Idiopathic Interstitial Pneumonia

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Ping Li, Jifeng Zhang, Wei Yuan, and Shanshan Yu

Idiopathic interstitial pneumonia (IIP) is a group of diffuse nontumor, noninfectious lung diseases of unknown cause, involving pulmonary interstitium, with pulmonary inflammation and fibrosis as the main pathological changes. In 1968, Liebow and Carrington divided chronic interstitial pneumonia into five types according to different histological manifestations: usual interstitial pneumonia (UIP); bronchiolitis obliterans interstitial pneumonia (BIP); desquamative interstitial pneumonia (DIP); lymphoid interstitial pneumonia (LIP); giant cell interstitial pneumonia (GIP). The diagnostic gold standard of this classification method is pathological diagnosis. However, these five types of chronic interstitial pneumonia do not each represent five special diseases. They are just different tissue reactions of lung tissue to various pathogenic factors. Therefore, each type of interstitial pneumonia may occur in many different diseases, and a certain disease may have more than one interstitial pneumonia at the same time. For example, lung biopsy of rheumatoid arthritis patients can show UIP or DIP at the same time. With the deepening of research over time, some changes have been made in the histological classification and subgroup definition of idiopathic interstitial pneumonia.

In 2002, the American Thoracic Society and the European Respiratory Society organized pathology, radiation, thoracic surgery, immunology, radiotherapy and other disciplines to hold an international coordination meeting on idiopathic interstitial pneumonia. This meeting reached the "International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias" [1]. The new classification includes seven subtypes: idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonia (NSIP), cryptogenic organizing pneumonia (COP), acute interstitial pneumonia (ACIP), respiratory bronchiolitis-associated interstitial lung disease (RB), and desquamate interstitial pneumonia (DIP) and lymphocytic interstitial pneumonia (LIP). The key of this classification method is that the above seven types of idiopathic interstitial pneumonia are independent diseases, and it is emphasized that in the diagnosis process of idiopathic interstitial pneumonia, correct diagnosis requires close cooperation among clinical, imaging and pathological disciplines.

In 2013, the American Thoracic Society and the European Respiratory Society revised the classification of idiopathic interstitial pneumonia again [2]. The new classification divides idiopathic interstitial pneumonia into three categories: major, rare and unclassifiable. The common types include idiopathic pulmonary fibrosis, NSIP, RB-ILD, DIP, COP and acute interstitial pneumonia. The rare types include lymphocytic interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis (IPPFE). At the same time, the unclassifiable idiopathic interstitial pneumonia is clearly defined. In addition, according to the clinical process, the major types can be divided into chronic fibrous interstitial pneumonia (including IPF and NSIP), smoking-related interstitial pneumonia (including RB-ILD and DIP) and acute and subacute interstitial pneumonia (COP and acute interstitial pneumonia) [3].

25.1 Acute Interstitial Pneumonia

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25.1.1 Overview

Acute interstitial pneumonia (AIP) is a severe respiratory disease with unknown etiology, in which diffuse pulmonary interstitial infiltration is the main pathological change, rapid progressive ventilation dysfunction and respiratory failure are the clinical features. This disease is rare in clinical practice, and the mortality rate is very high, which can reach 50%–88%, with no difference in age and gender of onset [4].

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The incidence may be related to the following conditions: ① virus (adenovirus or EB virus) infection; ② Immune factors, such as autoantibodies in peripheral lymphocytes and other cells of some patients, deposited immune complexes on alveolar wall, increased red blood cell sedimentation rate, gamma globulin, antinuclear antibody and titer of other substances, positive rheumatoid factor and lupus cells, decreased complement level; ③ Genetic factors.

Before the onset of the disease, most patients have symptoms similar to upper respiratory tract viral infection without obvious inducement, which lasts for one week to several weeks. More than half of cases may have fever and dry cough, as well as purulent sputum when secondary infection occurs. Rapid progressive cases show chest tightness, fatigue, cyanosis, wheezing and chest urgency, accompanied by progressive dyspnea. The disease may rapidly develop into respiratory failure. Laboratory examination has no obvious specificity, and blood gas analysis often suggests type I respiratory failure [5]. Moist rales can be heard in the lungs in the early stage, and Velcro rales can be heard in the middle and later stage.

25.1.2 Pathological Manifestations

AIP was first proposed by Katzenstein in 1986, who summarized the clinical data of 38 patients with acute respiratory failure. Its histological feature is diffuse alveolar damage (DAD) [6]. The pathological process can be divided into three stages: acute exudation stage, subacute hyperplasia stage and chronic fibrous tissue generation stage [7]. The pathological features of each stage are as follows: ① In the acute exudation stage, alveolar epithelium and basement membrane injury, inflammatory cell infiltration, type II alveolar cell proliferation, alveolar space filled with hyaline membrane (exfoliated epithelium and fibrin); ② In subacute hyperplasia stage, organizing alveolar and interstitial tissues, gradually increased fibroblasts in alveolar cavity, edema of alveolar septa and alveolar hemorrhage; ③ In chronic fibrous tissue generation stage, mostly in 2 weeks after onset, showing thickened alveolar septa, proliferation of fibroblasts, fibrosis of alveolar space and alveolar septa.

25.1.3 Imaging Manifestations

1. X-ray: Chest radiographs show fan-shaped light patchy opacities with hilum as the center and distributed along the lung markings in multiple lung fields, accompanied by different degrees of thickened interlobular septa and thickened bronchovascular bundles with their routes in the fan-shaped light patchy opacities.
2. CT: The imaging changes of AIP often show progressive development [8]. In the early stage (1–2 weeks after onset), the main symptom is exudative changes, showing patchy consolidation shadow and ground-glass opacities, especially in the periphery of bilateral middle and lower lungs. In the middle stage, exudative lesions progress rapidly, and extensive thickening of pulmonary interstitial structure occurs, which is manifested as diffuse ground-glass opacities in both lungs, accompanied by consolidation (Fig. 25.1), more significant in the lower lung than in the upper lung, but consolidation shadow is not as common as ground-glass opacities. The interlobular septa and

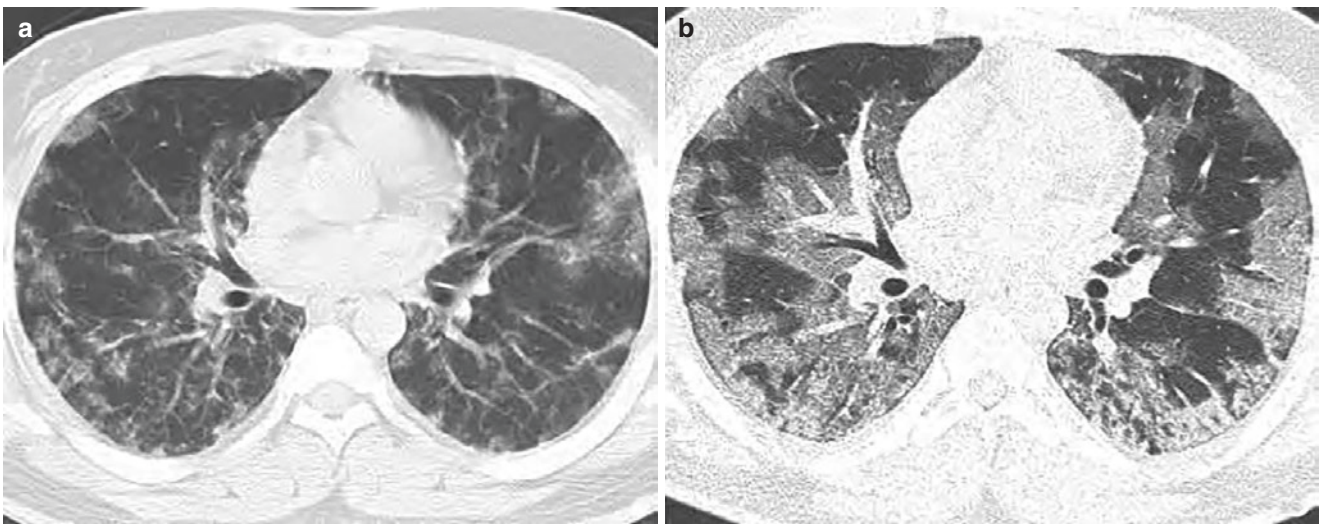

Fig. 25.1 Acute interstitial pneumonia (I). (**a**) CT lung window showed scattered patchy opacities and ground-glass opacities around bilateral middle and lower lungs; (**b**) In the middle stage, exudative lesions progressed rapidly, the density of ground-glass opacities in both lungs increased, with expanded scope and clear edges

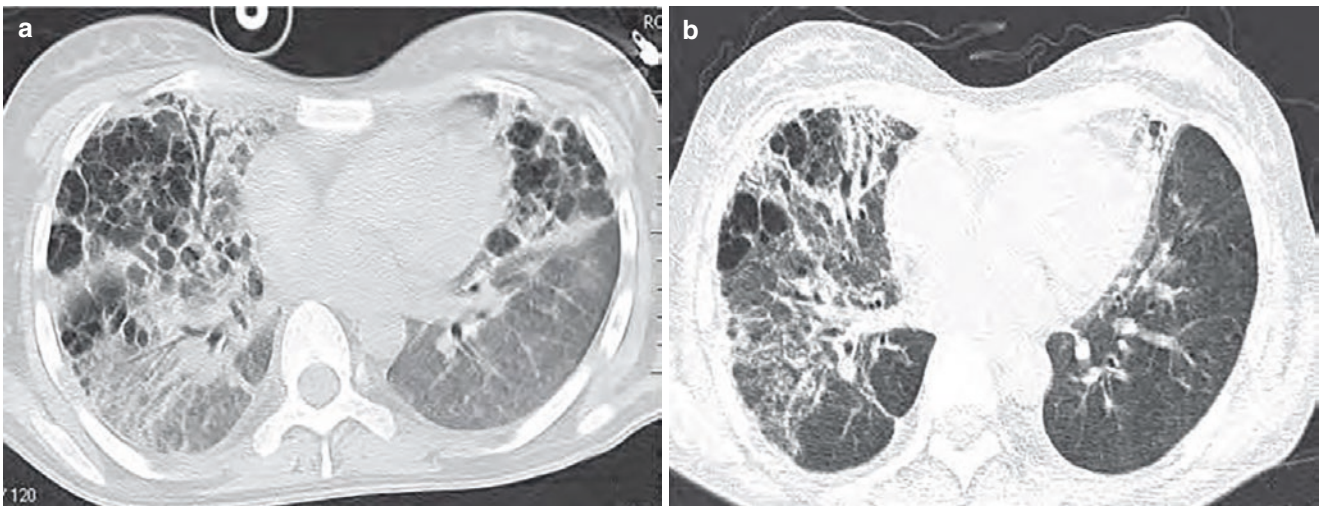

Fig. 25.2 Acute interstitial pneumonia (II). (**a**) CT lung window showed multiple patchy opacities, ground-glass opacities, cystic opacities in both lungs, and local bronchus showed mild bronchiectasis due to traction; (**b**) After 20 days of treatment, the ground-glass opacities of both lungs were significantly absorbed, and the residual fibrosis, cystic opacities and bronchiectasis were not significantly changed

intralobular septa are thickened, becoming smoother, showing "paving stone" sign [9]. Rapid progressive fibrosis and progressive destruction of lung tissue structure are the main features of AIP in the later stage (3–4 weeks later) [10] (Fig. 25.2). Bronchiectasis and honeycomb shadow are the most typical manifestations, and beads-like traction bronchiectasis is the specific manifestation [11]. Honeycomb shadow and microcystic changes represent fibrosis, and are both independent predictors of poor prognosis of interstitial pneumonia [12].

The imaging change process of rapid progression is the characteristic manifestation of AIP, and the diagnosis of AIP requires careful analysis on a series of imaging data. Because HRCT can show the microstructure of lung, it is superior to conventional CT and chest radiograph in displaying pulmonary interstitial changes. As a preferred option, it is helpful for early judgment and treatment of pulmonary interstitial changes in AIP.

25.1.4 Diagnostic Key Points

1. Patients have acute lower respiratory diseases over the past 60 days.
2. Imaging findings show diffuse lung infiltration.
3. Lung biopsy shows organizing or proliferative diffuse alveolar damage.
4. There is no etiology, such as infection, systemic inflammatory response syndrome, poisoning, connective tissue disease and previous pulmonary interstitial diseases.
5. Previous imaging findings were normal.

25.1.5 Differential Diagnosis

1. Acute respiratory distress syndrome (ARDS): Because ARDS and Severe Acute Respiratory Syndrome (SARS) and AIP have similar clinical and pathological manifestations, differential diagnosis is often required in clinical practice [13, 14]. ARDS is often secondary to severe diseases inside and outside the lung, with less severe pulmonary fibrosis and destruction of lung structure than those of AIP, and glucocorticoid treatment is often ineffective.
2. Pulmonary edema: Patients have a history of primary disease, and the distribution of bilateral lung lesions is usually diffuse. There is no normal lung tissue area between lesions, and the fusion trend is obvious.

Other pulmonary inflammations: Usually manifested as small patchy opacities and irregular light patchy opacities widely distributed in both lungs. The biggest difference is that they are randomly scattered, the fusion trend is not obvious, the short-term changes of lung imaging manifestations are not obvious, and some inflammations are characterized by migratory relapse. It is significantly different from AIP in distribution and phase of imaging changes.

25.1.6 Research Status and Progress

HRCT findings of AIP can better reflect its pathological changes. Rapid progression is a characteristic clinical feature, and clinical diagnosis is not difficult. It is significant to predict and judge the prognosis and outcome based on some

imaging manifestations [13]. Early use of extracorporeal membrane oxygenator (ECMO) during treatment can mitigate the degree of lung injury [15], while making imaging manifestations different, which needs further study.

25.2 Idiopathic Pulmonary Fibrosis

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25.2.1 Overview

Definition of idiopathic pulmonary fibrosis (IPF): According to the definition of ATS/ERS, IPF is considered as chronic fibrotic interstitial pneumonia confined to the lungs, with unknown origin, and its histopathological change is usual interstitial pneumonia (UIP) [16]. IPF is the most common idiopathic interstitial pneumonia, accounting for 50%–60% of all cases. Although IPF accounts for the majority of UIP cases, UIP lesions can also be related to drug or dust exposure, chronic hypersensitivity pneumonitis, collagen vascular diseases, asbestos exposure and so on. Therefore, when diagnosing UIP as idiopathic pneumonia, UIP caused by the above underlying diseases should be excluded first [17].

The clinical manifestations are progressive shortness of breath, dry cough and dyspnea. The manifestations are common in male patients. The manifestations are more common among smokers. Therefore, smoking seems to be a risk factor for IPF. The clinical process gradually deteriorates. Different from other types of interstitial pneumonia, corticosteroids are ineffective in treating IPF, so the prognosis is worse.

25.2.2 Pathological Manifestations

The histological features of UIP are a variety of coexisting pathological changes such as interstitial inflammation, fibroblast foci, fibrosis and honeycomb changes, which are mixed with normal lung tissue. This transient diversity of lesions is the characteristic of UIP, with different lesion phases, coexistence of new and old lesions, and a large number of collagen fiber deposition and fibroblast foci can be found in the lesions. The periphery and basal part of the lung are the most seriously affected areas [18].

25.2.3 Imaging Manifestations

1. X-ray: In the early stage of onset, chest radiographs of most patients are normal. In the advanced stage, chest radiographs show decreased lung volume and gradually increased reticular opacity areas from the apex to the basal part of the lung.
2. CT: The CT manifestations of UIP are various, and the fibrotic lung area is mixed with the normal lung area. HRCT features of UIP are subpleural and basal pulmonary reticular opacities, honeycomb shadow and traction bronchiectasis. Another common manifestation of UIP is the deformation of lung structure caused by pulmonary fibrosis. In most UIP patients, honeycomb lung is the most prominent manifestation [19].
   (a) Reticular opacities: Showing thickened interlobular septa and centrilobular structure, which is more common in subpleural area of lower lobes of both lungs, and thickened interlobular septa in lung manifested as branched shadows or polygonal shadows (Fig. 25.3a).

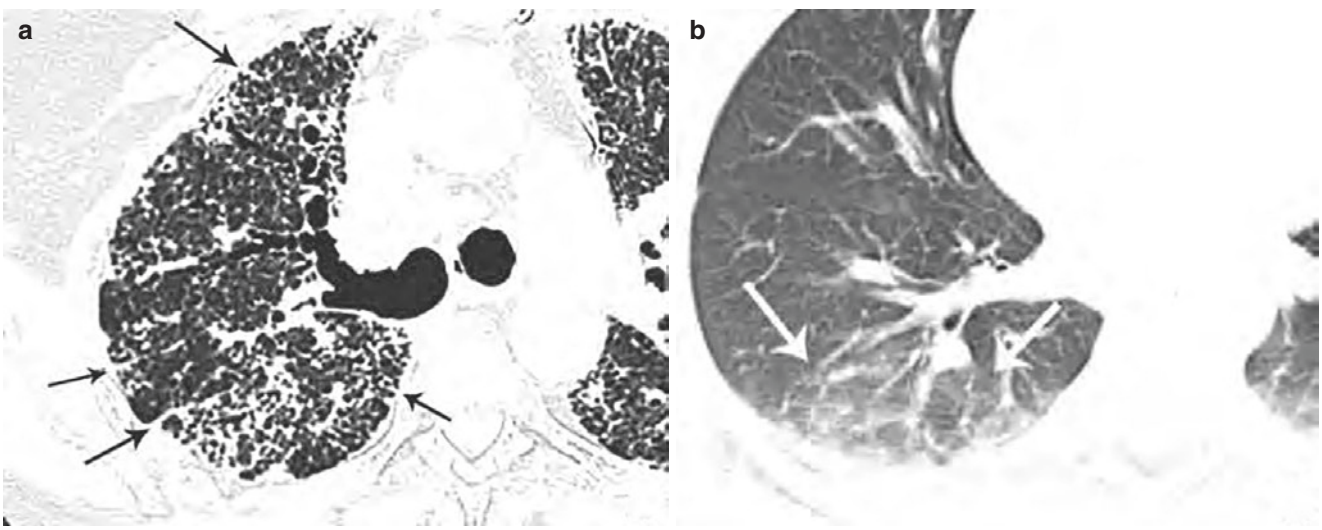

Fig. 25.3 Idiopathic pulmonary fibrosis (I). (**a**). CT lung window showed thickened interlobular septa and centrilobular structure, showing thin line shadows, branched shadows and reticular opacities perpendicular to pleural surface (arrow); (**b**). The density of the posterior basal segment of the lower lobe of the right lung was slightly increased, showing ground-glass changes with blurred edges (arrow)

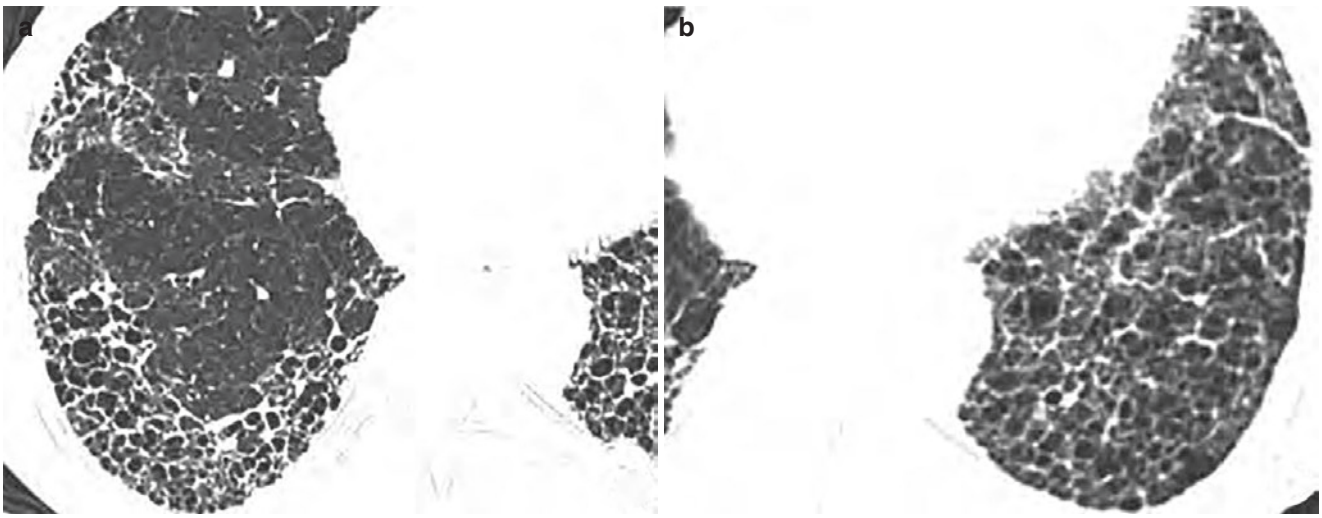

Fig. 25.4 Idiopathic pulmonary fibrosis (II). (**a** and **b**). CT lung window showed honeycomb changes in both lungs, thickened interlobular septa and multiple gas-filled cavities of different sizes

(b) Ground-glass opacities: It is also a common CT manifestation of idiopathic UIP, but with limited distribution, not as wide as reticular opacities (Fig. 25.3b), which reflects the activity degree of acute exacerbation of IPF in patients with acute respiratory diseases. Ground-glass opacities are often located in the area of structural deformation, representing microfibrosis but not inflammation [20].
(c) Honeycomb change: It is the most characteristic CT manifestation, which can be found in the later stage of lesions. It is manifested as round or oval gas-filled cavities ranging from several millimeters to 2 cm in size, with thin and clear wall, and well-defined interface with normal lung, mainly distributed in subpleural area at the basal part of both lungs (Fig. 25.4). Honeycomb shadow indicates that the lesions have entered a quiescent phase.
(d) Bronchiectasis: It occurs in the severe part of pulmonary interstitial fibrosis, mainly bronchiectasis below the segment or smaller bronchi, mostly showing columnar dilatation, which can be accompanied by bronchial distortion and closing.
(e) Emphysema: Centrilobular emphysema or total lobular emphysema are common in the lesion area.

25.2.4 Diagnostic Key Points

1. The characteristic triad signs of UIP is subpleural and basal pulmonary reticular opacities, large cystic honeycomb shadow and traction bronchiectasis.
2. Typical clinical manifestations include ineffective hormone and ventilation treatment, and poor prognosis.
3. Diagnosis should exclude UIP caused by other underlying diseases.

25.2.5 Differential Diagnosis

The imaging and clinical manifestations of idiopathic pulmonary interstitial fibrosis are nonspecific, but the lesions are mainly distributed in the subpleural area of the lower part of both lungs. Even if the lesions involve the central part of the lung, the lesions normally show gradual mitigation from the subpleural area to the hilum [21]. This disease needs to be differentiated from the following diseases.

1. Pulmonary rheumatoid disease: It has extensive pulmonary interstitial fibrosis, which eventually develops into honeycomb lung, similar to idiopathic pulmonary interstitial fibrosis. However, the former has progressive necrotic nodules, namely granuloma and pleural effusion.
2. Systemic lupus erythematosus: It is manifested as cardiac enlargement, interstitial pneumonia, segmental discoid atelectasis and pleural effusion caused by myocarditis, which is different from idiopathic pulmonary interstitial fibrosis.
3. Scleroderma: Honeycomb lung may occur in the later stage of pulmonary interstitial fibrosis in scleroderma. If there are skin changes and reduced esophageal tension or stenosis in esophageal angiography, it is helpful for the diagnosis of scleroderma.
4. Asbestosis: Common manifestations include pleural reaction and zonal changes of lung parenchyma, and subpleural linear opacities. Honeycomb changes are less significant.

5. Chronic hypersensitivity pneumonitis: Common manifestations include air retention with mosaic sign and ground-glass opacities. Honeycomb changes are less significant. Therefore, idiopathic pulmonary interstitial fibrosis can only be diagnosed if pulmonary interstitial fibrosis caused by other reasons has been excluded.

25.2.6 Research Status and Progress

The diagnosis of IPF requires comprehensive analysis on various data, and the joint research of clinicians, radiologists and pathologists to get an accurate diagnosis under the multidisciplinary diagnosis and treatment (MDT) mode. In the past, honeycomb shadow was considered as a characteristic imaging manifestation. Recently, the value of traction bronchiectasis has been paid more attention to [22]. More imaging features are used to differentiate the subtle categories of idiopathic interstitial pneumonia and minimize invasive lung biopsy.

In 2017, Fleischner Society established an international multidisciplinary committee, and published its white paper on IPF diagnostic criteria in the same year [23]. In 2018, experts from American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) reviewed the clinical studies on IPF diagnosis from 2011 to 2018, and formulated the 2018 IPF diagnosis guidelines based on the 2011 edition of the guidelines [24]. The 2018 edition of the guidelines divides IPF into four types: UIP type, possible UIP type, uncertain UIP type and other diagnoses, further refining the diagnosis of IPF and standardizing the diagnostic criteria of high-quality HRCT. At the same time, the indications and operating standards of surgical lung biopsy were proposed.

25.3 Nonspecific Interstitial Pneumonia

Ping Li and Jifeng Zhang

25.3.1 Overview

Nonspecific interstitial pneumonia (NSIP) is a common type of idiopathic interstitial pneumonia, which is less common than usual interstitial pneumonia (UIP). NSIP was first reported by Katzenstein et al. in 1994 [25]. Because of its clinical, pathological, imaging and pulmonary function changes, especially its response to glucocorticoid treatment and prognosis significantly different from those of IPF, NSIP has been differentiated from IPF in recent years and regarded as an independent idiopathic pulmonary interstitial disease.

Typical NSIP patients are usually at the age of 40 to 50, which is 10 years later than that of IPF. Symptoms are similar, but relatively mild. The main clinical manifestations are progressive dyspnea and cough. Compared with UIP, most NSIP patients have better response to glucocorticoid. If the lesions are limited to the lung and no other diseases can be found as the pathogenic cause, it is regarded as idiopathic nonspecific interstitial pneumonia (INSIP), and others with pathogenic factors such as connective tissue disease, organic dust inhalation, some drug reactions and the organizing period of acute lung injury are regarded as NSIP [26].

25.3.2 Pathological Manifestations

The main pathological features of NSIP are pulmonary interstitial inflammation and fibrosis in different degrees. The lesions may show patchy distribution, but the most important feature is the consistency in lesion phase, that is, the lesions in different parts seem to be caused by injuries occurring in a short period, all in a certain stage in the process of inflammatory fibrosis, and fibroblast lesions rarely occur. The consistency of lesions is the key diagnosis point different from that of UIP [27]. Based on the variability in size of inflammation and fibrosis, NSIP can be further divided into cellular type and fibrotic type. The thickening of alveolar septa in cellular NSIP is mainly caused by inflammatory cells. Interstitial fibrosis and mild inflammation can be found in fibrotic NSIP. Cellular NSIP is less common than fibrotic NSIP [25].

25.3.3 Imaging Manifestations

1. X-ray: In the early stage of NSIP, the chest X-ray radiographs of patients are normal. Interstitial infiltration lesions are evenly distributed in bilateral lungs, mainly in the middle and lower lung fields and subpleural areas, which may be manifested as ground-glass opacities. As the disease progresses, linear and reticular or nodular opacities occur, but honeycomb lung rarely occurs, and within a limited scope. Lung volume may be reduced in the later stage of NSIP [28].
2. CT: The main manifestations of HRCT are patchy ground-glass opacities, linear or reticular opacities and scattered tiny nodules. The main signs of HRCT are symmetrical ground-glass opacities, mainly distributed in the middle and lower lung fields and subpleural areas. In the advanced stage, traction bronchiectasis and lung

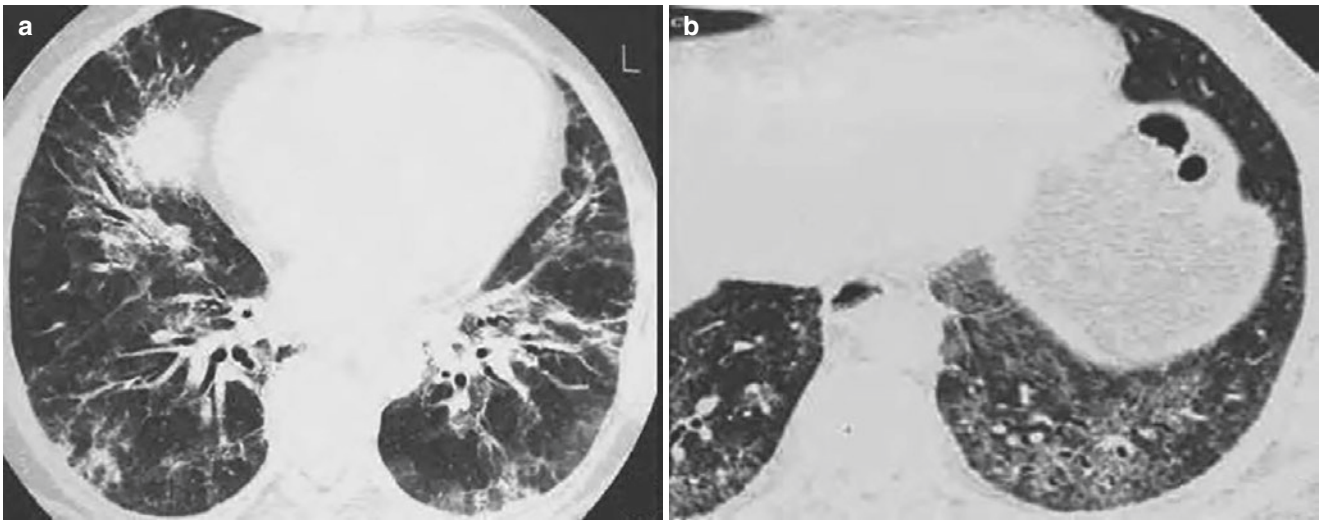

Fig. 25.5 Nonspecific interstitial pneumonia. (**a**) CT lung window showed ground-glass opacities of both lungs, with patchy distribution, mostly in subpleural areas, accompanied by small patchy consolidation; (**b**) Irregular linear opacities and traction bronchiectasis

consolidation can be found (Fig. 25.5). The incidence rate of honeycomb changes is very low, and even if cystic changes occur, they are small and within a limited scope. Other manifestations include thickened bronchovascular bundles, traction bronchiectasis and lung tissue structure distortion, all of which occur in fibrotic NSIP [29].

25.3.4 Diagnostic Key Points

1. Typical features of HRCT are symmetrical ground-glass opacities distributed in the middle and lower lung fields and subpleural areas, with temporal and spatial homogeneity.
2. If there are no typical clinical symptoms and imaging manifestations, lung biopsy should be performed to confirm the diagnosis.
3. Hormone and immunosuppressant treatment are effective.

25.3.5 Differential Diagnosis

1. UIP: The main CT findings of NSIP different from those of UIP are homogeneous lung tissue, no obvious "apex distribution and basal distribution tendency," extensive ground-glass opacities, reticular and tiny nodular opacities. Follow-up examination with CT is helpful to differentiate the two. Even if NSIP patients have bronchiectasis, the ground-glass opacities do not progress to honeycomb lung. The clinical symptoms and imaging of IPF have their special manifestations, which can be diagnosed easily. Lung biopsy should be performed if clinical symptoms and imaging manifestations are atypical.
2. Respiratory bronchiolitis associated interstitial lung disease (RBILD)/desquamating interstitial pneumonia (DIP): Most of patients are smokers, more common in male than in female, and mostly in middle-aged and elderly people. Imaging manifestations of DIP show blurred shadows and ground-glass changes in both lungs in the early stage, and linear, reticular or reticular nodular opacities in the later stage, generally without honeycomb lung. Imaging manifestations of RBILD mainly include reticular, nodular and ground-glass opacities. The lesions are in patchy distribution, confined to the alveoli around bronchioles, without the diffuse and uniform changes in DIP.
3. Cryptogenic organizing pneumonia (COP): The predilection age is 50–60, with no difference between male and female, almost not related to smoking. Most of cases show subacute and flu-like symptoms, exertion dyspnea and dry cough, rarely with expectoration or hemoptysis, chest pain, night sweat, etc. Acropachia almost never occur. On imaging, multiple patchy infiltration opacities, ground-glass opacities or consolidation can be found in both lungs, and air bronchogram can be found in consolidation. These are the manifestations of alveolitis. The pathological changes are characterized by migration. In addition, interstitial inflammation can be found, showing reticular, reticular nodular and nodular shadows, but no honeycomb lung occurs. Glucocorticoid is the first choice for the treatment of COP, with great curative effect, which can significantly improve within 24–48 h, and it often takes several weeks for the pulmonary shadow to disappear.

25.3.6 Research Status and Progress

The diagnostic criteria of NSIP are constantly updated, and NSIP is associated with many diseases, especially connective tissue disease, that is, NSIP associated with connective tissue disease (CTD-NSIP). Some scholars have made further classification and improve the diagnostic accuracy by comparing the imaging manifestations of idiopathic nonspecific interstitial pneumonia (IN-SIP) with CTD-NSIP [30].

25.4 Desquamative Interstitial Pneumonia

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25.4.1 Overview

Desquamative interstitial pneumonia (DIP) is a type of idiopathic interstitial pneumonia, which is a chronic pulmonary inflammation characterized by air cavity monocyte infiltration. DIP is a clinically and pathologically independent disease, involving smokers aged 30–40 years. The etiology of desquamative interstitial pneumonia is unknown. Most people think that the occurrence of DIP is closely related to long-term smoking, but it is not clear whether it is a reaction to foreign bodies, an autoimmune phenomenon or an infection sequela. Because rheumatoid factor, antinuclear antibody and lupus erythematosus cells were found in the examination, it was once considered as a connective tissue disease. Some people think that it is related to alveolar proteinosis. Others have reported that it is secondary to lung infection, or with no obvious inducement [31].

The symptoms of this disease are quite similar to diffuse pulmonary fibrosis, and the onset is mostly occult, but may be acute. The main manifestations include polypnea, progressive dyspnea, tachycardia, cyanosis, dry cough, weight loss, weakness and loss of appetite, and fever. The body temperature does not exceed 38 °C. In severe cases, heart failure may occur and lead to sudden death. Physical examination sometimes shows acropachia. Pulmonary signs are not obvious, sometimes fine moist rales can be heard in both lower lungs, and peripheral blood eosinophils may be increased. After smoking cessation and corticosteroid treatment, the prognosis is good.

25.4.2 Pathological Manifestations

The most prominent histological feature of DIP is the pigmented macrophages and a small amount of desquamated alveolar epithelial cells in the alveolar space. The pulmonary changes of DIP are diffuse and uniform. There is usually mild fibrosis in pulmonary interstitium. The pathological diagnostic criteria proposed by Ashen in 1984 are as follows: ① A large number of macrophages containing PAS staining positive granules in alveoli; ② Swelling and hyperplasia of type II epithelial cells in alveoli; ③ Lymphocytes, plasma cells and eosinophils infiltration in the interstitium, with mild interstitial fibrosis [32].

25.4.3 Imaging Manifestations

1. X-ray: Chest radiographs of DIP have no specificity, or manifested as blurred opacities, forming a triangular shadow, extending from the hilum along the heart to the base of both lungs, with the bottom of the triangle on the side, the shadow darkens at the edge of the heart, and becomes lighter and reduced at the periphery of the lung. This typical shadow sometimes lasts for 4–6 years, but sometimes changes or is gradually absorbed within a few months [33].
2. CT: The lung imaging of DIP is nonspecific, all patients with DIP can show ground-glass opacities, which is the characteristic sign of this disease. Ground-glass opacities are mainly located around the lung, and more common in the middle and lower lungs. A few patients can show focal distribution or diffuse distribution. Other manifestations include localized irregular stripe-like and reticular opacities, but limited to patients with extensive lesions, which are generally located in the lower lungs. Honeycomb shadow is rare and only found in patients with extensive lesions, which is usually mild and confined to the periphery of lower lung. After hormone treatment, the ground-glass opacities can disappear completely, but a few ground-glass opacities can progress to reticular opacities [34].

Once DIP is diagnosed, patients must be actively persuaded to quit smoking immediately and take glucocorticoids as soon as possible. The prognosis of DIP is good. The 5-year and 10-year survival rates are 95.2% and 69.6%, respectively. Most patients have a stable course of disease, and a few patients still progress to pulmonary fibrosis despite hormone therapy.

25.4.4 Diagnostic Key Points

1. HRCT manifestations mainly include ground-glass opacities, irregular reticular opacities and stripe-like opacities in both lungs, especially in the bottom of lung and subpleura areas.

2. Hormone therapy is effective to typical clinical manifestations.
3. The diagnosis mainly depends on pathological examination of lung biopsy. A large number of brown-pigment alveolar macrophages in bronchoalveolar lavage fluid can be helpful in the diagnosis of DIP.

25.4.5 Differential Diagnosis

RBILD and DIP are similar in clinical manifestations, imaging and response to corticosteroid therapy, and pathological biopsy is needed to distinguish the two. The difference is that the lesions of RBILD show patchy, mainly concentrated around respiratory bronchioles, less significant in the distal air cavity, and there are obvious respiratory bronchiolitis and pulmonary interstitial inflammation, but the fibrosis is mild. The lesions of DIP are diffuse and extensive, the inflammation and fibrosis of pulmonary interstitial are relatively severe, but the manifestations of respiratory bronchiolitis are relatively mild.

25.4.6 Research Status and Progress

Although DIP is classified as a smoking-related disease, some patients have no smoking history. The imaging manifestations of such patients are atypical, and the diagnosis mainly depends on lung biopsy. The imaging characteristics of such patients need to be further summarized [35].

25.5 Respiratory Bronchiolitis-Associated Interstitial Lung Disease

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25.5.1 Overview

Respiratory bronchiolitis-associated interstitial lung disease (RBILD) is a smoking-related interstitial lung disease with unknown origin and significant symptoms, which is a common histological type of respiratory bronchiolitis. The clinical, imaging and histological manifestations of RBILD and DIP are significantly overlapped, and the severity of pathomorphology is different in the development of the same disease. Histopathology mainly shows a large number of pigmented macrophages gathered in the lumen around respiratory bronchioles, and scattered multinucleated giant cells, and the distal air cavity is not involved. Compared with usual interstitial pneumonia (UIP), glucocorticosteroid treatment has remarkable effect and better prognosis [36].

RBILD usually occurs in patients at the age of 30–40, and with a history of smoking. The incidence rate of males is nearly twice that of female, showing mild dyspnea and cough. The main treatment is to quit smoking. However, most patients also receive corticosteroids therapy.

25.5.2 Pathological Manifestations

The histopathological feature of RBILD is the pigmented macrophages gathered in the lumen around the respiratory bronchioles. There is mild inflammation and fibrosis around bronchi. The manifestations of RBILD are not histologically distinguishable from those of atypical respiratory bronchiolitis [37].

25.5.3 Imaging Manifestations

1. X-ray: Chest radiograph is insensitive to the diagnosis of RBILD, which is often normal. Sometimes, thickened bronchial wall and reticular opacities can be found, with normal lung volume.
2. CT: The manifestations of HRCT show diffuse distribution of mainly centrilobular nodules [38], ground-glass opacities and thickened bronchial wall. Ground-glass opacities are caused by macrophages deposited in alveolar ducts and alveoli. Centrilobular nodules are caused by intraluminal emphysema distributed around bronchi. Patients with a history of smoking are often accompanied by centrilobular emphysema [39].

25.5.4 Diagnostic Key Points

1. The most common HRCT findings of RBILD are thickening of the central bronchi and surrounding bronchi. Other HRCT findings include small lobular nodules, ground-glass opacities and emphysema with gas retention.
2. If alveolar lavage fluid contains brown granular macrophages, without typical changes of other lesions, then other lesions can be excluded.
3. Patients have a history of smoking.

25.5.5 Differential Diagnosis

It is very difficult to distinguish RBILD from other subtypes of IIP by clinical manifestations, laboratory examinations

and imaging findings. RBILD mainly needs to be distinguished from the following diseases.

1. DIP: It is similar to RBILD in clinical manifestations, imaging manifestations and response to corticosteroid therapy, and pathological biopsy is needed to distinguish the two. The difference is that the lesions of RBILD show patchy, mainly concentrated around respiratory bronchioles, less significant in the distal air cavity, and there are obvious respiratory bronchiolitis and pulmonary interstitial inflammation, but the fibrosis is mild. The lesions of DIP are diffuse and extensive, the inflammation and fibrosis of pulmonary interstitial are relatively severe, but the manifestations of respiratory bronchiolitis are relatively mild.
2. UIP: It is more common in middle-aged people, older than those of RBILD (average 50–70 years old), and more common in women. HRCT can show subpleural and basal pulmonary reticular opacities, large cystic honeycomb shadows and traction bronchiectasis. Histologically, the main pathological features of UIP are patchy uneven interstitial inflammation, fibrosis and honeycomb lung changes with varied distribution, including focal and alternate distribution between normal lung tissues. These pathological changes mainly involve the peripheral subpleural lung parenchyma. Different phase lesions composed of fibroblasts foci accompanied by scarring with collagen deposition and honeycomb lesions are important features in the diagnosis of UIP, and are also the key points to distinguish UIP from other ILD such as RBILD.
3. NSIP: The incidence is mainly in middle-aged and elderly people, which is different from RBILD in gender, more common in females than in males. The onset and clinical manifestations of RBILD are similar to those of RBILD, and some possible factors related to etiology include potential connective tissue diseases, organic dust inhalation, some drug reactions and remission period of acute lung injury. Chest X-ray radiographs show reticular opacities in the lower field of the lung, sometimes with patchy opacities. HRCT shows symmetrical ground-glass opacities of both lungs or consolidation shadow of alveolar cavity of both lungs. NSIP main CT findings are uniform extensive ground-glass opacities, reticular opacities and tiny nodular opacities in the affected lung tissue.

25.5.6 Research Status and Progress

There are few related studies on RBILD, and some studies have shown that RBILD can evolve into DIP, which may be in different stages of the disease [40].

25.6 Cryptogenic Organizing Pneumonia

Ping Li and Jifeng Zhang

25.6.1 Overview

Cryptogenic organizing pneumonia (COP) is a group of rare diseases with unknown etiology. Its corresponding clinical-radiation-pathological definition refers to organizing pneumonia without clear pathogen (such as infection) or other clinical concomitant diseases (such as connective tissue disease). According to the consensus of IIP classification published by ATS/ERS in 2002, COP is a type of idiopathic interstitial pneumonia (IIP). The pathological and clinical features of organizing pneumonia (OP) and COP are required to be described respectively. The etiology of COP is unknown. Because most patients have influenza-like manifestations at onset, it is speculated that COP may be related to infection. Elizabeth and others successfully replicated the lung pathological model of COP with respiratory enteroviruses, suggesting that respiratory viral infection is involved in the formation of COP [41].

The cause of the disease is not yet clear. Because most patients have influenza-like symptoms at the time of onset, it is speculated that it may be related to infection. The age of onset is mostly from 50 to 60, with an average of 55. The disease has no gender difference and is not related to smoking. Most of cases have subacute onset and the course of disease is less than 3 months. The clinical manifestations have no specificity, and the most common clinical symptoms are dry cough and dyspnea, intermittent fever, fatigue, etc., which are similar to those of infection. The above clinical symptoms progress within a few weeks. The symptoms respond well to corticosteroid therapy and rarely develop into respiratory failure.

25.6.2 Pathological Manifestations

The histological feature of organizing pneumonia is polypoid granulation tissue in alveolar ducts and alveoli. The organizing of exudative inflammation in alveoli leads to proliferation of fibroblasts. The typical manifestation is patchy involvement of the lungs, and the normal structure still exists, showing granulation tissue and fewer inflammatory cells at the same time. There is no difference in pathology between COP and connective tissue disease as well as drug-induced organizing pneumonia, and typical pathological manifestations can be found in bronchoscopic lung biopsy specimens [42].

25.6.3 Imaging Manifestations

1. X-ray: Chest radiographs often show unilateral or bilateral patchy lung consolidation, similar to pulmonary inflammatory infiltration. However, the consolidation of COP is not active pneumonia, but fibroblast proliferation in alveoli, which may be related to previous respiratory tract infection. Some patients may show nodular opacities, and most patients have normal lung volume [43].
2. CT: Usually the lesion is more extensive on CT than on chest radiograph. Pulmonary lesions are typically distributed around peripheral zone and bronchi, and often involve the lower lobes of both lungs. Lung consolidation and ground-glass opacities are the most common manifestations (Fig. 25.6), with small nodules, but reticular changes and stripe-like changes are less common. The distribution of ground-glass opacities is not specific, but the lung consolidation is mostly distributed along bronchovascular bundles or subpleural areas. The lesions have the characteristics of migration, polymorphism, multiple foci, variability, and multiple recurrence, mostly involving both lungs and rarely showing honeycomb lung [44].

25.6.4 Diagnostic Key Points

1. The disease has flu-like symptoms with subacute onset.
2. Imaging manifestations are migratory, multifocal and peripheral alveolar consolidation in both lungs.
3. The general conditions are good, but the imaging manifestations are severe, and the lesions cannot be absorbed after 2–3 months. Hormone therapy has good effect to the disease.

25.6.5 Differential Diagnosis

1. All kinds of secondary organizing pneumonia to be excluded: ① Organizing pneumonia caused by bacterial, fungal and viral infection; ② Organizing pneumonia caused by drug factors; common drugs include amiodarone, bleomycin, gold preparations, etc. ③ Organizing pneumonia-like changes found in connective tissue diseases such as Wegener's granulomatosis and interstitial pneumonia such as NSIP.
2. Usual interstitial pneumonia: Typical HRCT findings are basal and peripheral reticular opacities, usually accompanied by traction bronchiolectasis. Honeycombing changes are common, which is the key to determine the diagnosis. Ground-glass opacities are common, but their scope is smaller than that of reticular opacities.
3. *Staphylococcus aureus* pneumonia: ① Acute onset, chills, high fever, and significant toxemia; ② The lesions are extensive, often involving multiple lobes and segments of both lungs at the same time; ③ Multiple pulmonary infiltrations, pulmonary abscess, pneumatocele and empyema or pyopneumothorax are the four major imaging signs of *Staphylococcus aureus* pneumonia. ④ The lesions are changeable, and the changes of shape, location and size of the lesions can be found by CT reexamination in a short time.
4. Lung cancer: Drakopanagiotakis et al. put forward the imaging features of focal organizing pneumonia which are different from lung cancer [45]: ① The mass involves pleura or is distributed along bronchovascular bundle, with vasoconstriction and convergence; ② The shape of the mass is flat oval, trapezoidal or rhombic rather than round; ③ There are satellite foci.

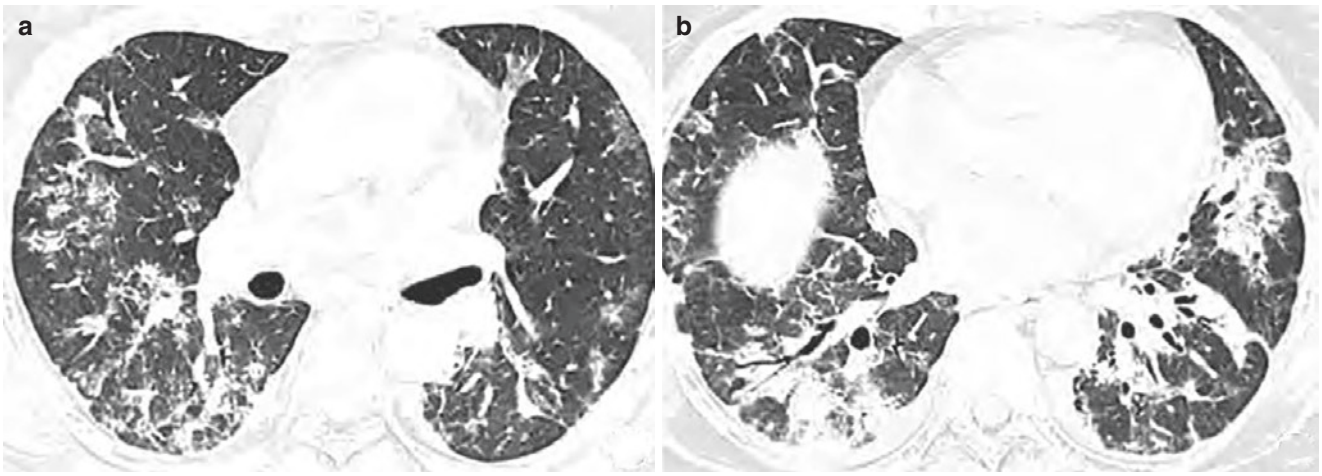

Fig. 25.6 Cryptogenic organizing pneumonia. (**a**) CT lung window showed multiple patchy consolidation and ground-glass opacities in both lungs; (**b**). Air bronchogram, thickened bronchial wall and dilatation of bronchial lumen were found in consolidation

25.6.6 Research Status and Progress

The imaging manifestations of COP are various, with rapid changes and common recurrence. Some scholars have found that "reversed halo" sign is also common in COP [46], but it is not specific, and can also be found in tuberculosis, mycosis and some tumors. Analysis combining with distribution and other characteristics is also helpful for the diagnosis of COP.

25.7 Lymphocytic Interstitial Pneumonia

Ping LiJifeng Zhang, and Shanshan Yu

25.7.1 Overview

Lymphocytic interstitial pneumonia (LIP) is used to describe the interstitial infiltration of diffuse lymphocytes in the lung [47, 48]. In 2012, ATS/ERS classified idiopathic LIP as rare interstitial pneumonia [41]. LIP is a rare idiopathic disease. Clinically, LIP is mostly secondary to hematological tumor, viral infection, etc. LIP belongs to lymphoproliferative diseases.

This disease is common in females, and the average onset age is 50. Clinical manifestations: dyspnea, cough, chest pain and occasional hemoptysis; emaciation, fever and joint pain; often complicated with immunoglobulin abnormalities; restrictive ventilation dysfunction and diffusion dysfunction of the lung.

25.7.2 Pathological Manifestations

The histological features of LIP are diffuse infiltration of lymphocytes, plasma cells and histiocytes into pulmonary interstitium. The inflammatory reaction around bronchioles is serious, with reactive hyperplasia of lymphatic follicles. Although it is mainly interstitial changes, there are secondary changes in parenchyma due to compression or protein-containing fluid and macrophage infiltration. Slight involvement can be found around bronchi. Interstitial fibrosis is rare [49].

25.7.3 Imaging Manifestations

1. X-ray: Chest radiographs show no specific manifestation, manifested as bilateral reticular opacities, nodules or alveolar opacities. The linear opacities on chest radiograph reflect the lymphocyte infiltration around bronchioles in histology.
2. CT: HRCT mainly shows ground-glass opacities with diffuse distribution on both sides or mainly distributed in unilateral lower lung, centrilobular nodules with blurred edges, small nodules and cystic changes under pleura, bronchovascular bundles, thickened interlobular septa and enlarged lymph nodes. Cystic changes of LIP are mainly located in the parenchyma of the middle zone of the whole lung field, which may be related to air retention caused by alveolar infiltration around bronchioles. These cystic changes accompanied by ground-glass opacities are highly indicative of DIP, sometimes showing centrilobular nodules and thickened septa [50–53].

25.7.4 Diagnostic Key Points

1. Typical features of HRCT include bilateral diffuse opacities or ground-glass opacities mainly distributed in unilateral lower lung, centrilobular nodules with blurred edges, and small subpleural nodules and cystic changes.
2. If there are no typical clinical symptoms and imaging manifestations, lung biopsy should be performed to confirm the diagnosis.
3. Hormone and immunosuppressant treatment are effective.

25.7.5 Differential Diagnosis

1. UIP: The main CT manifestations of LIP different from UIP include diffuse opacities or ground-glass opacities mainly distributed in one lower lung, without obvious "apex distribution and basal distribution tendency," extensive ground-glass opacities, reticular opacities and tiny nodular opacities. Contrary to the subpleural cystic changes of UIP, the cystic changes of LIP are mainly located in the pulmonary parenchyma of the middle zone of the whole lung field.
2. RBILD: Most of patients are smokers, more common in males than in females, and mostly in middle-aged and elderly people. In the early stage of DIP, both lungs show blurred shadows and ground-glass-like changes. In the later stage, both lungs show linear, reticular or reticular nodular opacities, generally without honeycomb lung.

RBILD is mainly characterized by reticular opacities, nodules and ground-glass opacities. The lesions show patchy distribution, confined to alveoli around bronchioles.

25.7.6 Research Status and Progress

LIP is a rare idiopathic interstitial pneumonia, which is related to the autoimmune function of patients. Its imaging manifestations must be recognized and summarized to better distinguish from some interstitial lung diseases related to rheumatism.

25.8 Idiopathic Pleuroparenchymal Fibroelastosis

Ping Li and Jifeng Zhang

25.8.1 Overview

Idiopathic pleuroparenchymal fibroplasia (IPPFE) is a rare disease manifested as fibrosis involving the pleura and subpleural lung tissue, mainly distributed in the upper lobes of both lungs. This disease is common in adults, with an average onset age of 57, without gender difference. Sixty percent of patients show progressive disease progression, with fatality rate of 40% [54]. Elastic fibers and alveolar fibrosis can be found in histological manifestations. The etiology of PPFE is unknown. It is idiopathic in some patients. Other patients have familial ILD. It may also be related to radiotherapy and chemotherapy, hematopoietic stem cell transplantation, lung transplantation and other factors. About half of the patients have repeated infection and nonspecific autoantibodies [55, 56]. The main symptoms are shortness of breath, dyspnea, dry cough, etc. Chest pain caused by pneumothorax may be the first symptom of some patients [57].

25.8.2 Pathological Manifestations

Pathologic manifestations include spherical fibrin deposition in alveolar cavity accompanied by organizing pneumonia, indicating diffuse alveolar damage and organizing pneumonia. Other manifestations include significantly thickened pleura, significant hyperplasia of elastic fibers in the visceral pleura and the lower lung parenchyma, and a little chronic inflammatory cell infiltration.

25.8.3 Imaging Manifestations

1. X-ray: Chest radiographs show hyperdensities of lung apex and bilateral upper lung, mostly in symmetrical distribution, and pleural thickening accompanied by pleural calcification [58].
2. CT: HRCT shows subpleural hyperdense consolidation in both lungs, accompanied by traction bronchiectasis, with distorted structure and reduced volume of upper lobes of both lungs.

25.8.4 Diagnostic Key Points

1. HRCT shows pleural thickening accompanied by traction bronchiectasis, with distorted structure and reduced volume of upper lobes of both lungs.
2. Pathological examinations show fibrosis of pleura and subpleural lung parenchyma.
3. Hormone and immunosuppressant treatment are effective.

25.8.5 Differential Diagnosis

1. Pulmonary tuberculosis: Tuberculosis often occurs in the posterior segment of the upper lobe and the dorsal segment of the lower lobe of both lungs, which overlaps with the onset site of PPFE, but the antituberculosis treatment is effective, and the detection results of Mycobacterium tuberculosis are mostly positive.
2. Nonspecific interstitial pneumonia (NSIP) and idiopathic pulmonary fibrosis: HRCT shows that the lesions are mainly distributed in the lower lobes of both lungs, and traction bronchiectasis is common. The former is manifested as reticular opacities distributed along bronchovascular bundles or diffusely distributed, while the latter is manifested as reticular opacities and honeycomb shadows mainly distributed at the basal part and subpleura.
3. Pulmonary interstitial fibrosis caused by other causes: Asbestosis patients have a history of exposure to asbestos, and asbestos bodies can be found in pathological examination. It should be differentiated from interstitial fibrosis associated with connective tissue disease.

25.8.6 Research Status and Progress

PPFE is a rare disease, and its diagnosis mainly depends on lung biopsy. CT-guided lung biopsy has less trauma and clear display, which can be accurately located by staining to improve the success rate of biopsy [59].

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