UPDATE IN RADIOLOGY

Idiopathic interstitial pneumonias☆

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KEYWORDS

Lung; High resolution computed tomography; Interstitial diseases; Idiopathic interstitial pneumonias; Pulmonary fibrosis

Abstract The idiopathic interstitial pneumonias are diffuse lung diseases characterized by interstitial inflammation and fibrosis. High resolution computed tomography (HRCT) is the best imaging technique for the study of interstitial disease.


The radiologist’s role consists of identifying the macroscopic morphological pattern and working together with clinicians and pathologists to generate an integrated clinical diagnosis. The objective of this article is to review the idiopathic interstitial pneumonias and to describe their different manifestations in HRCT.

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PALABRAS CLAVE

Pulmón; Tomografía computarizada de alta resolución; Enfermedades intersticiales; Neumonías intersticiales idiopáticas; Fibrosis pulmonar

Neumonías intersticiales idiopáticas

Resumen Las neumonías intersticiales idiopáticas son enfermedades pulmonares difusas caracterizadas por inflamación intersticial y fibrosis. La tomografía computarizada de alta resolución (TCAR) es la mejor técnica de imagen para estudiar las enfermedades intersticiales.

Bajo el término general «neumonía intersticial idiopática» se incluyen a la neumonía intersticial usual/fibrosis pulmonar idiopática, la neumonía intersticial no específica, la neumonía intersticial descompensativa, la bronquioloitis respiratoria asociada a enfermedad intersticial pulmonar, la neumonía organizada, la neumonía intersticial aguda y la neumonía intersticial linfocítica.

El papel del radiólogo consiste en identificar el patrón morfológico macroscópico y trabajar conjuntamente con el clínico y patólogo para generar un diagnóstico clínico integrado. El objetivo de este trabajo es realizar una revisión de las neumonías intersticiales idiopáticas y describir sus diferentes manifestaciones en la TCAR.

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Introduction

The estimated incidence of interstitial lung disease is 31.5 per 100,000 males and 26.1 per 100,000 females. The most common interstitial diseases are idiopathic interstitial pneumonias (IIPs), sarcoidosis and chronic extrinsic allergic alveolitis.\(^2,3\)

Idiopathic interstitial pneumonias are diffuse lung diseases characterized by interstitial inflammation and fibrosis. Each type of pneumonia represents a specific response to a variety of lung insults.\(^4\) This group of diseases has been reclassified several times. In 2001, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) reached a consensus on the classification of IIPs based on clinical, radiologic and histopathologic features. The term "idiopathic interstitial pneumonia" includes the entities of usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis associated with interstitial lung disease (RB-ILD), organizing pneumonia (OP), acute interstitial pneumonia (AIP), and lymphocytic interstitial pneumonia (LIP).\(^5\)

High resolution computed tomography (HRCT) is the best imaging technique for the study of interstitial lung diseases.\(^6-9\) The role of the radiologist is to identify the macroscopic morphological pattern and work together with clinicians and pathologists to generate an integrated clinical diagnosis.\(^10\) The definitive diagnosis, of both idiopathic interstitial pneumonias and other interstitial diseases, should always be made based on consensus among clinicians, radiologists and pathologists.\(^6,11\)

The objective of this article is to review the idiopathic interstitial pneumonias and to describe their HRCT manifestations.

Diagnostic methods in interstitial lung disease

Chest radiography remains useful to study interstitial lung disease. It is a readily available and inexpensive technique while delivering an acceptable radiation exposure. It can also help in the evaluation of associated complications such as pneumonia, pneumothorax and lung cancer. To compare the current radiologic findings with previous ones can be used to evaluate disease progression.

On radiographs, the interstitial pattern is characterized by linear and nodular images with diffuse bilateral distribution. Radiographic interpretation of interstitial diseases can be challenging; with up to 30% interobserver variability. The sensitivity of chest radiography in the early stages of the disease is very low. One study that correlated radiologic and pathological findings in patients with interstitial disease histologically confirmed revealed that 10% of these patients had normal chest radiographs.\(^12\)

High resolution computed tomography

HRCT is a widely accepted technique for the study of many lung and small airways diseases. This technique combines thin slices (1–2 mm thick) and a high resolution image reconstruction algorithm to show fine details of the lung parenchyma. HRCT provides morphologic images of the secondary pulmonary lobule similar to those of a gross pathological specimen. In studies that correlate CT and pathological findings in patients with proven interstitial disease, 11% of patients had normal HRCT.\(^13\)

New CT systems allow simultaneous data acquisition by using adjacent multidetector rows. Multidetector computed tomography (MDCT) provides high resolution images (1–2 mm) of the entire chest in a single breath-hold. With MDCT, almost isotropic volumetric images of high quality can be obtained in any plane.\(^14-17\) Although sequential HRCT has proved inefficient (false negatives) in the study of patients with known bronchiectasis and emphysema,\(^18\) it remains as useful as volumetric MDCT for the study of diffuse lung diseases. The use of multiplanar reconstructions with maximum intensity projection (MIP) and minimum intensity projection (MinIP) can provide additional information to conventional studies.

The indications for performing HRCT/MDCT are: (a) to detect clinically suspected lung disease when radiographic findings are normal; (b) to characterize more precisely a lung disease previously detected on chest radiograph; (c) to evaluate disease activity and therapy options; and finally, (d) to guide selection of the type and location of biopsy.

High resolution computed tomography findings of pulmonary fibrosis

HRCT findings suggestive of pulmonary fibrosis (Table 1) include reticulation, parenchymal distortion, traction bronchiectasis/bronchiolectasis and honeycombing. Recently, the Fleischner Society has compiled a glossary of terms for lung disease that describes these findings.\(^19\) The reticular pattern represents a thin thickening of the intralobular interstitium, a finding suggestive of pulmonary fibrosis (Fig. 1). Traction bronchiectasis/bronchiolectasis represent irregular airway dilatation caused by surrounding retractile pulmonary fibrosis (Fig. 2). Honeycombing refers to small subpleural cysts and is considered a specific finding of fibrosis and the most relevant diagnostic feature of the UIP pattern (Fig. 3).\(^19\)

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IIPs are a heterogeneous group of lung diseases histologically characterized by interstitial inflammation and fibrosis; a certain degree of alveolar involvement is not uncommon in these diseases.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>HRCT findings suggestive of fibrosis.</th>
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<td><strong>Specific findings</strong></td>
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<td>- Honeycombing</td>
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<td>- Traction bronchiectasis</td>
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<td><strong>Nonspecific findings</strong></td>
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<td>- Irregular reticulation</td>
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<td>- Architectural distortion</td>
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<td>- Ground-glass attenuation</td>
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In 2001, the ATS and ERS consensus statement classified the IIPs into IPF/UIP, NSIP, AIP, DIP, BR-EPI, LIP and COP based on clinical, radiologic and histopathologic features.

UIP and NSIP represent more than two thirds of all IIPs. However, similar radiologic and pathological findings can be seen in other conditions such as connective tissue diseases, chronic extrinsic allergic alveolitis, and drug-induced lung reactions.

HRCT is the imaging modality of choice for the evaluation of interstitial lung diseases. The definitive diagnosis of IIPs should always be made based on consensus among clinicians, radiologists and pathologists. Given the poor prognosis of UIP, the ultimate objective is to differentiate this condition from the rest of IIPs.

UIP/UIF is the most common form of idiopathic interstitial pneumonia, accounting for 25–50% of cases, and affects patients between the fifth and seventh decade of life. In the United States, the estimated incidence and prevalence are 14.0–42.7 and 6.8–16.3 per 100,000 people, respectively. IPF is the clinical entity associated with the UIP pattern. The histologic features of UIP are similar to those described in IPF. Thus, the terms UIP and IPF are used interchangeably. Patients with UIP/IPF present with progressive dyspnea, nonproductive cough, fatigue and fine inspiratory crackles on chest auscultation.

UIP is more common in men. The prognosis is grim and 5- and 10-year survival rates are 43 and 15%, respectively.

The histologic findings include areas of fibrosis of temporal heterogeneity, scattered fibroblastic foci, minimal inflammation and areas of honeycombing. There are areas of interstitial fibrosis with juxtaposition of normal lung tissue.

The main utility of HRCT in patients with UIP is to evaluate the degree of fibrosis and determine the stage of the disease. The most common chest radiographic findings include lung volume loss, bibasilar reticular opacity and subpleural honeycombing (Fig. 4). The presence of a ground-glass attenuation pattern is an uncommon HRCT finding in UIP. When present, it represents areas of microscopic fibrosis below the resolution of HRCT. Although the distribution is generally symmetrical, the asymmetry reflects the temporal heterogeneity of that pattern. Since IPF has a poor prognosis and is difficult to treat, biopsy should be avoided in patients with conspicuous honeycombing and characteristic CT features.

The differential diagnosis includes asbestos-related interstitial fibrosis, collagen diseases (rheumatoid
arthritides and scleroderma,23 and drug-induced lung toxicity.24-28 Chronic extrinsic allergic alveolitis and stage IV sarcoidosis may on occasions show a NIU pattern.27,28

An evidence-based guideline for diagnosis and management of FPI has been recently published.29 This document is a collaborative effort of the ATS, the ERS, the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT).30

Nonspecific interstitial pneumonia

NSIP is a clinical and pathological entity of unknown etiology, different from UIP and from DIP. Despite having similar clinical manifestations, the clinical outcome is better in NSIP than in UIP and similar to DIP.

An NSIP pattern can be identified in connective tissue diseases, drug-induced lung reactions, associated with lung infections and sometimes of unknown etiology (idiopathic).31

The histologic features of NSIP include temporal and spatial homogeneity and, depending on the degree of inflammation or fibrosis, there is a cellular and a fibrotic form of NSIP. Active fibroblastic foci and honeycombing are uncommon in NSIP.31

In some cases of NSIP, as often happens in other interstitial pneumonias, the chest radiograph is normal.32,33 The characteristic HRCT finding of NSIP is a peripheral and bilateral ground-glass pattern in the middle and lower lung zones.34,35 Honeycombing appears in 27% of patients and, as the fibrosis progresses, traction bronchiolectasis becomes more visible (Fig. 5).9,36 Radiographic findings may disappear completely after steroid therapy.

Desquamative interstitial pneumonia

The term DIP was initially used by Liebow in 1965, who believed that the free cells filling the alveoli were type II pneumocytes. Now DIP is known to be part of a spectrum of smoking-related interstitial diseases, including respiratory bronchiolitis and RB-ILD.37,38 A relevant fact is that 90% of patients with a DIP pattern are smokers.37 Unlike UIP, patients with DIP are significantly younger and have a good clinical outcome.32

Bilateral ground-glass opacity with symmetrical and basilar distribution is the most common chest radiographic abnormality of the DIP pattern.39 A reticular pattern has also been described, which sometimes cannot be differentiated from the radiographic findings described in UIP. Chest radiographic findings are normal in 22% of patients with NID.40

The HRCT shows areas of ground-glass attenuation in all patients (Fig. 6). These areas are secondary to a combination of diffuse filling of alveoli with macrophages and discrete intralobular fibrosis.41,42 In many cases the DIP has a basilar distribution and in 60% of cases a peripheral distribution (Fig. 7). Reticular and linear opacities are common but
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limited in extent. At HRCT, a differential diagnosis should be made with RB-ILD and COP.

Given the overlapping clinical, histologic and radiologic findings, DIP and RB-ILD are considered as a part of a spectrum of smoking-related diseases. While small areas of emphysema are frequent in DIP, honeycombing is rare.

Respiratory bronchiolitis associated with interstitial lung disease

Respiratory bronchiolitis is a common finding in smokers. The histologic analysis reveals pigmented macrophages within the alveoli and first- and second-order respiratory bronchioles. Approximately 90% of patients are asymptomatic smokers. However, in a small percentage of patients the disease is more extensive and resembles an interstitial disease (RB-ILD). RB-ILD represents the clinical manifestation of BR associated with interstitial disease. It is more common in young patients aged 30–40. RB-ILD and DIP have very similar histologic findings, and sometimes overlap. However, the accumulation of macrophages within the bronchioles helps differentiate RB-ILD from DIP, since in DIP the distribution is diffuse.

The histologic analysis reveals the coexistence of areas of Langerhans’ cell histiocytosis, RB-ILD and DIP in the same biopsy. These findings help confirm the spectrum of smoking-related histologic features. In addition, some patients with DIP have never smoked. On the other hand, although RB-ILD may be a part of the spectrum of the same disease process, RB-ILD and DIP are currently considered as free-standing entities. Chest radiographic findings are normal in approximately 30% of patients with BR-EPI; fine reticular abnormalities and areas of ground-glass attenuation are present in the remaining 70% of cases.

HRCT findings include multifocal areas of ground-glass attenuation, small ill-defined centrilobular nodules and minimal emphysematous changes (Fig. 8). Traction bronchiectasis and honeycombing are not HRCT features. The main differential diagnosis is with extrinsic allergic alveolitis.
Acute interstitial pneumonia

AIP is a rapidly progressive interstitial disease characterized by acute onset of diffuse opacities, dyspnea and hypoxia. The shortness of breath develops over a period of several days and/or one week. AIP is suspected when no risk factors of acute respiratory distress can be identified (sepsis, shock, major surgery, aspiration, pancreatitis, etc.). In the early phase, the histologic findings include thickening of the alveolar septa caused by edema and inflammation, protein-rich exudates into the alveolar spaces with formation of hyaline membranes. Subsequently, there are proliferative interstitial, bronchial and alveolar changes. The histopathologic findings are those of diffuse alveolar damage (DAD), indistinguishable from the histologic pattern found in acute respiratory distress. HRCT findings are multifocal areas of consolidation that tend to coalesce and progress to a diffuse pattern (Fig. 9). 9,32-35 If the condition progresses during days or weeks, the HRCT will show signs of fibrosis characterized by architectural distortion, traction bronchiectasis and honeycombing.

Organized pneumonia

OP, previously known as bronchiolitis obliterans with organizing pneumonia (BOOP), is characterized by granulation tissue within the bronchioles, alveolar ducts and adjacent alveolar spaces.

OP can be idiopathic (cryptogenic organizing pneumonia) or appear as a response to different processes such as collagen diseases, viral or bacterial infections, aspiration and drugs.

Patients present with subacute flu-like symptoms, including nonspecific symptoms such a nonproductive cough, dyspnea and fever. Patients with OP usually respond well to steroid therapy.

OP is generally bilateral (75%) and can be subpleural (25%) or peribronchial (25%). HRCT features include multiple areas of consolidation, uni- or bilateral, usually peripheral (subpleural) (Fig. 10).
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Figure 11  Organizing pneumonia. ''Reverse halo'' sign. (A) HRCT imagine through the lung bases (lung window) shows multiple round images characterized by areas of increased attenuation surrounding ground-glass opacities (''reverse halo'') (arrows).

56-58 Less common HRCT findings are focal consolidations, peribronchovascular consolidations, variable presence of nodular opacities, peribronchial opacities, band opacities and areas of increased attenuation surrounding rounded ground-glass opacities (''reverse halo'' sign) (Figs. 11 and 12). 9,57,59,60

Lymphocytic interstitial pneumonia

LIP is a clinocopathologic term61,62 that relates histologically to a diffuse interstitial infiltrate of polyclonal lymphocytes. The mean age of patients with LIP is 50 years and it is more common in women. Clinical manifestations include dyspnea, cough and chest pain.61,62 Characteristic HRCT findings are multifocal areas of ground-glass attenuation, usually with bilateral and basilar distribution, small centrilobular nodules with ill-defined margins and rounded cysts with thin walls (Fig. 13).

Figure 12  Organizing pneumonia. ''Reverse halo'' sign. (A) HRCT image of the lung apices (lung window) with multiple ground-glass opacities in the left apex. Typical ''reverse halo'' image in the right apex (arrows).

Figure 13  Lymphocytic interstitial pneumonia. (A) HRCT image through the lung bases (lung window) shows multiple cysts with rounded morphology, thin walls and random distribution (arrows). (B) Coronal reconstruction shows that the cystic lesions are more numerous in the lung bases.

Diagnostic problems of the idiopathic interstitial pneumonias

One of the problems of the histologic diagnosis of the IIP is the small size of biopsy samples and the heterogeneity of the lesions. Although conventional transbronchial biopsy has a limited role in the study of IIPs, a similar technique is now being used (transbronchial cryobiopsy) but the results are as yet preliminary.63

Regarding sample size, cryobiopsy provides better samples and better preservation of the biopsy material.

Another factor that greatly determines the definitive histologic diagnosis in this group of diseases is the sampling error. It is not unusual to find different histologic patterns in the same patient from biopsies taken from multiple sites. In cases with discordant histologic findings, the UIP pattern will determine both the diagnosis and prognosis.

HRCT allows the morphological evaluation of large areas of the lungs, in many cases suggesting a definitive
diagnosis. HRCT and histologic finding are complementary in many instances.

Lung biopsy in idiopathic interstitial pneumonias

The decision to forego lung biopsy in IIPs is complex and generally aimed to establish a diagnosis. The number of surgical biopsies is determined by several factors including the clinical condition of the patient, atypical clinical presentation, and experience of the medical team (surgeon, radiologist and pathologist), type of biopsy, morbidity associated with the biopsy, and associated complications.51

Lung biopsy can be avoided when clinical and HRCT manifestations are suggestive of a specific disease such as UIP, NSIP or OP. Characteristic HRCT findings of UIP are bibasilar reticulation with areas of honeycombing and minimal ground-glass opacities. The typical UIP pattern is identified in 40% of cases. In the non-fibrotic form of NSIP, characteristic HRCT manifestations include bilateral areas of consolidation and/or of ground-glass attenuation in the lung bases. In some cases, the peripheral area of the lungs is not involved, resulting in a radiolucent subpleural band.

Rapidly progressive forms of usual interstitial pneumonia and nonspecific interstitial pneumonia

Acute exacerbation of UIP, also termed the accelerated phase of IPF, is characterized by acute respiratory failure and diffuse lung opacities.64,65 The most common histologic feature is diffuse alveolar damage accompanied by histologic evidence of underlying UIP or NSIP. HRCT manifestations, one week after the onset of the symptoms, include architectural distortion, traction bronchiectasis and areas of ground-glass opacities (Fig. 14). Acute exacerbations of NSIP associated with collagen diseases have also been described.64,66

Prognosis and follow-up of idiopathic fibrosis

At HRCT, a reticular pattern with areas of honeycombing is characteristic of pulmonary fibrosis, therefore reflecting an irreversible stage of the disease. Conversely, a predominant ground-glass pattern is histologically associated with inflammatory infiltrate, corresponding to a potentially treatable stage of the disease. However, patterns suggestive of NSIP on HRCT imaging may have biopsy findings characteristics of UIP. On the other hand, HRCT findings do not allow differentiation between UIP and fibrotic NSIP.36,67 The prognostic value of the different HRCT patterns is a matter of debate.

Pulmonary function testing and HRCT can be used in the follow-up of these patients.68 Recent studies have demonstrated that the diffusing capacity of lung for carbon monoxide (D_{CO}) and the quantification (score) of fibrosis at HRCT are independent prognostic indicators of survival in patients with UIP and fibrotic NSIP.69

Conclusion

The diagnosis of IIPs requires a multidisciplinary approach. Radiologists play a very important role in the management of this complex group of diseases and they should be familiar with the radiologic manifestations. HRCT features are summarized in Table 2. If HRCT findings typical of entities such as UIP and OP are found, lung biopsy may be avoided. In general, symmetrical basilar reticulation accompanied by traction bronchiectasis and areas of honeycombing are characteristic of the UIP pattern. Conversely, a ground-glass pattern is suggestive of NSIP or DIP and the presence of multiple cysts suggests LIP. Nonetheless, the definitive diagnosis should be based on a multidisciplinary approach.
Table 2  HRCT findings of IIPs.

**Usual interstitial pneumonia (UIP)**
- Honeycombing
- Traction bronchiectasis
- Few areas of ground-glass attenuation
- Subpleural and basilar distribution of the findings

**Nonspecific interstitial pneumonia (NSIP)**
- Ground-glass attenuation
- Minimal fibrosis: traction bronchiectasis and reticulation
- Minimal or nonexisting honeycombing
- Subpleural and basilar distribution of the findings
- Sparing of the immediately subpleural area

**Desquamative interstitial pneumonia (DIP)**
- Ground-glass attenuation
- Minimal fibrosis
- Cysts
- Subpleural and basilar distribution of the findings

**Organizing pneumonia (OP)**
- Condensations or areas of ground-glass attenuation with patchy distribution
- Ill-defined centrilobular nodules
- "Reverse halo" sign
- Fibrosis (usually mild)

**Lymphocytic interstitial pneumonia**
- Multifocal areas of ground-glass attenuation
- Ill-defined centrilobular nodules
- Cysts

IIPs: interstitial pneumonias.

Ethical responsibility

**Protection of animals and humans.** The authors declare that all procedures were conducted in accordance with the ethical principles of the committee responsible for research on humans, the World Medical Association and the Declaration of Helsinki.

**Confidentiality of personal data.** The authors declare that no personal data of patients are included in this article.

**Right to privacy and informed consent.** The authors have obtained informed consent from the patients and/or subjects involved in this article. The informed consent forms are in possession of the corresponding author.

Authorship

1. Responsible for the integrity of the study: TF.
2. Conception of the study: TF.
3. Design of the study: TF.
4. Acquisition of data: TF and AG.
5. Analysis and interpretation of data: TF and AG.
6. Statistical analysis: N/A.
7. Bibliographic search: TF and AG.
8. Drafting of the paper: TF and AG.
9. Critical review of the manuscript: TF and AG.
10. Approval of the final version: TF and AG.

Conflicts of interest

The authors declare not having any conflicts of interest.

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