Idiopathic Interstitial Pneumonias: Updated

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Learning objectives

1. To discuss the ATS/ERS update of the classification of IIPs.
2. To enumerate the entities which constitute the spectrum of IIPs.
3. To highlight specific changes to the previous classification and to list the newer additions made.
4. To discuss their salient features and imaging characteristics.
Background

In 2013, the American thoracic society/European Respiratory Society (ATS/ERS) through an international multidisciplinary panel reviewed the literature from 2000-2011 and published its update to the classification of IIPs. Substantial progress has been made since the previous classification. The clinical course of IPF and NSIP is now recognized to be heterogeneous. NSIP being a separate entity in itself. It is understood that a good percentage of patients with IIPs are difficult to classify, often due to mixed patterns of lung injury. Therefore, classification based on observed disease behavior is proposed for entities with heterogeneity in clinical course. Lastly, a group of rare entities, including pleuroparenchymal fibroelastosis and Idiopathic lymphoid interstitial pneumonia were introduced.
Findings and procedure details

An international multidisciplinary panel was formed to review literature between 2000 and 2011 and propose changes in the various IIPs. This ATS/ERS update is a supplement to the previous 2002 IIP classification Table 1 on page 11 and outlines advances in the past decade.

Symptomatic patients were referred to our hospital for high resolution computed tomography of the chest. CT scan was done using 128slice CT scanner. Patients with findings of IIPs were carefully categorized into separate entities based on their clinical and radiologic characteristics, as per the latest ATS/ERS update.

**Summary of major revisions of the IIP classification.**

In the revision of the IIP classification, the main entities are preserved. However, there are several other important changes made.

- 1. A clinical disease behavior classification is proposed.
- 2. Cryptogenic fibrosing alveolitis is removed, leaving idiopathic pulmonary fibrosis (IPF) as the sole clinical term for the diagnosis.
- 3. Idiopathic nonspecific interstitial pneumonia (NSIP) is now accepted as a distinct clinical entity with removal of the term "provisional".
- 4. Major IIPs are specifically distinguished from the rare IIPs and unclassifiable cases.
- 5. Rare histologic patterns of acute fibrinous and organizing pneumonia (AFOP) and interstitial pneumonias with a bronchiolocentric distribution are recognized. (Not in the scope of this article)
- 6. Major IIPs are grouped into chronic fibrosing (IPF and NSIP), smoking-related (respiratory bronchiolitis-interstitial lung disease [RB-ILD] and desquamative interstitial pneumonia [DIP]), and acute/subacute IIPs (cryptogenic organizing pneumonia [COP] and acute interstitial pneumonia [AIP]). Table 3 on page 12

**Progress in specific IIPs since 2002 Table 2 on page 11**

A. Chronic Fibrosing IIPs

1. *Idiopathic pulmonary fibrosis Fig. 1 on page 12*
• Most common form of IIP.
• IPF has a substantially poorer prognosis than other IIPs with median survival time ranging from 2 to 4 years.
• No obvious gender predilection.
• Progressively worsening dyspnea and nonproductive cough with subtle onset of their symptoms months or even years before the diagnosis is made.
• Do not respond to high dose corticosteroid therapy. However they are used for acute exacerbation.

**Imaging features**

- Chest radiograph - normal in early disease. In advanced disease, it shows decreased lung volumes and subpleural reticular opacities with an apico basal gradient.
- On CT- trio of signs: subpleural reticular opacities and macrocystic honeycombing combined with traction bronchiectasis, in an apicobasal gradient.

**Specific changes as per ATS/ERS update:**

- An updated evidence-based guideline for the diagnosis of IPF was published.
- Three levels of patterns of UIP based on HRCT findings were introduced which included criteria for (UIP, possible UIP, and inconsistent with UIP).
- The diagnosis of IPF requires (1) exclusion of other known causes of ILD, (2) the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy and (3) specific combinations of HRCT and surgical lung biopsy patterns in patients subjected to it.
- As per the data gathered from 2000 to 2011, it was suggested that patients with IPF and definite UIP on HRCT have shorter survival than those with indeterminate HRCT findings.

2. **Idiopathic nonspecific interstitial pneumonia. Fig. 2 on page 13**

- Previously, NSIP was primarily defined as an idiopathic disease (Not anymore)
- Less common than UIP
- Seen in younger patients as compared to IPF.
- Symptoms are similar to those with IPF but are usually milder.
- No obvious gender predilection.
- Systemic corticosteroids in combination with cytotoxic drugs helps majority of patients improve and stabilize.
- Morphologic pattern of NSIP are encountered in association connective tissue diseases, hypersensitivity pneumonitis and drug exposure. Hence secondary forms of NSIP must be ruled out.
Imaging features

- Chest radiograph - normal in early disease. In advanced disease, bilateral pulmonary infiltrates are the most salient feature. Lower lobes are more frequently involved, without an obvious apicobasal gradient, as seen in UIP.
- On CT- Sub pleural and symmetric distribution of lung abnormalities. Patchy ground-glass opacities are the most salient feature, combined with irregular linear or reticular opacities and scattered micronodules. In advanced disease, subpleural cysts are seen, which are smaller - "microcystic honeycombing".

Specific changes as per ATS/ERS update:

- NSIP are now accepted as a distinct entity among the IIPs, with removal of the term "provisional" as NSIP pattern occurs not only as an idiopathic condition, but also in a variety of settings such as connective tissue disorders, Hypersentivity pneumonitis, and drug toxicity.
- Hence a multidisciplinary discussion is especially important to establish the diagnosis of idiopathic NSIP.

B. Smoking-related IIPs

RB-ILD and desquamative interstitial pneumonia (DIP) represent a histologic spectrum of macrophage accumulation, with the distinction between the two dependent on the extent and distribution of this process.

3. Respiratory bronchiolitis-interstitial lung disease Fig. 3 on page 15

- Average age is 30 - 40 years old.
- Average smoking history of 30 pack-years.
- Men are affected nearly twice as often as women
- Mild dyspnea and cough.
- Smoking cessation is the most important component in the therapeutic management of RB-ILD.

Imaging features

- Chest radiograph - normal in most cases.
- On CT- centrilobular nodules in combination with ground-glass opacities and bronchial wall thickening. The centrilobular nodules are due to the peribronchial distribution of the intraluminal infiltrates.

Specific changes as per ATS/ERS update:
• RB-ILD is now diagnosed without surgical lung biopsy in smokers with typical HRCT findings.
• Broncho alveolar lavage demonstrating smokers macrophages and the absence of lymphocytosis (suggestive of HP).

4. Desquamative interstitial pneumonia. Fig. 4 on page 15

• Strongly associated with cigarette smoking.
• Represents the end of a spectrum of RB-ILD.
• Prognosis is good with smoking cessation and corticosteroid therapy.
• As opposed to the bronchiolocentric distribution in RB-ILD, lung involvement in DIP is more diffuse and uniform.

Imaging features

• Chest radiograph - findings are nonspecific and may reveal hazy opacities.
• On CT- diffuse ground-glass opacities and thickening of alveolar septa with peripheral and lower lung lobe predominance.

Specific changes as per ATS/ERS update:

• No specific changes made.

C. Acute or Subacute IIPs

5. Cryptogenic organizing pneumonia Fig. 5 on page 14

• Mean age is 55 years.
• Histologic pattern of COP is organizing pneumonia
• No association with cigarette smoking; in fact, most patients are nonsmokers or ex-smokers
• Pattern of organizing pneumonia may occur in a wide variety of entities -- in collagen vascular diseases, infectious and drug-induced lung diseases
• Therefore, COP is a diagnosis of exclusion.

Imaging features

• On CT- patchy and often migratory consolidation in a subpleural, peribronchial, or bandlike pattern, associated with ground-glass opacity. Perilobular opacities and reversed halo (or atoll) sign may be helpful in suggesting the diagnosis.

Specific changes as per ATS/ERS update:
No specific changes made.

COP continues to be included in the classification of IIP because of its idiopathic nature and the tendency to be confused with other forms of IIP, especially when there is progression to fibrosis.

6. Acute interstitial pneumonia Fig. 6 on page 16

- It is the only entity among IIPs with acute onset of symptoms.
- In most cases of AIP, the clinical and imaging criteria for acute respiratory distress syndrome are fulfilled.
- Typically, a history of viral-like illness exists.
- Prognosis remains poor, with a mortality rate of 50% or more.
- Most patients who survive the acute phase of the disease later progress to lung fibrosis.
- As opposed to the heterogeneous appearance of UIP, fibrotic changes in AIP are uniform.

Imaging features

- On CT- symmetric, bilateral distribution with a lower lobe predominance.
- The costophrenic angles are often spared.
- In early disease, ground-glass opacities are the dominant CT pattern and reflect the presence of alveolar septal edema
- In the late phase, architectural distortion, traction bronchiectasis, and honeycombing are the most striking CT features and are more severe in the nondependent areas of the lung

Specific changes as per ATS/ERS update:

- No specific changes made.

D. Rare IIPs

The category of rare IIPs has been created (not present in the 2002 classification) to include idiopathic lymphoid interstitial pneumonia (LIP) and idiopathic pleuroparenchymal fibroelastosis (PPFE).

7. Idiopathic Lymphoid Interstitial Pneumonia Fig. 7 on page 16

- As an idiopathic disease, LIP is exceedingly rare.
• It is far more common as a secondary disease in association with systemic disorders --- Sjogren syndrome, human immunodeficiency virus infection, and variable immunodeficiency syndromes.
• It is more common in women than in men.
• Patients are usually in their fifth decade of life at presentation.

Imaging features

• Chest radiograph - nonspecific findings, such as bilateral reticular, reticulonodular, or alveolar opacities
• On CT- diffuse involvement with a lower lung predominance.
• Dominant feature is ground-glass attenuation.
• Thin-walled perivascular cysts within the lung parenchyma throughout the mid lung zone.

Specific changes as per ATS/ERS update:

• Idiopathic LIP has now been moved to the category of rare IIPs.
• The clinical, imaging, and histopathologic criteria for LIP proposed in 2002 remain unchanged, apart from recognition that some cases show striking cyst formation on HRCT.
• Both the 2002 IIP classification and the ATS NSIP project demonstrated that many of the cases previously diagnosed as LIP are now considered cellular NSIP.

8. Idiopathic Pleuroparenchymal Fibroelastosis Fig. 8 on page 17

• PPFE is a rare condition that consists of fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes.
• It presents in adults with a median age of 57 years and has no sex predilection.
• Approximately half of patients have experienced recurrent infection.

Imaging features

• On CT - dense subpleural consolidation with traction bronchiectasis, architectural distortion, and upper lobe volume loss.
• Pneumothorax is common.

Clinical classification of disease behavior Table 4 on page 17

• Newly introduced in the ATS/ERS update.
• This disease behavior classification is complementary to the IIP classification and should not be used as a justification for delaying SLB.
• Patterns of disease behavior in diffuse lung disorders and specific treatment approaches are broadly subdivided.
• This approach is most useful in unclassifiable cases and for some IIPs, such as NSIP, that can be associated with all five patterns of disease behavior.
Table 1: ATS/ERS classification of IIPs (2002)

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Major idiopathic interstitial pneumonias
- Idiopathic pulmonary fibrosis
- Idiopathic nonspecific interstitial pneumonia
- Respiratory bronchiolitis–interstitial lung disease
- Desquamative interstitial pneumonia
- Cryptogenic organizing pneumonia
- Acute interstitial pneumonia

Rare idiopathic interstitial pneumonias
- Idiopathic lymphoid interstitial pneumonia
- Idiopathic pleuroparenchymal fibroelastosis

Unclassifiable idiopathic interstitial pneumonias
Table 2: Revised American thoracic society / European Respiratory Society classification of IIPs.

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<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical–Radiologic–Pathologic Diagnoses</th>
<th>Associated Radiologic and/or Pathologic–Morphologic Patterns</th>
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Table 3: Categorization of major IIPs.

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**Fig. 1:** Idiopathic pulmonary fibrosis

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Fig. 2: Idiopathic nonspecific interstitial pneumonia.

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Fig. 5: Cryptogenic Organizing Pneumonia.

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Fig. 3: Respiratory Bronchiolitis- associated Interstitial Lung Disease.

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**Fig. 4:** Desquamative Interstitial Pneumonia.

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**Fig. 6:** Acute Interstitial Pneumonia.

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Fig. 7: Lymphoid Interstitial Pneumonia.

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Fig. 8: Pleuroparenchymal fibroelastosis.

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Table 4: Idiopathic interstitial pneumonias: classification according to disease behavior.

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Conclusion

In order to improve the sensitivity of diagnosis of IIPs the foremost thing a radiologists needs to know is that not every case can be categorized under a specific entity and that definitive diagnosis can sometimes be challenging on imaging alone. With wide variations in the clinical course and imaging characteristics of IIPs, it is crucial to have a thorough understanding about the heterogeneity of the spectrum of IIPs as treatment and clinical outcomes are varied for each of these entities.
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