic entities is of utmost importance. Smith reviewed the three major pathologic patterns of pulmonary fibrosis including UIP, fibrotic NSIP, and airway-centered fibrosis and provided accompanying illustrations [7]. These patterns correspond to the clinical syndromes of IPF, NSIP, and CrHP most often in clinical practice. The illustrations are a simple and powerful way to highlight the key microscopic features of the patterns of pulmonary fibrosis. Because microscopic anatomy and pathology is recapitulated at the macroscopic level, the illustrations also allow comparisons between the pathologic and radiologic patterns. These comparisons are useful in understanding the concepts of pulmonary fibrosis and may provide radiologists a better understanding of what is occurring at the microscopic level. Familiarity with the pathologic patterns of pulmonary fibrosis has the potential to increase diagnostic accuracy when interpreting high-resolution CT (HRCT) studies with pulmonary fibrosis.

2. Normal lung

The normal lung parenchyma is composed of secondary pulmonary lobules measuring approximately 1.7 cm, that are outlined by interlobular septa which act like the scaffolding of the lung and transport the

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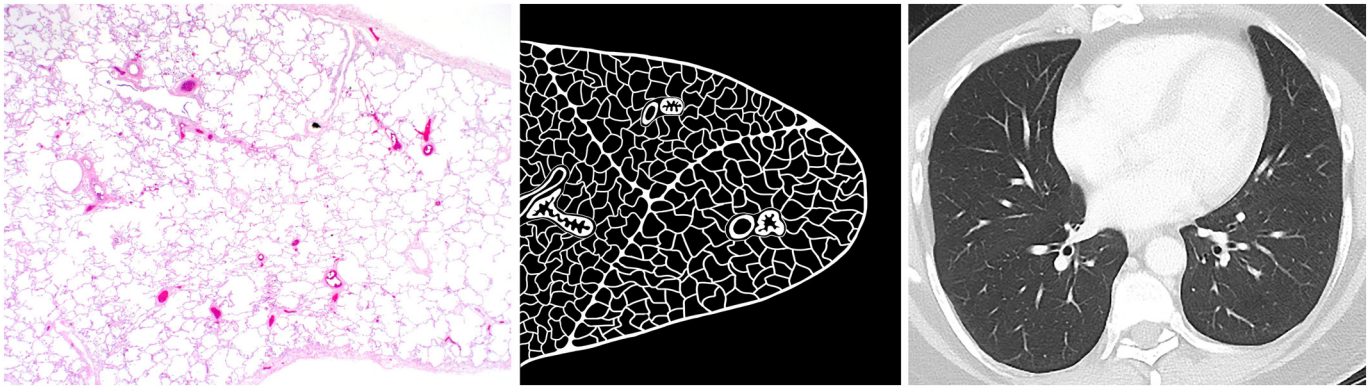

Fig. 1. A and B. Normal anatomy of the secondary pulmonary lobule. Each lobule contains a central bronchovascular bundle. At the periphery of the lobules are subtle interlobular septae. C. Normal CT image of the lung parenchyma with subtle interlobular septae. Reprinted from [Smith M, Update on Pulmonary Fibrosis: Not All Fibrosis Is Created Equally. Arch Pathol Lab Med. 2016; 140 (3):221–229] with permission from Archives of Pathology & Laboratory Medicine. Copyright 2016 College of American Pathologists.

pulmonary veins and lymphatics (Fig. 1). In the normal lung, the interlobular septa are nearly imperceptible. The pleura is typically thin in the normal setting. Fibrosis, pulmonary edema or lymphangitic spread of malignancy can cause thickening of these interlobular septa radiographically. If there is associated traction bronchiectasis or bronchiolectasis the process is fibrosis. The bronchus and its accompanying artery are centrally located in the bronchovascular bundle, and the alveoli, with their thin walls to allow gas transfer, surround the central artery and bronchus.

3. UIP pattern

UIP was first described by Liebow and Carrington in 1969. The pathologic hallmark for UIP is geographic and temporal heterogeneity. The geographic heterogeneity manifests as areas of dense fibrosis immediately adjacent to normal lung parenchyma with thin delicate alveolar walls. The temporal heterogeneity refers to the presence of advanced old scarring (dense mature collagenized scar, often with fatty and smooth muscle metaplasia) and young new scarring in the form of fibroblast foci. Fibroblast foci are small polyps of immature fibrosis often seen at the intersection between the advanced fibrosis and normal appearing lung. As the fibrosis progresses and destroys the pulmonary lobule, microscopic honeycomb remodeling occurs. This microscopic honeycombing is the earliest precursor to the macroscopic honeycomb cysts characteristic of the radiographic UIP-pattern.

In 2011, the ATS/ERS/JRS/ALAT provided criteria for the radiographic diagnosis of UIP-pattern that include sub-pleural, basilar predominant fibrosis with reticulations and honeycombing and absence of features which suggest an alternative diagnosis. The sub-pleural distribution of fibrosis is one of the most important because it is most consistent with UIP of IPF. Fig. 2 compares the pathology pattern of pulmonary fibrosis to the HRCT.

Notice in the pathology illustration that the peripheral fibrosis in white has scalloped edges as it abuts the normal lung parenchyma and how this is analogous on the adjacent CT image. On both the radiology and pathology images of UIP there is spatial heterogeneity with areas of normal tissue (dark) immediately adjacent to fibrosis (light). The fibrosis also is accentuated in the subpleural region in both figures. The lines of reticulation in the HRCT can be seen as dense paraseptal fibrosis in the pathology illustration. Microscopic honeycombing seen in the pathology figure will eventually become the macroscopic honeycomb cysts identified radiologically. Traction bronchiolectasis (in the pathology illustration) and bronchiectasis (in the radiology figure) are consistent airway alterations seen in the setting of UIP pattern fibrosis. Radiologic UIP pattern fibrosis does not show ground glass opacities (GGO) unless the patient is undergoing an acute exacerbation or has a superimposed acute lung injury. The rare FF seen microscopically is typically below the level of detectability on HRCT.

Distinguishing early UIP from NSIP can be a radiologic challenge. GGO in the periphery of the lungs may be seen in both entities [8]. However, the distribution of GGO in early disease may help in the distinction. Early UIP is more heterogeneously distributed and may be accentuated in the basilar, subpleural, and paraseptal regions. In contrast, NSIP is more homogenous and may spare the subpleural region. The distinction of UIP from CrHP and other ACF diseases also often rests in differences in distribution. While UIP is basilar, ACF is typically upper lung zone predominant (like many inhalation diseases).

Associated findings can assist in the radiologic UIP diagnosis. Older age and male sex support the correct diagnosis. A hiatal hernia may be an associated finding as GERD may be related to the development of the disease [9]. UIP is more common in smokers and as such emphysema is often associated with UIP [10]. Mediastinal lymphadenopathy has been reported in UIP, NSIP and sarcoid [11]. In patients with UIP and liver cirrhosis, short telomeres should be considered [12].

4. Fibrotic NSIP

Fibrotic nonspecific interstitial pneumonia (NSIP) was initially described as a cohort of patients with a temporally uniform fibrosing disease process that could not be easily classified as one of the three main categories of IIPs [13]. It was considered an “other” fibrosis. Now, following detailed exclusion of other causes, idiopathic fibrotic NSIP is one of the main patterns of fibrosis in the classification of IIPs. The fibrosis is uniform with simplification of the alveolar walls and thickening of the septum. Normal lung is typically absent in the areas of fibrosis. There may or may not be an associated inflammatory cell infiltrate. The fibrotic form of NSIP pattern is far more common than the cellular form. The geographic and temporal heterogeneity, honeycombing, and fibroblast foci of UIP are usually absent.

On HRCT, NSIP and UIP are both lower lobe predominant. In contrast to UIP, NSIP may show sub-pleural sparing [15]. The most common HRCT abnormality in NSIP is bilateral homogeneous lower lobe predominant ground-glass opacities with traction bronchiectasis [14]. The presence of ground glass opacities (GGO) may be related to the thickened alveolar walls if the fibrosis is advanced. The GGO on HRCT suggests more active inflammation and increased likelihood of response to steroids. There is often significant lower lobe volume loss. Honeycombing maybe present in advanced disease.

Fig. 3 shows the characteristic features of fibrotic NSIP. Note the similarities between the pathology illustration and the HRCT in NSIP.