Connective Tissue Disease-Associated Lung Disease

19

Yufeng Xu

Connective tissue disease (CTD) is a kind of autoimmune disease causing damage to organs of the whole body with the underlying chronic inflammation of blood vessels and connective tissue. The lung is rich in collagen, blood vessels and other connective tissues, and has the functions of immune regulation, metabolism and endocrine, so it has become the target organ often involved in CTD. If connective tissue disease invades respiratory system, loose connective tissue may suffer from myxedema, small vasculitis necrosis and fibrinoid degeneration, and lung changes such as interstitial lung disease (ILD), pleurisy, pleural effusion, pulmonary arterial hypertension, small airway disease, bronchiectasis and respiratory myasthenia, which are called CTD-associated lung disease [1–3]. Different types of connective tissue diseases have different manifestations in the involved lungs. For example, systemic sclerosis is most likely to involve pulmonary interstitium and blood vessels, while patients with systemic lupus erythematosus are less likely to have interstitial lesions (Table 19.1). It should be noted that patients with connective tissue diseases are prone to lung infection and drug-induced lung damage, which needs differential diagnosis by comprehensive analysis on clinical manifestations, laboratory examinations and imaging features.

Table 19.1 Changes and comparison of chest involvement in common connective tissue diseases

Connective tissue disease	Interstitial lung disease	Airway change	Pleural change	Vascular change	Diffuse pulmonary hemorrhage	Muscle change
RA	++	++	++	+	–	–
SSc	+++	–	–	+++		+
SS	++	++	+	+	–	–
PM/DM	+++	–	–	+	–	++
SLE	+	+	+++	+	++	+
MCTD	++	+	+	++	–	+
AS	++	+	+	–	–	–
IBD	+	+++	+	+	+/–	–

Note: *RA* rheumatoid arthritis, *SSc* systemic sclerosis, *SS* Sjogren syndrome, *PM/DM* polymyositis/dermatomyositis, *SLE* systemic lupus erythematosus, *MCTD* mixed connective tissue disease, *AS* ankylosing spondylitis, *IBD* inflammatory bowel disease. – none, + rare, + + common, + + + most common

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19.1 Rheumatoid Arthritis

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19.1.1 Overview

Rheumatoid arthritis (RA) is a systemic autoimmune disease mainly with clinical manifestations of invasive arthritis as well as progressive and symmetrical polyarthritis. Cardiovascular, respiratory and nervous systems may be affected.

RA can occur in patients at any age. Epidemiological investigation shows that the global incidence rate of RA is 0.5–1%, and the incidence rate in China is 0.42%. The total number of patients is about 5 million, and the ratio of male to female prevalence rate is about 1:4. The pathogenesis of RA is still unclear. The basic pathological manifestations include synovitis, pannus formation and gradual destruction of articular cartilage and bone, which eventually leads to joint deformity and loss of function. The disease may be complicated with lung diseases, cardiovascular diseases, malignant tumors and depressive disorder [4].

The onset of RA is usually occult, and the main symptoms are pain, stiffness and swelling of multiple joints. The predilection sites include metacarpophalangeal joints, proximal interphalangeal joints, wrist joints and metatarsophalangeal joints of toes. Synovial joints of other limbs, such as elbow joints, shoulder joints, ankle joints and knee joints, are often involved. Some manifestations of RA involving the lungs include pleural effusion, rheumatoid nodules and interstitial pneumonia, more common in male patients. Smoking can promote the occurrence of lung manifestations in RA patients, and the exact pathogenic effect of smoking is not clear, but the risk of pulmonary involvement in RA patients increases with more tobacco smoke exposure. Pulmonary involvement can occur before, at the same time of or later than arthritis. The most common clinical respiratory symptoms are exertional dyspnea or cough. Airway diseases can be manifested as wheezing, but may also be asymptomatic.

Rheumatoid factor (RF) can be found in serum of RA patients (70–80%), but the specificity of RF is poor with limited diagnostic value. The higher the titer of RF (at least 3 times the normal upper limit), the higher the specificity of RA diagnosis. The sensitivity of anti-CCP antibody in diagnosing RA is similar to that of RF, but the specificity is high (95–98%). The higher the titer of anti-CCP antibody (at least 3 times the normal upper limit), the higher the specificity. The elevated erythrocyte sedimentation rate (ESR) and (or) C-reactive protein (CRP) in RA patients in acute stage suggest acute inflammation.

19.1.2 Pathological Manifestations

RA-related lung changes are mainly interstitial lung diseases. The clinical manifestations, pathological and imaging features of rheumatoid arthritis-associated interstitial lung disease (RAILD) are similar to those of idiopathic interstitial pneumonia (IIP), so their histopathology is usually classified according to IIP classification methods issued by American Thoracic Society (ATS) and European Respiratory Society (ERS). The histological types of RA-ILD are mainly usual interstitial pneumonia (UIP) and nonspecific interstitial pneumonia (NSIP). The proportion of UIP and NISP in RA is basically equal, and UIP is more common than other connective tissue diseases (Table 19.2). Organizing pneumonia (OP), desquamative interstitial pneumonia (DIP) and acute interstitial pneumonia (AIP) can also be found in the histological types of RA-ILD. Some patients with RA may show multiple histopathological types.

Pulmonary rheumatoid nodules are uncommon, and the prevalence of pulmonary nodules in RA has been reported differently, ranging from 0.4% to 33% [5]. Rheumatoid nodules in the lungs are usually located in the subpleural area or near the interlobular septa, ranging in size from several millimeters to several centimeters, showing single or multiple lesions. Its pathological manifestations are the same as those of subcutaneous rheumatoid nodules, including central necrosis, palisade-like arrangement of epithelial-like cells, monocyte infiltration and associated vasculitis. Rheumatoid nodules in the lungs can cause cavities, thereby leading to severe hemoptysis or pneumothorax. Generally speaking, pulmonary rheumatoid nodules usually occur in patients with long medical history, complicated with subcutaneous rheumatoid nodules, and showing high RF titer. The progno-

Table 19.2 Types and comparison of common interstitial lung diseases associated with connective tissue diseases

CTD	UIP	NSIP	OP	LIP	DAD
RA	+++	++	+		+
SSc	+	+++			+
SS	+	+++	+	++	
PM/DM	+	+++	+++		+
SLE	+	+	+		++
MCTD	+	++	+	+	
AS		+		–	–
IBD		+	+		

Note: *RA* rheumatoid arthritis, *SSc* systemic sclerosis, *SS* Sjogren syndrome, *PM/DM* polymyositis/dermatomyositis, *SLE* systemic lupus erythematosus, *MCTD* mixed connective tissue disease, *AS* ankylosing spondylitis, *IBD* inflammatory bowel disease, *CTD* connective tissue disease, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *LIP* lymphocytic interstitial pneumonia, *DAD* diffuse alveolar damage. – none, + rare, + + common, + + + most common

sis of rheumatoid nodules is good, and some can shrink or subside by themselves. Pneumoconiosis patients complicated with RA are prone to a large number of pulmonary nodules, which is called Caplan syndrome, also known as rheumatoid pneumoconiosis [6]. The histological manifestations of Caplan syndrome nodules are similar to those of simple rheumatoid nodules, but the central necrotic area of Caplan syndrome nodules is often surrounded by a layer of black dust.

Pulmonary airway lesions in RA include bronchiectasis, bronchiolitis obliterans and follicular bronchiolitis. Bronchiolitis obliterans usually occur after joint symptoms, characterized by progressive centripetal stenosis of membranous bronchioles. Follicular bronchitis is characterized by proliferation of lymphoid follicles in bronchus-associated lymphoid tissue, which are usually distributed along bronchioles. More and more studies have found the relationship between bronchiectasis and RA. Foreign studies have shown that the incidence of bronchiectasis confirmed by CT in RA patients is as high as 12–62%, while domestic studies have found that the incidence of bronchiectasis in RA patients is 43.3%, which is much higher than that of the general population [7].

Pleural lesions are common in RA patients. Pleural lesions mainly include pleurisy and pleural effusion. A few cases may show empyema, pneumothorax and bronchopleural fistula.

Most drugs used to treat RA include methotrexate (MTX), leflunomide, biological agents, sulfasalazine, gold preparations, penicillamine and nonsteroidal anti-inflammatory drugs (NSAID), which may induce alveolar inflammation, pulmonary interstitial inflammation and/or pulmonary interstitial fibrosis.

In addition to direct pulmonary toxicity, antirheumatic drugs also have immunosuppressive effect, which will increase the risk of bacterial infection and opportunistic infection in the lungs.

Other respiratory diseases related to RA include pulmonary apical fibrobullous lesions, venous thromboembolism, vasculitis and pulmonary arterial hypertension.

19.1.3 Imaging Manifestations

1. X-ray.
   (a) Pleural lesions: RA chest radiographs show thickened pleura with or without pleural effusion, mostly in unilateral site, sometimes in bilateral sites.
   (b) Interstitial pneumonia: Most cases are nonspecific, and early mild lesions may not be easily found on chest radiographs. Chest radiographs of typical lesions show reticular nodules and honeycomb shadow in both lungs, mainly distributed in both lower lung fields.
   (c) Rheumatoid nodules: Manifested as single or multiple pulmonary nodules distributed in subpleural area, with a diameter of 5 mm–7 cm.
   (d) Caplan syndrome: It mainly shows multiple nodular opacities. Single or multiple lesions are round or oval hyperdensities, with clear edges, different sizes of 0.5–1.5 cm in diameter, occasionally 3–5 cm, often in the middle and lower lung fields. Multiple lesions are similar to metastases, but the central necrosis can form a thin-walled cavity, generally without gas–liquid plane, and a few cases may show calcification.
2. CT: Chest radiographs are often normal for the early or mild RA, so CT is the most valuable noninvasive imaging examination for finding lung abnormalities in RA. A large proportion of RA patients can show various abnormalities on chest CT radiographs.
   (a) Pleural disease: It is the most common abnormal manifestation of chest, mostly with thickened pleura and pleural effusion.
   (b) Interstitial pneumonia: The most common histological types are UIP and NSIP. UIP is manifested as subpleural or basal reticular opacities of the lower lobes of both lungs, thickened interlobular septa and intralobular septa, accompanied by traction bronchiectasis, and honeycomb lung (Fig. 19.1). NSIP is manifested as ground-glass opacities and reticular opacities at the base of both lungs (Fig. 19.2).
   (c) Organizing pneumonia: It usually occurs in the middle and lower fields of the lung, and mostly distributed around bronchial vessels or at peripheral lung.

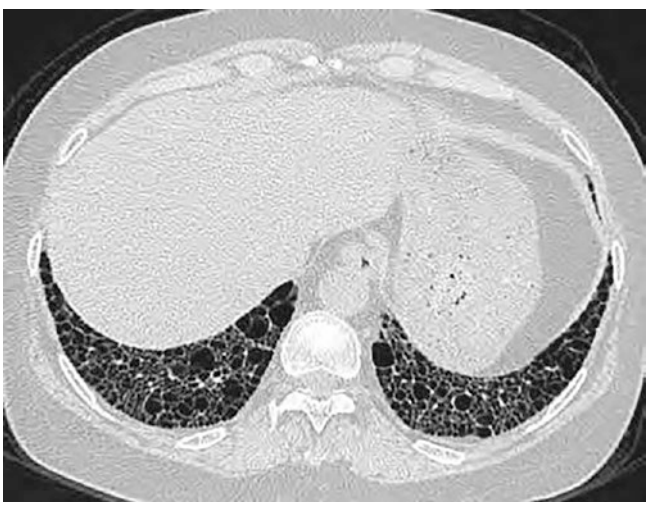

Fig. 19.1 Rheumatoid arthritis (UIP). CT lung window showed subpleural honeycomb lung in lower lobe of both lungs without ground-glass opacities

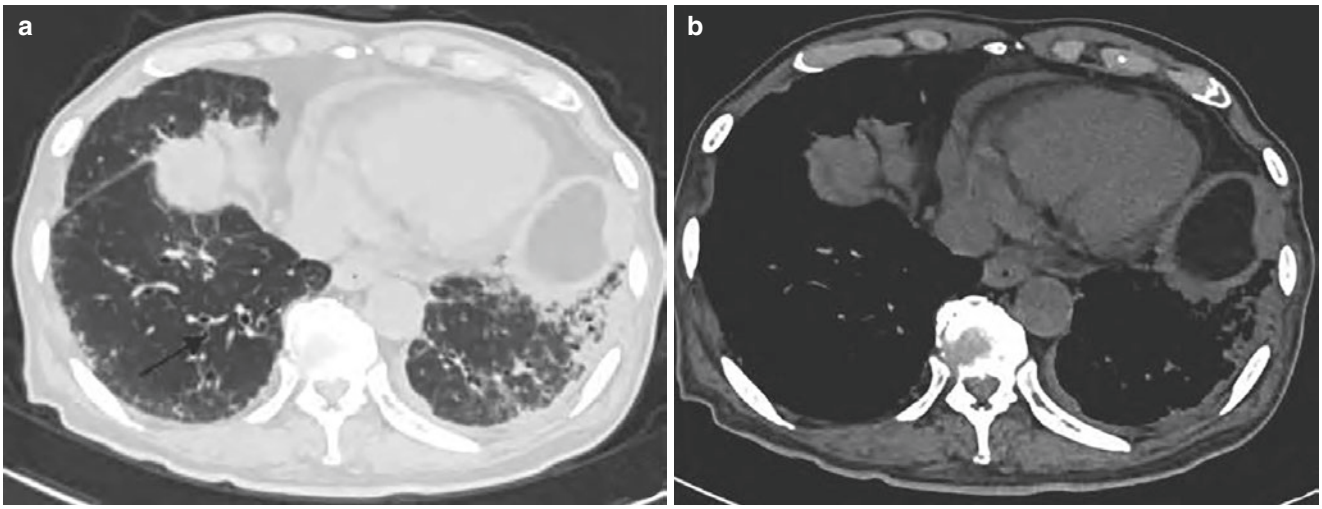

Fig. 19.2 Rheumatoid arthritis (NSIP). (**a**) CT lung window showed subpleural reticular opacities with ground-glass opacities in the lower lobe of both lungs, showing partial bronchiectasis (arrow); (**b**) Mediastinal window showed thickened left pleura and pericardial effusion

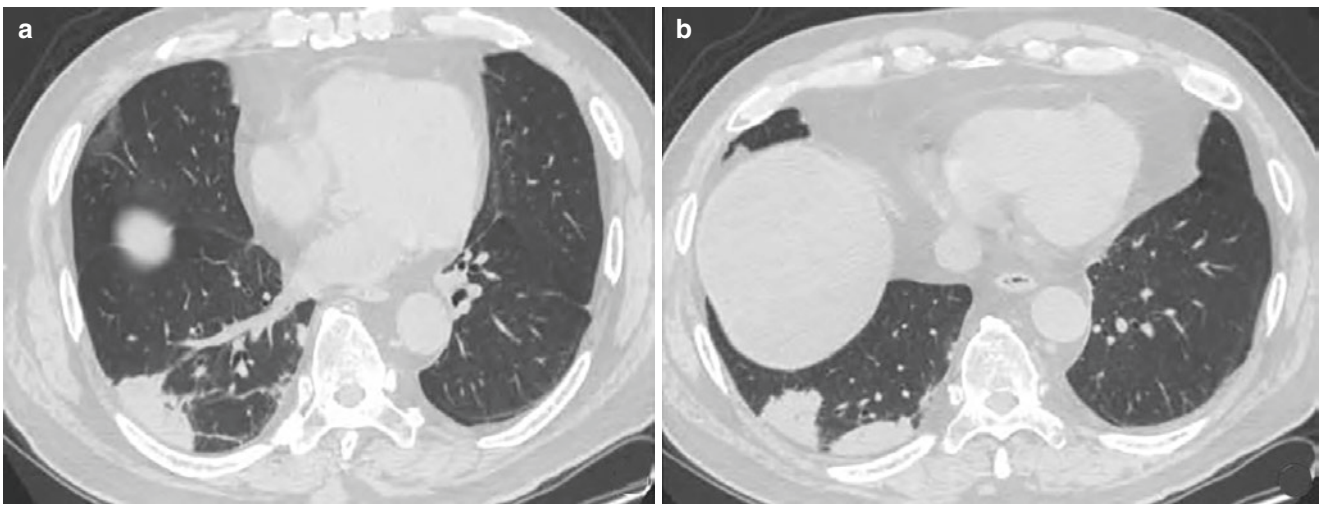

Fig. 19.3 Rheumatoid arthritis (organizing pneumonia). (**a**, **b**) CT lung window showed subpleural patchy consolidation in the lower lobe of the right lung

Organizing pneumonia can be manifested in the following forms: focal consolidation, lesions distributed around lobules, patchy consolidation, acinar shadow and nodules (Fig. 19.3).

(d) Rheumatoid nodules: Single or multiple small nodules distributed under the pleura, ranging in size from several millimeters to several centimeters (Fig. 19.4). About 50% cases show thick-walled cavity with smooth inner surface, which may lead to pneumothorax and other complications.

(e) Airway lesions: Thickened bronchial wall and bronchiectasis can be found.

(f) Bronchiolitis obliterans: It is characterized by thickened bronchiole wall, hyperinflation and mosaic sign.

(g) Follicular bronchiolitis: It is manifested as centrilobular micronodules and branched hyperdensities distributed under pleura or beside bronchi ("tree-in-bud" sign) (Fig. 19.5).

(h) Others: Pulmonary arterial hypertension, pulmonary heart disease; mediastinal lymphadenovarix, pericarditis.

19.1.4 Diagnostic Key Points

1. RA often involves more than 3 middle and small joints in wrist or foot, and its clinical manifestations are joint swelling, pain and morning stiffness.

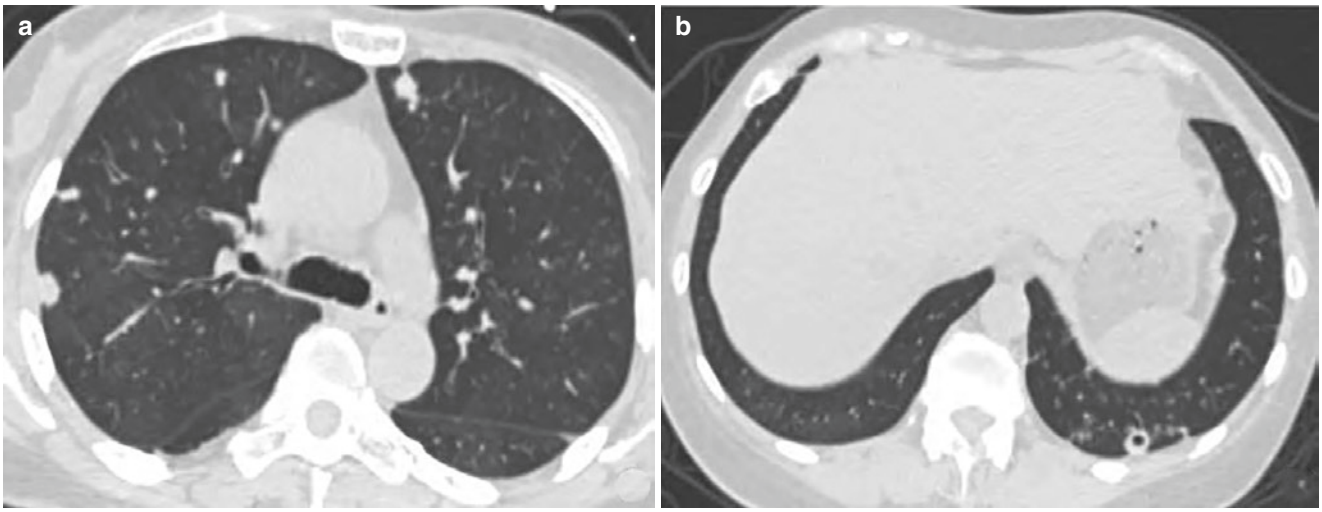

Fig. 19.4 Rheumatoid arthritis (rheumatoid nodules). (**a**) CT lung window showed multiple subpleural soft tissue nodules in both lungs; (**b**) Some nodules showed cavities inside

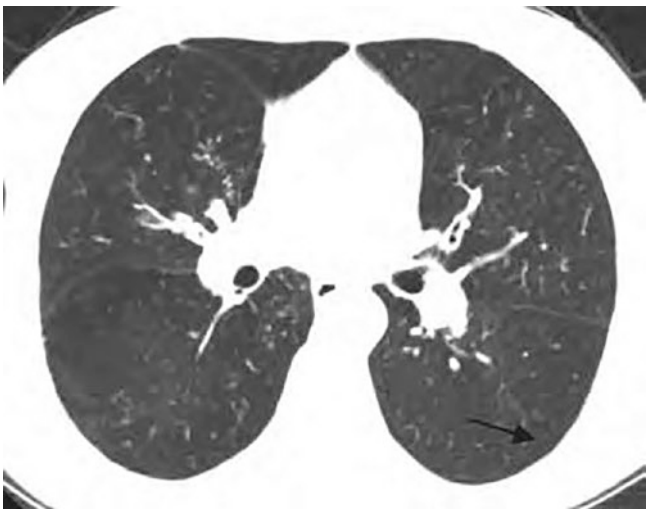

Fig. 19.5 Rheumatoid arthritis (follicular bronchiolitis). CT lung window showed scattered centrilobular nodules and "tree-in-bud" sign in both lungs (arrow)

2. The serological manifestations of RA are RF and positive CCP antibody, and elevated CRP or ESR.
3. The main manifestations of joint involvement by RA are bone erosion and osteoporosis at the joint margin.
4. The common imaging manifestations of pulmonary involvement in RA are as follows: (1) Thickened pleura and pleural effusion are common lung changes in RA; (2) UIP and NSIP are common interstitial pneumonia of pulmonary involvement in RA, with reticular opacities, with or without ground-glass opacities, mainly distributed in the periphery of both lower lungs; (3) Bronchiectasis and bronchiolitis obliterans, hyperinflation and mosaic sign.
5. Rare imaging manifestations of pulmonary involvement in RA: (1) Rheumatoid nodules, single or multiple nodules distributed under pleura, sometimes with cavities; (2) Organizing pneumonia, peritracheal and subpleural consolidation.

19.1.5 Differential Diagnosis

1. Idiopathic pulmonary fibrosis: UIP is the main feature of idiopathic pulmonary fibrosis (IPF). RA is the most common disease in UIP patients with connective tissue diseases. The lung imaging features of the two are sometimes similar. IPF is generally not accompanied by thickened pleura, pericarditis and small airway lesions. Analysis in combination of joint symptoms of RA is also helpful to distinguish the two.
2. Other connective tissue disease-related interstitial pneumonia: NSIP is the main manifestation of many connective tissue disease-related lung diseases, such as scleroderma. The manifestations of NSIP in lung are very similar, and the manifestations of other related systems are helpful for differentiation. For example, scleroderma may be accompanied by esophageal dilatation, while RA may be accompanied by joint destruction.
3. Lung cancer: Rheumatoid nodules need to be distinguished from lung tumors, especially in patients with a history of smoking. Rheumatoid nodules are usually located near the pleura in the lung periphery. For nodules with increasing size or diameter greater than 8 mm, biopsy is needed if imaging differentiation is difficult.

19.1.6 Research Status and Progress

1. Pulmonary ultrasound: It can display pleural and subpleural lesions and B line formed by thickened interlobular septa, which is of certain value in the diagnosis and evaluation of interstitial lung diseases. Some researchers believe that pulmonary ultrasound is convenient and fast, without radiation, and has certain advantages in screening interstitial pneumonia in patients with connective tissue diseases [8].
2. Pulmonary MRI: It is useful in evaluating RA-ILD. MRI is helpful in differentiating active interstitial inflammation and fibrosis. Active inflammation is characterized by T2WI hyperintensity in interstitium, while fibrosis is characterized by isointensity, which has important clinical significance for evaluating the condition of interstitial lung disease and predicting its response to therapy.
3. Interstitial pneumonia with autoimmune features (IPAF): Idiopathic interstitial pneumonia (IIP) is a kind of diffuse inflammatory and/or fibrotic lung disease with similar clinical manifestations, imaging and histological features. Before diagnosing IIP, it is necessary to exclude the known causes of interstitial pneumonia, such as environmental exposure, drugs or connective tissue diseases. Interstitial pneumonia is one of the common clinical manifestations of patients with connective tissue disease, but it is not uncommon for interstitial pneumonia to be the first or even the only manifestation of occult connective tissue disease. Therefore, it is sometimes difficult to distinguish IIP from some CTD-ILD. More and more studies have shown that some patients diagnosed with IIP have some potential clinical features suggesting the existence of certain connective tissue diseases, and some patients only have the clinical manifestations of these autoimmune diseases, but lack autoantibodies. Other patients have highly specific serum autoantibodies, but have no typical systemic or extrapulmonary manifestations. However, these manifestations cannot confirm the diagnosis of connective tissue diseases. Therefore, the IIP with some CTD characteristics but not yet diagnosed as an exact connective tissue disease has been named IPAF by the Working Group on Undifferentiated Connective Tissue Disease of European Respiratory Society and American Thoracic Association [9].

19.2 Systemic Sclerosis

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19.2.1 Overview

Systemic sclerosis (SSc), also known as scleroderma, is a systemic autoimmune disease characterized by localized or diffuse skin thickening and fibrosis. Most of patients are female, with the age of 30–50. According to the skin involvement of patients, SSc can be divided into five subtypes: (1) Localized cutaneous SSc, in which skin thickening is limited to the distal end of elbow (knee), but may involve face and neck; (2) CREST syndrome, a subtype of localized cutaneous SSc, manifested as calcinosis (C), Raynaud's phenomenon (R), esophageal dysmotility (E), sclerodactyly (S) and telangiectasia (T); (3) Diffuse cutaneous SSc, in which skin thickening also involves the proximal limbs and trunk apart from face and distal limbs; (4) SSc without skin sclerosis, showing Raynaud phenomenon, SSc characteristic visceral manifestations and serological abnormalities in SSc, but no skin thickening; (5) Overlapping syndrome, diffuse or localized cutaneous SSc occur simultaneously with other diagnosed connective tissue diseases, including systemic lupus erythematosus, polymyositis/dermatomyositis or rheumatoid arthritis [10].

SSc often causes multiple system damage. The most common initial manifestations are Raynaud's phenomenon and occult acral swelling and facial swelling, with gradual thickening of finger skin. Raynaud's phenomenon is the first symptom in about 70% of the patients. Raynaud's phenomenon may occur 1–2 years before other symptoms of SSc (such as finger swelling, arthritis and visceral involvement) or simultaneously with other symptoms. Polyarthralgia and muscle pain are often early symptoms. In visceral involvement, digestive tract involvement is the most common, second only to skin involvement and Raynaud's phenomenon. Any part of the digestive tract can be involved, among which esophageal involvement is the most common.

More than 80% of SSc patients have pulmonary involvement, which is a common visceral complication, second only to esophageal involvement. Interstitial lung disease and pulmonary arterial hypertension are the most common lung manifestations. The most common symptoms of respiratory system are shortness of breath and decreased activity tolerance during exercise. Dry cough occurs in the later stage. With the progress of the disease, the probability of pulmonary involvement increases, and once the lung is involved, the disease develops progressively, with poor response to treatment. Pulmonary involvement has become the most common cause of death in SSc patients.

There is no special abnormality in routine laboratory examination, and the erythrocyte sedimentation rate may normal or slightly increased. In immunological examination,

the positive rate of serum antinuclear antibody is over 90%, and the karyotypes are speckled type, antinucleolar type and anticentromere type. Antinucleolar antibody has relative specificity in the diagnosis of SSc. Anti-Scl-70 antibody is a specific antibody of SSc, the positive rate is 15–20%. The positive rate of anti-Scl-70 antibody is associated with diffuse skin sclerosis, pulmonary fibrosis, joint deformity and distal osteolysis. The positive rate of anticentromere antibody in SSc ranges from 15% to 20%, which is a specific antibody for CREST syndrome and is often associated with severe Raynaud's phenomenon, fingertip ischemia and pulmonary arterial hypertension.

19.2.2 Pathological Manifestations

The pathological features of SSc are fibrosis and vascular hyperplasia and obstruction of skin, digestive tract, lung, heart, kidney and other organs. Interstitial lung disease (ILD) is the main manifestation of pulmonary involvement in SSc. SSc-related ILD contains many histopathological subtypes, the most common of which is nonspecific interstitial pneumonia (NSIP). In SSc-related NSIP, fibrotic features are more significant and inflammatory features are less significant, so it is fibrotic NSIP rather than cellular NSIP. Occasionally, SSc-related ILD is usual interstitial pneumonia (UIP) [11, 12].

Pulmonary arterial hypertension is the most common pulmonary vascular disease in SSc patients. Pulmonary arterial hypertension is the result of long-term pulmonary interstitium and peribronchial fibrosis or intimal hyperplasia of pulmonary arterioles. Pulmonary arterial hypertension usually progresses slowly and is generally difficult to detect clinically, unless serious irreversible lesions occur in the later stage.

Pleural effusion is not common in SSc (<10%) and airway involvement is not common.

19.2.3 Imaging Manifestations

1. X-ray.
   (a) Interstitial pneumonia: Diffuse, symmetrical basal reticular nodular opacities and pulmonary interstitial fibrosis in different degrees lead to honeycomb changes of lung tissue and reduction of lung volume.
   (b) Pulmonary arterial hypertension: Pulmonary artery widening and/or right ventricle enlargement. Radiological examination of early pulmonary arterial hypertension often shows normal result, so radiological examination is not helpful for screening pulmonary arterial hypertension.
   (c) Esophageal dilatation: Patients sometimes show esophageal inflation and dilatation.
   (d) Others: Lung consolidation may sometimes occur in SSc patients, which may be caused by aspiration pneumonia or organizing pneumonia.
2. CT.
   (a) Interstitial pneumonia: The common type of interstitial pneumonia in SSc is NSIP (Fig. 19.6), which is mainly manifested as subpleural ground-glass opacities in the lower lobe of both lungs, with reticular opacities and irregular linear opacities, occasionally with honeycomb shadow and traction bronchiectasis [13].
   (b) Pulmonary arterial hypertension: The main pulmonary artery is widened, with diameter > 29 mm, or larger than that of the adjacent ascending aorta.
   (c) Esophageal dilatation (Fig. 19.6): Gas–liquid plane may occur (80%).
   (d) Consolidation: If complicated with aspiration pneumonia or organizing pneumonia, it is manifested as patchy consolidation on CT.
   (e) Pleural lesions: Rare occurrence, which can be manifested as thickened pleura and pleural effusion.
   (f) Lymphadenectasis: SSc patients with interstitial lung disease often show lymphadenectasis, whose degree is related to the severity of interstitial disease, but not related to the type of interstitial disease.
3. Ultrasonography: Ultrasound echocardiography is an auxiliary means to screen early pulmonary arterial hypertension, and can also be used to evaluate ventricular function.

19.2.4 Diagnostic Key Points

1. Fibrosis of skin and/or internal organs includes thickened skin of hands and fingers, pulmonary arterial hypertension and interstitial lung diseases.
2. Vascular lesions: Raynaud's phenomenon and fingertip lesions (fingertip depressed scar, fingertip ulcer, fingertip gangrene and nailfold capillary abnormality, etc.).
3. Specific autoantibodies: Antinuclear antibody (ANA), anticentromere antibody (ACA) and antitopoisomerase I antibody are positive.
4. Common chest manifestations of SSc were: (1) Interstitial lung disease (ILD) (80%), NSIP; (2) Pulmonary arterial hypertension; (3) Esophageal involvement.
5. Uncommon chest manifestations of SSc: (1) Lung consolidation and ground-glass opacities; (2) Bronchiectasis; (3) Pleural lesions.

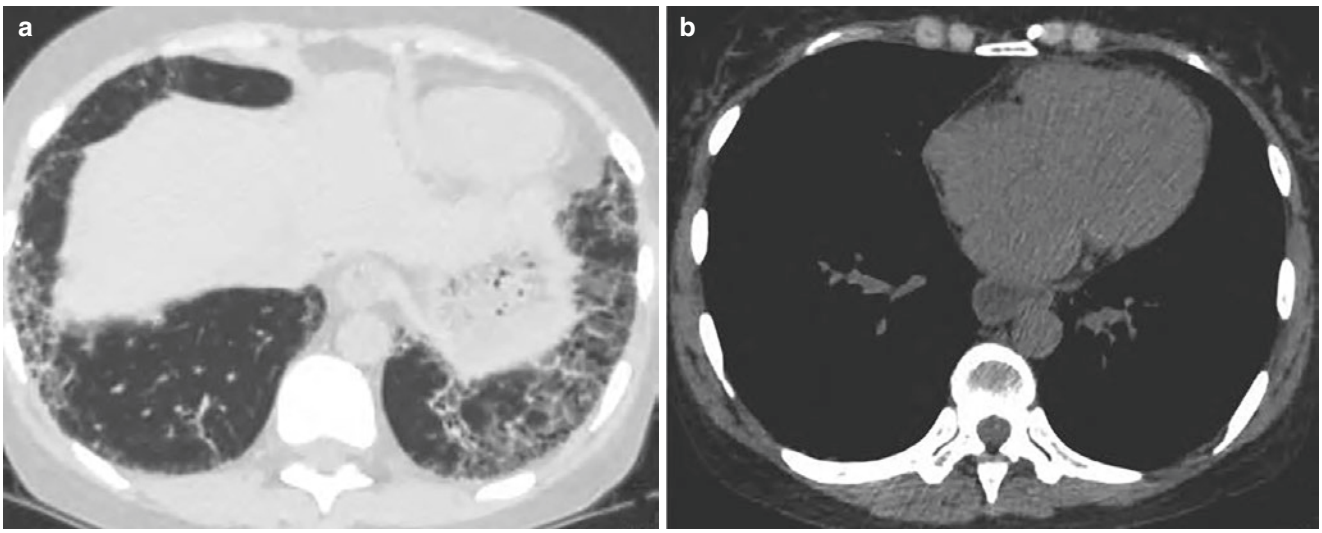

Fig. 19.6 Systemic sclerosis (NSIP). (**a**) CT lung window showed reticular opacities in lower lobe of both lungs accompanied by ground-glass opacities; (**b**) Mediastinal window showed esophageal dilatation

19.2.5 Differential Diagnosis

1. Idiopathic interstitial fibrosis: CT manifestations include thickened reticular opacities and honeycomb lung, but ground-glass opacities are rare, mainly distributed under pleura, without esophageal dilatation.
2. Aspiration pneumonia: CT features are ground-glass opacities and consolidation mainly distributed on the dorsal side of the lower lobes of both lungs. Recurrent episodes may show localized pulmonary fibrosis. Aspiration pneumonia is more common in the elderly, and disturbance of consciousness, gastroesophageal reflux and dysphagia are the risk factors of aspiration pneumonia.
3. Other connective tissue diseases: NSIP is the most common type of interstitial pneumonia in connective tissue diseases. The lung manifestations are similar, and the characteristic changes of other systems are helpful for differentiation.

19.2.6 Research Status and Progress

1. Interstitial lung disease is the main manifestation of pulmonary involvement in SSc, and SSc-ILD indicates poor prognosis of patients. Some patients with SSc-ILD may have no or mild clinical symptoms, so necessary examinations are required for early diagnosis and follow-up of SSC-ILD patients. Pulmonary function test (PFT) plays an important role in screening SSc-ILD patients. Because the change of lung function can occur before the onset of significant clinical symptoms, all SSc patients should receive PFT routinely at the initial diagnosis, especially vital capacity and diffusion capacity for carbon monoxide (D_LCO). Compared with HRCT, ultrasound has the advantages of rapid minimally invasive examination without cumulative radiation exposure risk, and can also be used as a screening method. Mohammadi et al. put forward an improved version of transthoracic ultrasound scoring system. The results have shown that compared with HRCT, the sensitivity, specificity, positive predictive value and negative predictive value of this scoring system in diagnosing SSC-ILD are 73.58%, 88.23%, 95.12% and 51.72%, respectively. Transthoracic ultrasound to monitor the disease progression of SSc-ILD patients during long-term treatment can partially replace HRCT examination to reduce radiation dose [14]..
2. Pulmonary MRI is useful in evaluating CTD-ILD. MRI is helpful in differentiating active interstitial inflammation and fibrosis. Active inflammation shows hyperintensity on interstitial T2WI, while fibrosis shows isointensity, which has important clinical significance in evaluating ILD condition and predicting its response to treatment.

19.3 Polymyositis and Dermatomyositis

Yufeng Xu

19.3.1 Overview

Polymyositis and dermatomyositis belong to idiopathic inflammatory myopathy (IIM), with the common characteristic of proximal skeletal muscle weakness and muscle inflammation. Idiopathic inflammatory myopathy is a group of systemic autoimmune connective tissue diseases. Based

on clinical features and immunopathological features, it is mainly divided into three types: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM), and the most common ones are polymyositis and dermatomyositis (PM/DM). The incidence of PM/DM in China is not very clear. The reported incidence of PM/DM in foreign countries is 5–10/1 million, female patients are more common than male patients, and DM cases are more common than in PM cases [15].

PM mainly occurs in adults, but rarely in children. DM may occur in adults and children. PM/DM usually has subacute onset, symmetrical proximal limb myasthenia occurs within weeks to months, and only a few patients (especially DM) have acute onset. PM/DM is often accompanied by systemic manifestations, such as fatigue, anorexia, weight loss and fever.

Symmetrical proximal limb myasthenia is the characteristic manifestation of PM/DM. About 50% of patients may also have myalgia or muscle tenderness. If the proximal muscles of upper limbs are involved, patients may have difficulty lifting their arms and cannot comb their hair and dress. If the proximal muscles of lower limbs are involved, patients often have difficulty going up stairs and steps, squatting or standing up from the seat. Distal myasthenia is not common in PM/DM patients, but patients may have different degrees of distal myasthenia throughout the course of disease.

Interstitial lung disease, pulmonary fibrosis and pleurisy are the most common pulmonary manifestations of PM/DM, which can occur at any stage during the course of the disease. Lung manifestations have various onsets, including fulminant, acute (diffuse alveolar damage, pneumonia) and chronic progression (fibrotic lung disease, pulmonary arterial hypertension, weakened respiratory muscle function), etc. A few patients have a small amount of pleural effusion. Laryngeal myasthenia can cause difficulty in pronunciation and hoarseness. If respiratory muscles such as diaphragm are involved, the manifestations include hypopnea, dyspnea or acute respiratory insufficiency and aspiration pneumonia. Pulmonary involvement is one of the important factors affecting the prognosis of PM/DM. Patients with PM/DM complicated with ILD often have severe illness, rapid progress, poor prognosis and high mortality.

PM/DM patients may have mild anemia and the increased total number of leukocytes. About 50% of PM patients have normal erythrocyte sedimentation rate and C-reactive protein. Serum muscle enzymes can increase significantly in patients with PM/DM in acute stage. Creatine kinase (CK) is the most commonly used in clinical practice. CK is the most sensitive to myositis, and the increasing degree is parallel to the degree of muscle injury. Myositis-specific autoantibodies (MSA) can be found in 30% of PM/DM patients. MSA can be divided into three types: antiaminoacyl tRNA synthetase antibody, antisignal recognition particle (SRP) antibody and anti-Mi-2 antibody. There are also some nonspecific myositis-related antibodies in PM/DM. Antinuclear antibody (ANA) is positive in 60–80% of PM/DM patients, and rheumatoid factor (RF) is positive in about 20% of PM/DM patients, but the titer is low [16].

19.3.2 Pathological Manifestations

Immune-mediated myositis and vascular injury are the characteristics of polymyositis and dermatomyositis. ILD is the most common lung change of PM/DM. The histological types of ILD related to PM/DM include nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), diffuse alveolar damage (DAD) and usual interstitial pneumonia (UIP). At present, NSIP is considered to be the most common histopathological type in PM/DM patients. Pathologically, PM/DM can gradually progress from DAD to OP, and finally become fibrotic NSIP. At first, the manifestation is acute lung epithelial injury, and then granulomatous inflammation and organizing of alveoli. The patchy consolidation of OP can be partially reversed, or may progress to reticular opacities. Therefore, OP and NSIP often coexist in lung biopsy tissues.

19.3.3 Imaging Manifestations

Chest manifestations of primary PM/DM include one or more types of ILD. The manifestations of vascular diseases include vasculitis, capillary angiitis/hemorrhage and pulmonary arterial hypertension. Secondary manifestations include respiratory failure, atelectasis, aspiration pneumonia, drug-related diseases, heart failure and tumors.

1. X-ray.
   (a) Interstitial pneumonia: The incidence of abnormal chest radiograph is low, and the most common manifestation is irregular linear opacities or consolidation at the base of both lungs, usually indicating the existence of NSIP, OP or DAD.
   (b) Consolidation: Aspiration pneumonia or secondary lung infection is manifested as patchy consolidation of both lungs.
   (c) Elevated diaphragm: The diaphragm is elevated and the lung field shrinks.
   (d) Pleural lesions: Pleural thickening or a small amount of pleural effusion.
2. CT.
   (a) Interstitial pneumonia: HRCT shows reticular opacities, consolidation and ground-glass opacities in PM/DM, and honeycomb shadow is rare. CT findings are

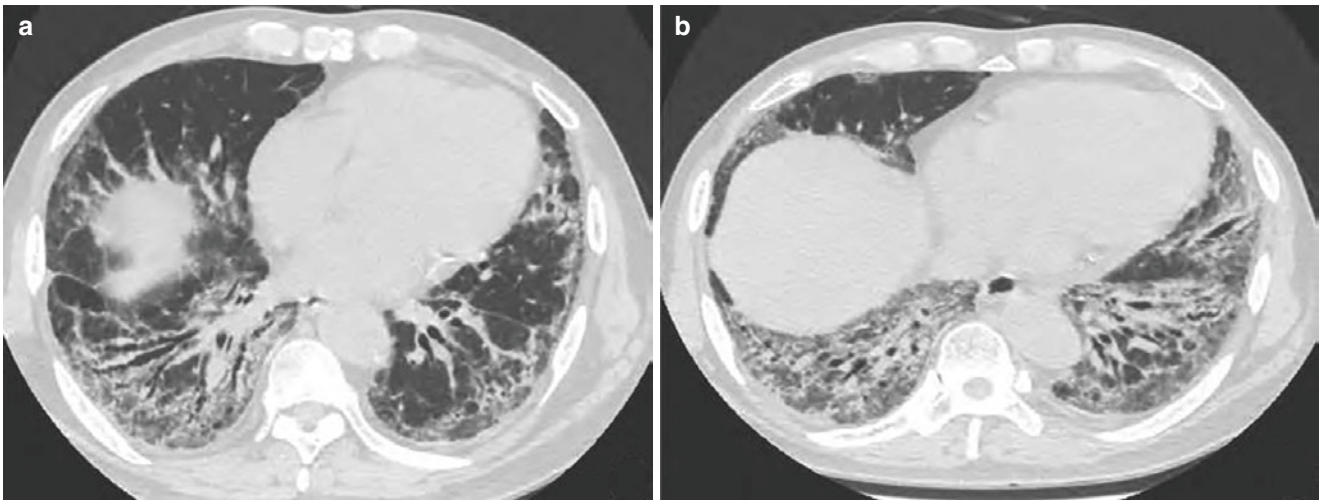

Fig. 19.7 Polymyositis (interstitial lung disease). (**a** and **b**) CT lung window showed grid shadow of lower lobe of both lungs with ground-glass shadow and traction bronchiectasis

related to NSIP, OP and DAD. The typical manifestation of NSIP is patchy ground-glass opacities around the lower lobes of both lungs, with or without reticular opacities. Depending on the ratio of inflammation to fibrosis in NSIP, cellular NSIP may have no reticular opacities or mild reticular opacities. With the progression of fibrosis, the reticular opacities of fibrosis NSIP can gradually increase and become the main manifestation (Fig. 19.7). OP is usually manifested as patchy consolidation in both lungs, mainly distributed along bronchovascular bundle or under pleura. DAD is manifested as patchy ground-glass opacities and consolidation in both lungs. PM/DM patients usually have both NSIP and OP on CT and histological examination.

(b) Pulmonary arterial hypertension: The main pulmonary artery is widened, with diameter > 29 mm, or larger than that of the adjacent ascending aorta.

(c) Pleural lesions: Pleural thickening or a small amount of pleural effusion.

19.3.4 Diagnostic Key Points

1. Symmetrical proximal myasthenia of limbs may be accompanied by myalgia or muscle tenderness.
2. Skin lesions, Gottron sign, erythema, heterochromia, nail fold changes, scalp involvement and skin calcification are common in DM.
3. Laboratory examination: Increased muscle enzyme; positive myositis-specific antibodies (anti-aminoacyl tRNA synthetase antibody, anti-SRP antibody and anti-Mi-2 antibody) and myositis-associated antibody (antinuclear antibody).
4. Common manifestations of chest involvement in PM/DM: Interstitial pneumonia is a common lung manifestation of PM/DM, and its histological types include nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP) and diffuse alveolar damage (DAD). CT manifestations mainly include ground-glass opacities and reticular opacities in both lower lung fields, and patchy consolidation around bronchus or under pleura.
5. The rare manifestation of PM/DM chest involvement is pulmonary arterial hypertension.

19.3.5 Differential Diagnosis

1. Drug-induced lung injury: It includes diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP), which need to be differentiated from interstitial pneumonia caused by connective tissue diseases.
2. Idiopathic nonspecific interstitial pneumonia (INSIP): It is a type of interstitial pneumonia. CT manifestations include ground-glass opacities and reticular opacities mainly in the lower lobe and subpleura of both lungs, usually without honeycomb lung. NSIP can be secondary to infection, connective tissue disease, drug-induced lung injury and organic dust inhalation, which is called secondary NSIP. Those with unknown reasons are called INSIP.
3. Idiopathic pulmonary fibrosis (IPF): CT shows larger reticular opacities and honeycomb lung, and ground-glass opacities are rare, mainly distributed under pleura.
4. Aspiration pneumonia: It is a common pulmonary complication of PM/DM, which is secondary to weak respiratory muscle strength. CT shows patchy consolidation at

the basal part of both lungs of aspiration pneumonia, which needs to be differentiated from PM/DM-related lung diseases.

19.3.6 Research Status and Progress

Positive anti-Jo-1 antibody, fever, arthritis/pain, Gottron sign and positive antinuclear antibody can be the main predictors of PM/DM complicated with ILD. Anti-Jo-1 antibody is a myositis specific antibody, and the positive rate of anti-Jo-1 antibody in patients complicated with ILD can be as high as 50–75%, which is because the content of anti-aminoacyl tRNA synthetase antibody in lung tissue is much higher than that in other organs, and anti-Jo-1 antibody accounts for 80% of anti-aminoacyl tRNA synthetase antibody, the lung tissue of patients with anti-Jo-1 antibody becomes the target organ attacked by immune cells. Serum type II alveolar cell surface antigen 6 (KL-6), monocyte chemoattractant protein 1 (MCP-1), surfactant protein A (SP-A), surfactant protein D (SP-D) and anti-aminoacyl tRNA synthetase antibody are effective serum markers of PM/DM complicated with ILD, among which KL-6 has the highest diagnostic and predictive value.

Epidemiological studies have found that inflammatory myopathy is associated with malignant tumors, and DM is most significantly associated with malignant tumors. It is estimated that the cancer incidence of DM patients is 5–7 times that of the general population. The results of a study in Taiwan, China have shown that the incidence of cancer in DM patients is 9.4%, and that in PM is 4.4% [17]. Malignant tumors associated with PM/DM may occur in various systems and organs of the whole body, but the disease spectrum of malignant tumors associated with different races is quite different. The common tumors in western countries are ovarian cancer, lung cancer, breast cancer, colorectal cancer, melanoma and non-Hodgkin's lymphoma, while in some Asian countries, nasopharyngeal carcinoma is the most common [18, 19], followed by breast cancer, ovarian tumor and uterine tumor, lung cancer, pancreas cancer, stomach cancer, colon and rectum tumors and lymphoma. Cancer can occur before, after or at the time of diagnosis of inflammatory myopathy. The peak incidence of cancer in DM/PM patients was at the time of myopathy diagnosis and within 1 year after the diagnosis.

19.4 Systemic Lupus Erythematosus

Yufeng Xu

19.4.1 Overview

Systemic lupus erythematosus (SLE) is a diffuse connective tissue disease mediated by autoimmunity and characterized by immune inflammation. The presence of multiple autoantibodies represented by antinuclear antibodies in serum and multisystem involvement are two main clinical features of SLE.

SLE often occurs in women of childbearing age (females: males = 8:1), and the onset age ranges from 15 to 45. A single-round large-scale survey in China has shown that the prevalence rate of SLE is 70/100,000, while that of women is as high as 113/100,000. SLE often involves many systems and organs, such as kidney, joints, skin and lung, and its clinical manifestations are complex and diverse. Most patients have occult onset, involving only one or two systems at first, manifested as mild arthritis, rash, occult nephritis, thrombocytopenic purpura, etc. Some patients are stable in subclinical state or have mild lupus for a long time, some patients can suddenly change from mild lupus to severe lupus, and more patients gradually show multisystem damage from mild symptoms. There are also some patients who have multiple systems involved and even show lupus crisis. The natural course of SLE is characterized by alternating periods of remission and exacerbation [20].

The erythema distributed in butterfly shape on the bridge of nose and both zygomatic and buccal areas is the characteristic change of SLE. Fever and fatigue are common systemic symptoms of SLE. The main manifestations of pulmonary involvement in SLE are pleurisy, pneumonia, pulmonary arterial hypertension and interstitial lung disease. Most SLE patients will have clinical manifestations involving lung and its blood vessels, pleura and/or diaphragm. Common clinical manifestations include dyspnea, dry cough and pleurisy chest pain. Recurrent pleurisy chest pain is the most common chest symptom of SLE, and pulmonary infection is also a common complication. Acute lupus pneumonia is characterized by acute fever, cough (sometimes accompanied by hemoptysis) and dyspnea.

Serum antinuclear antibody (ANA) is a sensitive detection index of SLE, which exists in almost all patients. The diagnostic sensitivity and specificity of ANA for SLE are 95% and 65%, respectively. The specificity and sensitivity of anti-dsDNA antibody are 95% and 70%, respectively. The specificity of anti-Sm antibody is as high as 99%, but the sensitivity is only 25%. High titer of anti-dsDNA antibody is considered to be the best marker of SLE activity, while anti-Sm antibody is not significantly related to disease activity.

19.4.2 Pathological Manifestations

SLE often involves pleura and lung, and the changes of the lung are related to circulating immunocomplex (CIC). The lung manifestations of SLE include pleurisy (with or without pleural effusion), pneumonia, interstitial lung disease, pulmonary arterial hypertension, shrinking lung syndrome and alveolar hemorrhage. Pleural involvement is common in SLE, which can be manifested as pleurisy chest pain with or without pleural effusion, but spontaneous pneumothorax is rare.

Pleural effusion in SLE is usually bilateral exudative and is characterized by elevated lactate dehydrogenase (LDH) in pleural effusion. Fibrothorax is a rare complication of lupus pleurisy, which can hinder lung expansion and lead to expiratory dyspnea.

The incidence of interstitial lung disease associated with SLE is low, and the results of a study of 525 SLE patients have shown that the incidence rate is 12% [21]. Histopathologically, nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP) and lymphoid interstitial pneumonia (LIP) have been reported, among which NSIP is the most common in SLE.

Diffuse alveolar damage caused by SLE is called acute lupus pneumonia. The pathological manifestations of acute lupus pneumonia are diffuse alveolar damage, alveolar edema, hyaline membrane formation and mononuclear cell infiltration. Immunoglobulin and complement deposition may occur in capillary wall. The incidence of lupus pneumonia is relatively low, which needs to be differentiated from lung infection, organizing pneumonia, pulmonary embolism, drug toxicity and diffuse alveolar hemorrhage caused by SLE.

The incidence of diffuse alveolar hemorrhage is low. A study found that only 2 of 525 SLE patients had diffuse alveolar hemorrhage [21]. Small airway diseases, such as bronchiolitis obliterans, are rare in SLE patients.

Shrinking lung syndrome (SLS), also known as vanishing lung syndrome, can be found in 1–6% of SLE patients [22]. This syndrome is characterized by dyspnea, pleurisy chest pain, progressive reduction of lung volume measured by PFT, and no evidence of interstitial fibrosis or severe pleural disease on chest CT. There is no consensus about the underlying pathogenesis of this disease. One possible mechanism is that myositis or myopathy affects diaphragm, which leads to diaphragm elevation and dysfunction.

SLE is one of the main connective tissue diseases that cause pulmonary arterial hypertension. Recent studies have reported that the incidence of SLE-related pulmonary arterial hypertension (SLE-PAH) is the highest among connective tissue disease-related pulmonary arterial hypertension (CTD-PAH) in China (49%) [23]. At present, pulmonary arterial hypertension has become the third leading cause of death from SLE. The causes and pathogenesis of increased pulmonary arterial hypertension caused by SLE are very complex and have not been fully clarified. The results of lung biopsy have shown that the histopathology of SLE-PAH includes plexiform hemangioma in pulmonary artery tunica media and thickened muscular artery wall, as well as immunoglobulin and complement deposition in artery wall related to SLE inflammation.

SLE patients are often complicated with pulmonary infections, including bacterial pneumonia and viral pneumonia, as well as opportunistic infections caused by *Pneumocystis jirovecii*, Candida, Cryptococcus, Aspergillus and others.

19.4.3 Imaging Manifestations

1. X-ray.
   (a) Pleural lesions: The common abnormal manifestations of SLE are bilateral or unilateral pleural effusion or thickened pleura, often accompanied by pericardial effusion.
   (b) Lung consolidation: Lupus pneumonia is characterized by ground-glass opacities or consolidation of bilateral or unilateral lungs, mainly distributed in the lower lungs. Secondary pulmonary infection can also show patchy consolidation. It is difficult to distinguish acute lupus pneumonia from infectious pneumonia by chest radiograph.
   (c) Pulmonary hemorrhage: Manifested as bilateral patchy opacities or diffuse ground-glass opacities or consolidation.
   (d) Interstitial lung disease: Chest radiographs usually show mild symptoms, mainly reticular opacities in the lower lung field.
   (e) Pulmonary arterial hypertension and pulmonary infarction: Pulmonary arterial hypertension is manifested as widened pulmonary artery. Pulmonary infarction is insensitive and nonspecific on chest radiographs, mainly manifested as wedge-shaped or patchy opacities under pleura.
   (f) Shrinking lung syndrome: Elevated diaphragm is its characteristic manifestation, accompanied by adjacent atelectasis and a small amount of pleural effusion.
2. CT (Figs. 19.8 and 19.9).
   (a) Pleural lesions: unilateral or bilateral pleurisy or pleural effusion, which is common on both sides and often accompanied by pericardial effusion.
   (b) Ground-glass opacities and consolidation: Acute lupus pneumonia is manifested as patchy ground-glass opacities and consolidation of bilateral middle

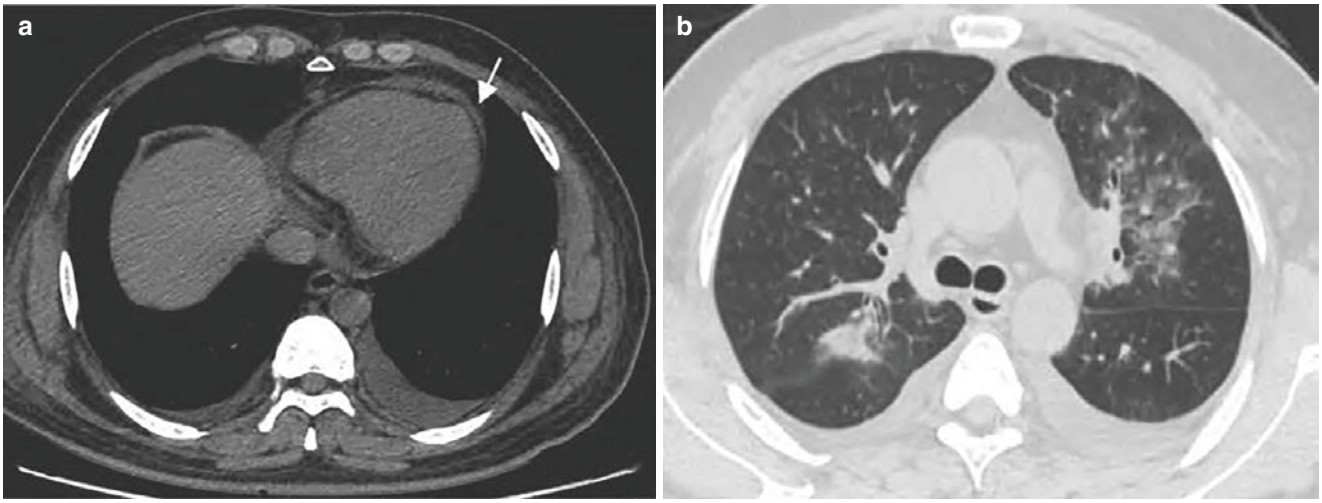

Fig. 19.8 Chest changes in systemic lupus erythematosus (I). (**a**) CT mediastinal window showed bilateral pleural effusion and pericardial effusion (arrow); (**b**) The lung window showed patchy consolidation and ground-glass opacities in the upper lobes of both lungs

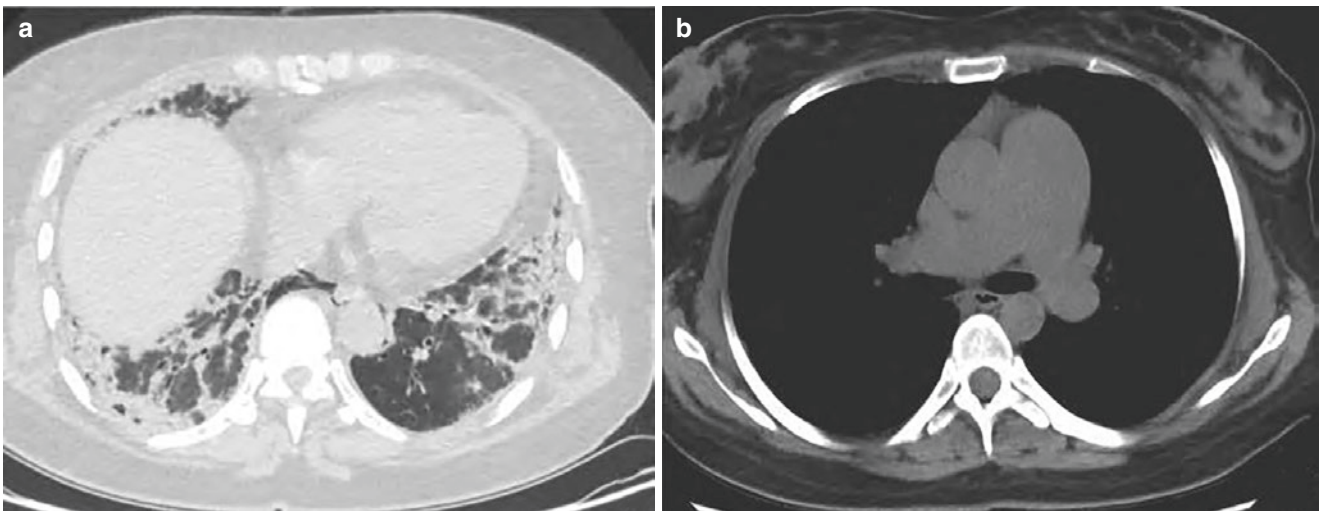

Fig. 19.9 Lung changes in systemic lupus erythematosus (II). A. CT lung window showed patchy consolidation in the lower lobes of both lungs; B. The mediastinal window showed significant dilation of pulmonary artery, suggesting pulmonary arterial hypertension

and lower lungs, often accompanied by elevated diaphragm and a small amount of pleural effusion on both sides, which is difficult to distinguish from infectious pneumonia.

(c) Alveolar hemorrhage: Manifested as dotted or patchy ground-glass opacities of both lungs.

(d) Interstitial pneumonia: NSIP is more common, manifested as ground-glass opacities and reticular opacities in the lower lobe of both lungs and subpleura, and honeycomb lung is rare.

(e) Pulmonary arterial hypertension and pulmonary infarction: Pulmonary arterial hypertension is manifested as widened diameter of main pulmonary artery, the diameter is greater than 29 mm, or exceeds the diameter of adjacent ascending aorta. Pulmonary infarction is manifested as subpleural wedge-shaped opacities with the tip pointing to the hilum.

19.4.4 Diagnostic Key Points

1. Most of cases occur in women of childbearing age, with multiple systems involved. The common clinical manifestations are fever, facial butterfly erythema, skin damage, occult nephritis, joint involvement, anemia, leukopenia or thrombocytopenia, and nervous system involvement.
2. Serological indexes: Antinuclear antibody (ANA), anti-dsDNA antibody, anti-Sm antibody and antiphospholipid antibody are positive.

3. Common imaging manifestations of SLE-involved chest: (1) Pleural lesions, pleural effusion and pericardial effusion; (2) Lung consolidation, infectious pneumonia and lupus pneumonia; (3) Pulmonary arterial hypertension.
4. Uncommon imaging findings of SLE-involved chest: (1) interstitial lung disease, NSIP; (2) Bronchiectasis.

19.4.5 Differential Diagnosis

1. Pulmonary infection: SLE is often complicated with pulmonary infection, which is mostly manifested as patchy consolidation and ground-glass opacities of both lungs. In fact, most of the lung consolidation in SLE patients is the result of infection. It is difficult to differentiate pulmonary infection from lupus pneumonia, which needs comprehensive diagnosis by combining clinical symptoms with laboratory examinations.
2. Idiopathic interstitial pneumonia: UIP and NSIP are the most common pathological types of idiopathic interstitial pneumonia. UIP shows thickened reticular opacities and honeycomb lungs on CT, while ground-glass opacities are rare, mainly distributed under pleura. NSIP shows ground-glass opacities and reticular opacities on CT, mainly in the lower lobe of both lungs and subpleura, usually without honeycomb lung. The incidence of interstitial pneumonia in SLE patients is low, mainly with NSIP.
3. Drug-induced lung injury: It includes diffuse alveolar damage (DAD), nonspecific interstitial pneumonia (NSIP) and organizing pneumonia (OP), which need to be differentiated from lupus pneumonia or alveolar hemorrhage caused by SLE.
4. Rheumatoid arthritis and other connective tissue diseases associated with pneumonia: Compared with other connective tissue diseases such as rheumatoid arthritis, SLE has a lower incidence of interstitial pneumonia and mild interstitial thickening.
5. Goodpasture syndrome: The diffuse alveolar hemorrhage caused by Goodpasture syndrome is more diffuse and extensive than that caused by SLE.

19.4.6 Research Status and Progress

1. Pulmonary arterial hypertension (PAH) is one of the serious complications of SLE patients, and its incidence reports are quite different. Studies have found that systemic lupus erythematosus-related pulmonary arterial hypertension (SLE-PAH) is more common in Asian population than in European and American population. The death risk of SLE-PAH patients is still significantly higher than that of SLE patients without PAH. Compared with SLE patients without PAH, SLE-PAH patients have significantly increased antibodies including antinuclear antibodies, anti-endothelial cell antibodies, antiribonucleoprotein (RNP) antibodies and anticardiolipin antibodies. It has been reported that positive anticardiolipin antibody is an independent predictor of PAH in SLE patients [24].
2. Infection is the main cause of death in SLE patients. If accompanied by infection, SLE often shows similar clinical manifestations and imaging features to disease activity, so it is sometimes difficult to distinguish SLE accompanied by infection from disease activity in clinical practice.

At present, the commonly used scoring systems for evaluating SLE activity include Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group Index 2004 (BILAG-2004), Systemic Lupus Activity Measure (SLAM), Systemic Lupus Activity Index (SLAI), European Consensus Lupus Activity Measure (ECLAM) and Systemic Lupus Activity Questionnaire.

The questionnaire mainly includes anti-dsDNA antibody, complement (C3 and C4), ESR anti-C1q antibody and urine sediment and other serological indexes.

Possible biomarkers for evaluating coinfection in SLE patients include:

(a) C-reactive protein (CRP): SLE patients with infection show CRP increased significantly, while lupus patients with active disease or no infection show CRP increased slightly or not. If the high-sensitivity C-reactive protein (hsCRP) is higher than 6 μg/L, it may be related to infection [25].

Another study found that the ratio of ESR/CRP may be useful to distinguish SLE patients with infection and disease activity. When the ratio is higher than 15, it may be significantly related to disease activity, while when the ratio is lower than 2, it may be related to infection [26].

(b) Procalcitonin (PCT): It has more diagnostic value than CRP in detecting bacterial infection in patients with autoimmune diseases, with sensitivity of 75% and specificity of 90% [27]. If PCT level > 0.38 μg/L in SLE patients, the sensitivity and specificity for the diagnosis of coinfection are 74.5% and 95.5%, respectively. The positive predictive value and negative predictive value for the differentiation of infection and disease activity are 84.2% and 92.1%, respectively [28]. PCT can also effectively monitor the therapeutic effect of antibiotics on infection.

(c) Neutrophil CD64 (nCD64): CD64 is a marker with high specificity and sensitivity in blood bacterial infectious diseases, and it is expected to be one of the most efficient markers to distinguish bacterial infection from SLE activity.

The combination of two or more markers can more accurately predict, diagnose and monitor the severe infection associated with SLE.

19.5 Sjogren Syndrome

Yufeng Xu

19.5.1 Overview

Sjogren syndrome (SS) is a chronic inflammatory autoimmune disease mainly involving exocrine glands, characterized by decreased function of lacrimal and salivary glands. SS is divided into primary SS and secondary SS. The former is not accompanied by other diseases, while the latter is complicated or overlapped with other connective tissue diseases. The most common ones are rheumatoid arthritis and systemic lupus erythematosus. The prevalence rate of primary SS in Chinese population ranges from 0.29% to 0.77%. Most of the patients are female, and the age of onset is from 40 to 50 [29].

Serum immunological examination: Anti-SSA antibody is the most common autoantibody in SS, which is found in about 70% of patients. Anti-SSB antibody is the marker antibody of SS, which is found in about 45% of patients. Patients with primary SS often have positive anti-SSA or anti-SSB antibodies, and many patients have the two antibodies. Anticentromere antibody is found in a small number of patients (about 5%).

Rheumatoid factor is found in 70–80% of patients, and its titer is high, often accompanied by hyperglobulinemia, such as hyperimmunoglobulinemia, which is polyclonal and is found in about 90% of patients [29].

The onset of SS is mostly occult. Besides dry eyes and dry mouth caused by the function decline of lacrimal gland salivary gland, there are also symptoms of multisystem damage caused by the involvement of exocrine glands and other organs outside glands, including skeletal muscles, urogenital organs, skin, lung and gastrointestinal tract. According to statistics, the incidence of significant lung damage is 9–24%, but most patients usually have no respiratory symptoms in the early stage [30]. Mild cases have dry cough, while severe cases have shortness of breath. Airway and pulmonary interstitial tissue are the main involved sites of lung diseases in SS patients. Bronchiolitis is the main airway disease. NSIP is the most common histopathological type of interstitial lung disease, and LIP is significantly correlated with primary SS [31, 32].

19.5.2 Pathological Manifestations

SS is characterized by lymphocytes infiltrating exocrine glands such as salivary gland lacrimal gland. Lymphocyte infiltration also involves trachea, lung, kidney and liver, with nonspecific manifestations such as thrombocytopenia, purpura-like rash, pulmonary interstitial fibrosis and lymphoma. Airway and interstitium are the main affected sites of pulmonary diseases in SS patients, and bronchiolitis is the main airway lesion, including follicular, chronic and occlusive lesions. Follicular bronchiolitis is characterized by the formation of proliferative lymphoid follicles in the bronchioles, resulting in obstruction of bronchioles. Subsequent submucosal and peribronchial fibrosis can also lead to luminal stenosis. Then valve effect may occur, which may cause pneumatocele or bullae.

There are many pathological types of interstitial lung diseases in SS patients, including nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP) and organizing pneumonia (OP). The histological features of NSIP are interstitial inflammation and fibrosis in different proportions. LIP is characterized by diffuse pulmonary interstitial lymphocyte and plasma cell infiltration, as well as lymphocyte infiltration in alveolar space, and follicular bronchiolitis may also occur in patients.

SS-related pulmonary amyloidosis is rare [33], and bronchopulmonary amyloidosis secondary to SS mainly has three manifestations: tracheobronchial amyloidosis, nodular pulmonary amyloidosis and diffuse alveolar septal (interstitial) amyloidosis. It is currently believed that the main causes of amyloidosis may be long-term chronic inflammation or abnormal structure caused by some antigens stimulating immune cells, or excessive normal immunoglobulins beyond the body's clearance ability as well as granules secreted by macrophages being transported to form extracellular deposition, or the disintegration of macrophages in situ deposition to form amyloid plaques.

The most common lung malignant tumor associated with SS is non-Hodgkin's lymphoma, and the most common one is bronchus-associated lymphoid tissue (BALT) lymphoma. LIP may be the prophase lesion of BALT lymphoma [34].

Pulmonary arterial hypertension is rare in SS patients. Unilateral and bilateral pleural effusions are occasionally found in SS patients.

19.5.3 Imaging Manifestations

1. X-ray: The chest radiographic manifestations of SS-ILD usually show fine reticular or nodular opacities, and the lesions of both lower lungs are significant, but the chest radiograph may also be normal.

2. CT.
   (a) Interstitial pneumonia: The typical manifestations of NSIP are ground-glass opacities with or without intralobular linear opacities, and many linear opacities form reticular opacities, which is mainly distributed in the lower lobes of both lungs (Fig. 19.10). The reticular opacities may not occur or be mild. HRCT of LIP shows ground-glass opacities, thickened centrilobular nodules and interlobular septa, reticular opacities, and multiple pneumatoceles with diameter of several millimeters to several centimeters (Fig. 19.11). In some cases, ground-glass opacities are more prominent, while in other cases, cystic changes are the main manifestations. Diffuse pneumatoceles can be the first manifestation of SS, which are mainly distributed in the lower lobe of lung and located around bronchial vessels, and the number may range from 1 to nearly 100 (Fig. 19.12).
   (b) Follicular bronchiolitis: HRCT features include nodules with diameter of 1–12 mm in the center of lobules and around bronchi and thickened bronchial/bronchiolar wall. Follicular bronchiolitis may occur alone or with LIP or NSIP (Fig. 19.10).
   (c) Pulmonary amyloidosis secondary to SS: It shows diverse imaging manifestations. Cases with predominating diffuse interstitial amyloidosis can be manifested as increased lung markings, bronchiectasis, atelectasis and pulmonary interstitial fibrosis, and

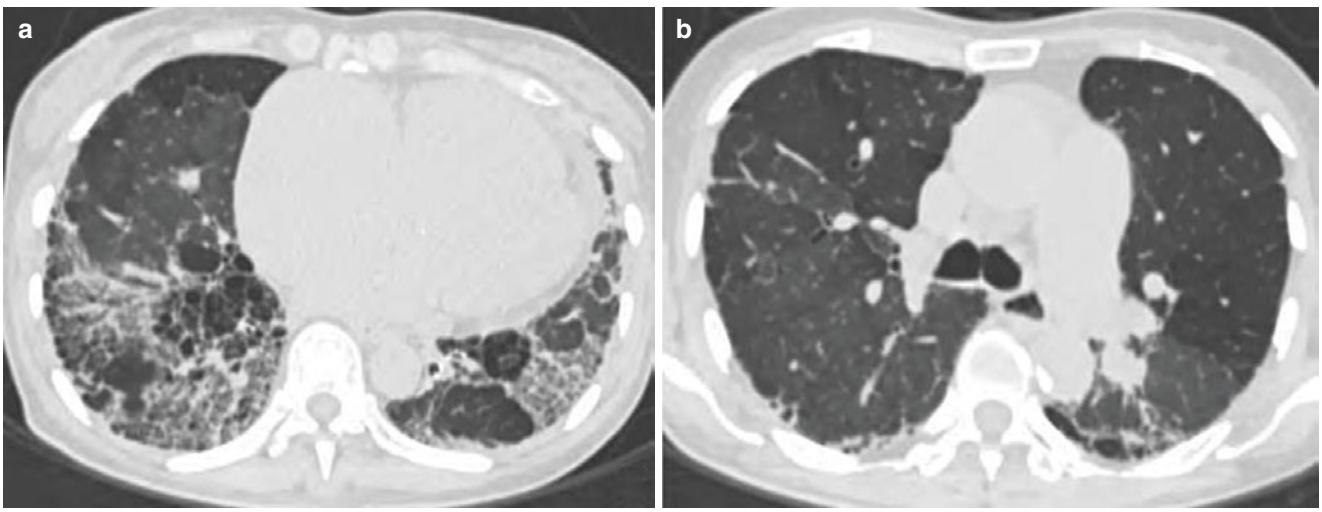

Fig. 19.10 Lung changes in Sjogren syndrome. (**a**) CT lung window showed reticular opacities accompanied by ground-glass opacities in lower lobe of both lungs, suggesting NSIP changes; (**b**) Lesions accompanied by multiple lobular core nodules and mosaic-like changes, suggesting bronchiolitis changes

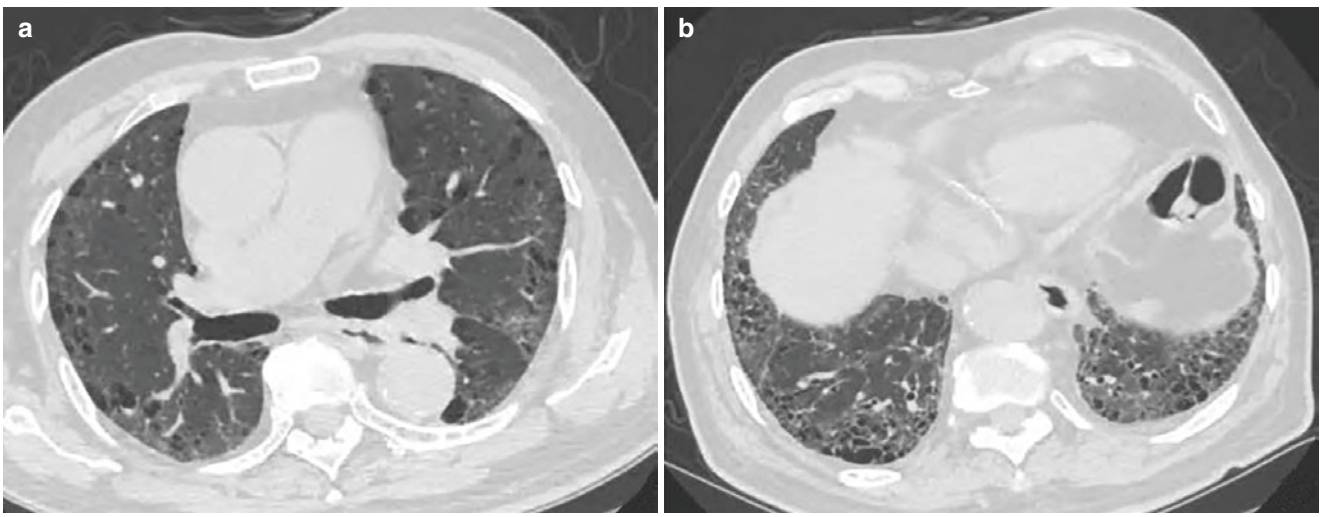

Fig. 19.11 Sjogren syndrome (LIP, I). (**a** and **b**) CT lung window showed multiple cystic cavities of different sizes in both lungs (arrow), with a few patchy ground-glass opacities and reticular opacities (arrow), suggesting LIP changes

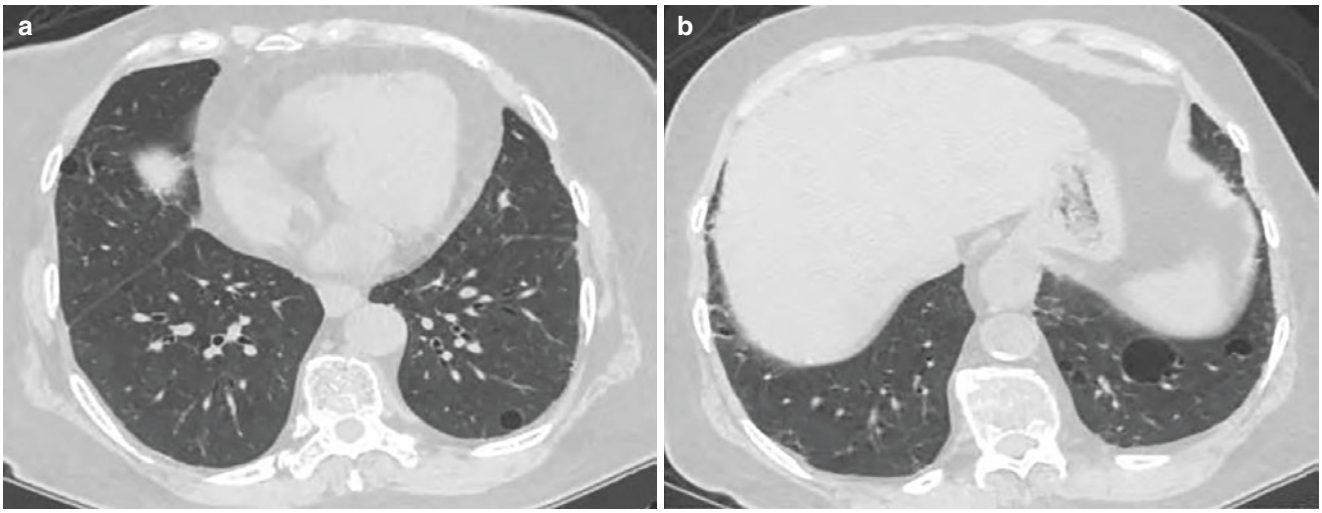

Fig. 19.12 Sjogren syndrome (LIP, II). (**a** and **b**) CT lung window showed multiple cystic cavities of different sizes scattered in both lungs

severe cases can be manifested as honeycomb lung in the later stage. Cases with predominating nodular pulmonary amyloidosis can be manifested as solitary or multiple nodules with clear edges, most of which are located in the peripheral part of the lower lobe of the lung. The nodules progress slowly, and about one-third of them form cavities or calcification, accompanied by hilar lymphadenectasis. Cases with predominating tracheobronchial amyloidosis can be manifested as thickened tracheobronchial wall, uneven inner surface and calcification.

19.5.4 Diagnostic Key Points

1. Dry mouth and dry eyes for more than 3 months, and recurrent or persistent enlargement of parotid gland in adulthood.
2. Serological examination shows positive anti-SSA antibody or anti-SSB antibody, positive rheumatoid factor, and polyclonal hyperimmunoglobulinemia.
3. The results of labial gland biopsy are positive (focal lymphocytic sialadenitis with focal index ≥1).
4. Common chest manifestations of SS: (1) Interstitial lung disease, NSIP is the most common, and LIP is significantly related to primary SS; (2) Airway involvement, bronchiolitis and bronchiectasis.
5. Uncommon chest manifestations of SS: (1) Pulmonary arterial hypertension; (2) Lymphoma; (3) Pleural lesions.

19.5.5 Differential Diagnosis

1. Pulmonary multiple cystic cavities: If SS is manifested as diffuse pneumatoceles, it should be differentiated from pulmonary lymphangioleio-myomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH) and Birt–Hogg–Dube syndrome (BHD). The typical CT manifestations of lung LAM are diffuse and uniformly distributed thin-walled cystic cavities with clear edges in both lungs, which is more diffuse than those of SS. The CT manifestations of PLCH vary in different stages. Multiple nodules and cystic cavities can be found, mainly involving the middle and upper lungs, and subpleural involvement is less common. BHD is a rare autosomal dominant hereditary disease, which is characterized by cutaneous fibrofollicular tumor, pulmonary cystic lesion, spontaneous pneumothorax and renal tumor. CT manifestations of BHD show round vesicles with clear edges of pulmonary parenchyma, mainly involving the lower lung, distributed bilaterally, close to interlobar fissure, visceral pleura, pulmonary artery and pulmonary vein, with different numbers of vesicles ranging from several millimeters to over 2 cm in diameter. Cutaneous fibrofollicular tumor and renal tumor are helpful to differentiate BHD from other cystic lesions.
2. Other diseases complicated with lymphocytic interstitial pneumonia (LIP): In addition to SS, common causes include connective tissue diseases such as idiopathic RA or SLE, infection, especially viral infection (such as HIV infection) or immunodeficiency.
3. Amyloidosis: Many inflammatory, infectious and tumor diseases can be complicated with amyloidosis. Lung parenchyma is the most common part of respiratory system involvement in amyloidosis, which can be manifested as single nodule, multiple nodules or diffuse thickened interstitium, and cystic lesions can also occur. Nodules are distributed in the periphery or subpleura, progressing slowly, and cavities or calcification may occur. Amyloidosis complicated with other diseases has no clinical manifestations of dysfunction of lacrimal gland salivary gland.

19.5.6 Research Status and Progress

Primary Sjogren syndrome (pSS) is a diffuse connective tissue disease which mainly involves exocrine glands and is characterized by significant lymphocyte infiltration. Lymphoma is a common feature of pSS, and the risk of lymphoma in pSS patients is 16–44 times higher than that in normal people [35]. The common lymphoma types are mucosa-associated lymphoid tissue (MALT) lymphoma, diffuse large B cell lymphoma (DLBCL), T-cell lymphoma and Hodgkin's lymphoma [36]. Pulmonary MALT lymphoma is manifested as consolidation, nodules and ground-glass opacities. Consolidation is the main manifestation and the lesions are characterized by distribution under pleura or along bronchovascular bundles. The pathological basis may be as follows: Tumor cells infiltrate and grow along the interstitium and pleura surrounding bronchovascular bundle, forming interstitial changes such as thickened interlobular septa and thickened bronchovascular bundle, further infiltrating alveolar wall and filling alveolar space.

19.6 Mixed Connective Tissue Disease

Yufeng Xu

19.6.1 Overview

Mixed connective tissue disease (MCTD) is a kind of connective tissue disease with the clinical characteristics of SSc, RA, SLE, PM/DM and other diseases, which is not satisfied with the classification criteria of any of the above diseases, and is accompanied by positive results of high-titer antinuclear antibody (ANA) and anti-U1 ribonucleoprotein (RNP) antibody (also called anti-nRNP antibody) in serology. Mixed connective tissue disease was first proposed by Sharp in 1972. It was originally defined as a connective tissue disease, characterized by high-titer anti-U1RNP antibody and overlapping syndrome with specific clinical features of complication with SLE, SSc and PM [37, 38].

As the disease progresses, lesions in some patients develop into certain diffuse connective tissue diseases, such as SSc, SLE, PM/DM, RA. The incidence rate of mixed connective tissue disease is unknown and is estimated to be higher than that of polymyositis, lower than that of SLE, and similar to that of SSc. The incidence rate of female is significantly higher than that of male, and the average age of onset is 37 [37].

The early clinical features of mixed connective tissue disease are nonspecific, which may include general malaise, arthralgia, myalgia and low fever. Mixed connective tissue disease can involve almost any organ system. Pulmonary involvement is very common in patients with mixed connective tissue disease, and there are many possible lung problems, including pleural lesions, pulmonary arterial hypertension and interstitial lung diseases [39, 40]. Early symptoms of pulmonary involvement include dry cough, dyspnea and pleurisy chest pain. Pulmonary arterial hypertension is the most serious complication of mixed connective tissue disease.

19.6.2 Pathological Manifestations

Chest involvement is common in mixed connective tissue disease, including pleural lesions, interstitial pneumonia, pulmonary hemorrhage, diffuse alveolar damage and airway lesions. These findings are consistent with other manifestations of mixed connective tissue disease, which is also common in SSc, SLE and PM/DM patients. NSIP is the most common in interstitial lung disease, followed by UIP.

Pulmonary arterial hypertension is the most serious complication and the main cause of death in patients with mixed connective tissue disease, and its incidence rate is generally 20–25% [41, 42]. The pathological changes of pulmonary arterial hypertension are mild intima hyperplasia and media hypertrophy of pulmonary arterioles.

19.6.3 Imaging Manifestations

1. X-ray.
   (a) Interstitial lung disease: In the early stage, there was no obvious X-ray change or the manifestations are ground-glass opacities at the base of both lungs, then nodular opacities and reticular stripe-like opacities occur, and the manifestations are honeycomb opacities in the later stage. Due to its low diagnostic sensitivity, X-ray examination has been gradually replaced by HRCT.
   (b) Pleural effusion: About 10% of patients may show pleural effusion or thickened pleura.
2. CT.
   (a) Interstitial lung disease: HRCT is the first choice for diagnosis of interstitial lung disease, which is characterized by reticular opacities, ground-glass opacities, traction bronchiectasis, thickened interlobular septa, air cavity consolidation, etc. (Fig. 19.13).HRCT findings of mixed connective tissue disease include SSc, SLE and PM/DM.

      Pulmonary arterial hypertension: Chest radiograph or CT can show pulmonary artery dilatation, and pulmonary arterial hypertension can be accompanied by pulmonary interstitial disease or the only thoracic manifestation of mixed connective tissue disease.

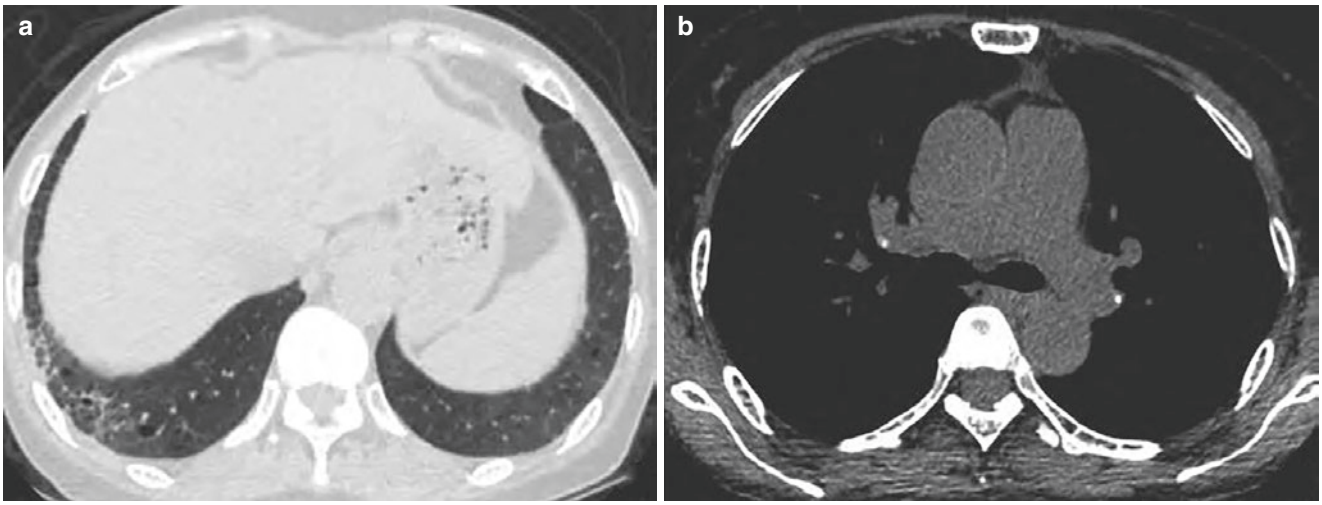

Fig. 19.13 Chest changes in mixed connective tissue disease. (**a**) CT lung window showed reticular opacities of right lower lobe accompanied by a small amount of ground-glass opacities; (**b**) The mediastinal window showed slightly widened main pulmonary artery

19.6.4 Diagnostic Key Points

1. The disease may be manifested as the clinical symptoms of various connective tissue diseases (SLE, SSc, PM/DM or RA). However, multiple clinical manifestations of mixed connective tissue disease do not occur at the same time, overlapping features may occur one after another, and different patients may have different manifestations. The common clinical manifestations related to anti-U1RNP antibody in the early stage are swelling of both hands, arthritis, Raynaud's phenomenon, inflammatory myopathy and sclerosis of fingertips.
2. Antinuclear antibody (ANA) and anti-U1RNP antibody are positive with high titer, while anti-Sm antibody is negative.
3. Common chest manifestations: (1) Interstitial lung disease, NSIP; (2) Pulmonary arterial hypertension; (3) Pleural effusion.

19.6.5 Differential Diagnosis

Mixed connective tissue disease is mainly differentiated from other connective tissue diseases.

1. SLE: Pleural effusion and thickened pleura are the most common. Lung consolidation, ground-glass opacities and interstitial lung disease are rare.
2. SSc: Interstitial lung disease is the most common, and pulmonary arterial hypertension is common.
3. PM/DM: NSIP is common, and organizing pneumonia is common.
4. RA: Interstitial pneumonia UIP and NSIP are common; bronchiolitis and bronchiectasis are common.

19.7 Relapsing Polychondritis

Yufeng Xu

19.7.1 Overview

Relapsing polychondritis (RP) is a recurrent degenerative inflammation of cartilaginous tissue, which is manifested as the involvement of organs such as ears, nose, larynx, trachea, eyes, joints, heart valves and connective tissues such as blood vessels. RP is a rare systemic disease, which mainly involves cartilage and proteoglycan-rich connective tissue. At present, the etiology is unknown, but in-vivo and in-vitro experiments have confirmed that RP is an autoimmune disease stimulated by multiple factors on the basis of unique genetic background and mediated by cellular immunity and humoral immunity. Cartilage matrix shows antigenicity due to trauma, inflammation and other factors, which leads to the immune response of the body to local cartilage or tissues with common matrix components, such as uvea, vitreous body, heart valve, tracheal submucosal basement membrane, joint synovium, glomerulus and renal tubular basement membrane [43, 44].

The incidence of RP has no gender tendency, and is more common in middle-aged and elderly people. In the initial stage, the disease shows acute inflammation, which improves after several weeks to several months, and then shows chronic recurrent attack, which lasts for several years. RP usually has occult onset, but may show acute onset or sudden aggravation. Symptoms may include fever, local pain, fatigue, weight loss and lack of appetite during the active stage. Ear involvement is the most common feature, and the lesions are mostly limited to the cartilage of auricle, includ-

ing helix and tragus, sometimes invading the external auditory canal, which is often symmetrically involved, but the earlobe is not involved. At the initial stage, the auricle may be red, swollen, hot, painful with erythema nodules, which often subside spontaneously in 5–10 days. Repeated attacks may lead to auricle collapse or deformity as well as conductive deafness caused by atrophy and stenosis of external auditory canal. The inner ear can be involved in the later stage, showing auditory or vestibular dysfunction. Lesions involving labyrinth can lead to rotational dizziness, nystagmus, ataxia, nausea and vomiting. Other systemic systems, including costal cartilage, eyes, nose, airway, heart, vascular system, skin, joints, kidney and nervous system, can be involved with local symptoms. In addition, nonspecific systemic symptoms, such as fatigue, malaise and fever, may also occur.

About half of the patients have laryngeal, tracheal and bronchial cartilage involved, and different clinical manifestations may occur according to the degree and scope of airway involvement, including hoarseness, irritating cough, dyspnea and inspiratory wheezing. Thyroid cartilage, cricoid cartilage and tracheal cartilage tenderness may occur in the early stage of laryngeal and tracheal inflammation. Inflammation of larynx and epiglottis cartilage can lead to collapse of upper respiratory tract, thereby resulting in asphyxia. Focal or diffuse airway stenosis caused by inflammation, edema and scar formation also occurs in the bronchus at the later stage of the disease [45].

19.7.2 Pathological Manifestations

In the early stage, most cartilage tissues show nonspecific acute inflammatory changes, and polymorphonuclear inflammatory cell infiltration at the junction of cartilage and perichondrium, mainly neutrophils, accompanied by macrophages and plasma cells infiltration in different proportions. With the further development of RP, the inflammatory scope expands, granulation tissue invades cartilage, and chondrocytes and matrix are destroyed. In the later stage of the disease, chondrocytes undergo apoptosis, necrosis and atrophy after repeated inflammation and destruction, and finally calcified. The organized fibrous granulation tissue gradually replaces the original structure to form scars, which shrink and pull, and finally lead to collapse and deformation of tissues or organs.

The pathological process of RP airway involvement varies from mild inflammation to granulation tissue and scar, and generally includes three stages: Early inflammatory swelling leads to narrow airway, middle stage shows bronchial injury and tracheal cartilage collapse, and in the later stage, airway fibrous scar occurs, causing narrower airway. The lesions may be localized or involve the entire upper airway [46].

19.7.3 Imaging Manifestations

Laryngeal and/or tracheal chondritis is one of the important criteria for diagnosing RP. At present, imaging examination is the main examination method for evaluating airway chondritis.

1. X-ray: Chest radiograph can show stenosis and calcification of airway or trachea, but X-ray examination has no specificity and diagnostic value for RP, so chest CT examination is recommended for patients with suspected RP. Calcification of auricles or other cartilage can sometimes be found on chest radiographs, but it is not a specific manifestation of RP.
2. CT: RP mostly involves the central airway, rarely with the middle and small airway involvement or the full length of respiratory tract involvement. Thyroid cartilage, cricoid cartilage, costal cartilage, anterior wall and lateral wall of trachea can be involved, while posterior wall and membrane of trachea are hardly involved due to lack of cartilage components.

On CT, laryngeal chondritis shows concentric subglottic stenosis, which can continuously involve trachea and bronchi, manifested as uniform thickened tracheal and bronchial walls. On CT, thickened tracheal wall except posterior wall of trachea is a specific manifestation of RP (Fig. 19.14). As the disease progresses, thickened tracheal wall, calcification of cartilage and scar formation will occur in the later stage, resulting in stenosis or collapse of trachea (Fig. 19.15).

The destruction of bronchial cartilage in lung segment and lobe can lead to airway softening, and then collapse of bronchi in lung segment and lobe, which leads to air retention in lung segment and lobe. More than half of patients with abnormal respiratory function show normal routine inspiratory CT scan, while expiratory CT can show functional airway abnormality. Expiratory CT scan is recommended for RP patients [47].

19.7.4 Diagnostic Key Points

1. According to McAdam's diagnostic criteria in 1975, there are three or more of the following clinical features: Bilateral auricular chondritis, noninvasive polyarthritis, nasal chondritis, ophthalmia including conjunctivitis, keratitis, scleritis, superficial scleritis and uveitis, laryngeal and/or tracheal chondritis, cochlear and/or vestibular

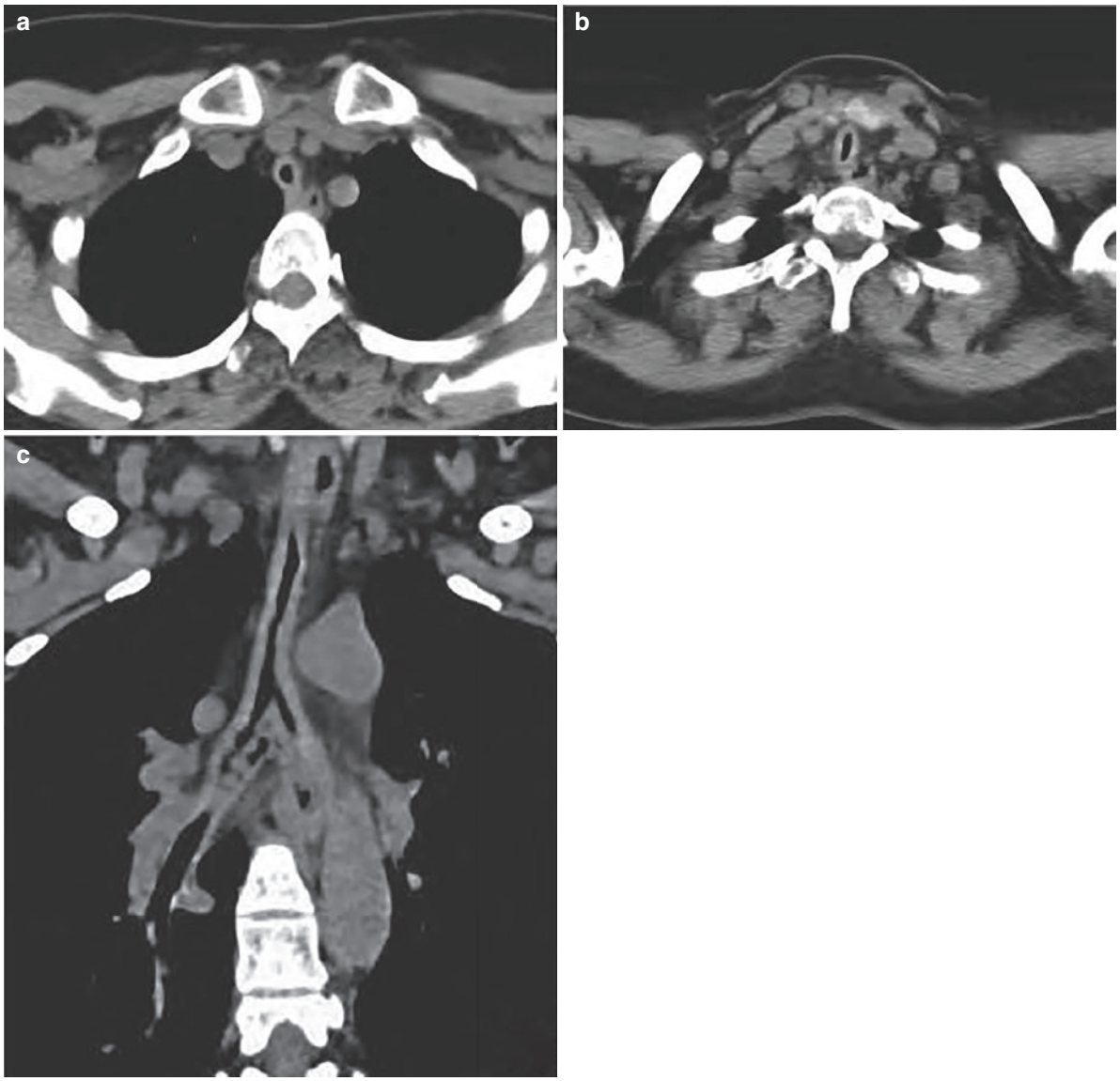

Fig. 19.14 Recurrent polychondritis (I). (**a** and **b**) CT lung window showed thickened anterior and lateral walls of trachea and significant stenosis of lumen; (**c**) Oblique coronal multiplanar reconstruction (MPR) showed long-range involvement of trachea and bronchus

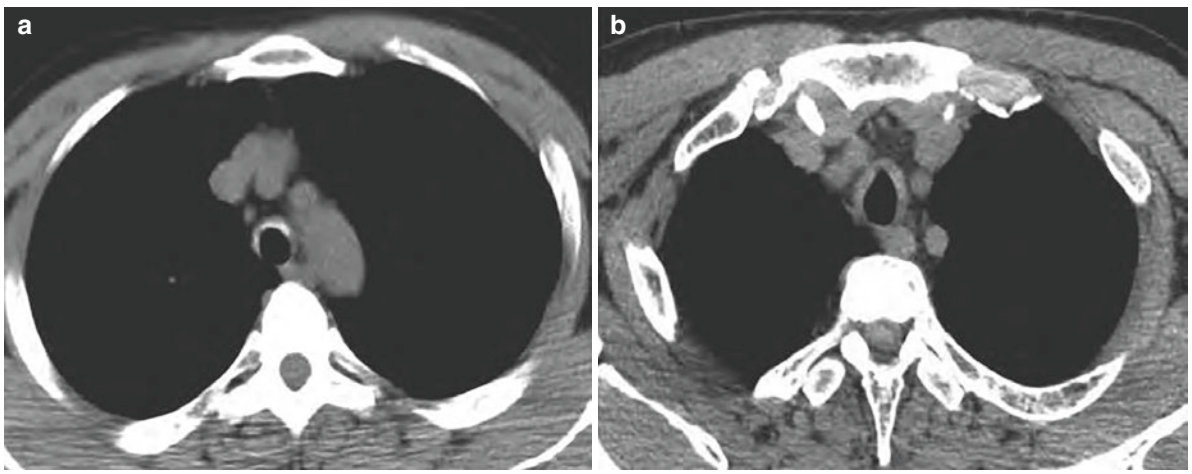

Fig. 19.15 Recurrent polychondritis (II). A. CT mediastinal window showed thickened anterior and lateral walls of trachea and significant stenosis of lumen; B. After 14 months, re-examination showed calcification in the anterior and lateral walls of the trachea

dysfunction (manifested as hearing loss, tinnitus and dizziness).
2. Histopathological findings of ear cartilage biopsy in the active stage of disease are of diagnostic significance.
3. Typical imaging manifestations of chest involvement: (1) thickening and density increase of airway wall involved in cartilage, and stenosis of tracheal or bronchial lumen; (2) Softening and collapse of tracheal wall and air retention during expiratory scanning.

19.7.5 Differential Diagnosis

1. Differential diagnosis of diffuse airway stenosis: RP, amyloidosis of the trachea and tracheobron-cheopathia osteochondro-plastica (TO) can cause diffuse thickening, calcification and stenosis of tracheobronchial wall. Besides trachea and bronchus, cartilage in other parts of RP can be involved, such as laryngeal cartilage and thyroid cartilage. Amyloidosis may involve other organs such as liver and kidney, and amyloidosis may be accompanied by lung changes, showing multiple peripheral subpleural nodules in both lungs, 50% of which may be accompanied by calcification. Amyloid is deposited in small airways and pulmonary interstitium, which can be manifested as reticular or honeycomb interstitial lung disease changes. TO is manifested as multiple calcified nodules protruding into the lumen in the anterior and lateral walls of the trachea, while the membranous part of the posterior part of the trachea is not involved. Serious lesions can cause significantly thickened trachea and stenosis of the lumen.
2. Granulomatosis with polyangiitis (GPA): Subglottic trachea, main bronchi and segmental/subsegmental bronchi can be involved, manifested as smooth annular or irregular thickened wall, with cartilage and membrane involved, accompanied by tracheal luminal stenosis. RP is characterized by tracheal cartilage involvement, often accompanied by other cartilage involvement, such as ear, nose, throat, peripheral joints and so on. In addition, positive antineutrophil cytoplasmic antibody (ANCA) is the characteristic of GPA.
3. Rhinosclerosis: It is a chronic granulomatous disease caused by Bacterium rhinoscleromatis, which often occurs in nose first, and then develops to lips, pharynx, trachea, bronchi and sinuses. Tracheal and bronchial involvement is characterized by nodular malformation of mucosa, or severe annular thickened wall with significant luminal stenosis. Histopathological examination and culture can confirm the diagnosis.

19.7.6 Research Status and Progress

1. ^{99m}Tc-MDP bone imaging: It can clearly reflect the bone metabolism of RP, and can be used to show the cartilage lesions in costal cartilage and auricle, but cannot be used to observe the morphological changes of cartilage.
2. ^{18}F-FDG PET/CT imaging: Inflammatory lesions usually show high uptake of ^{18}F-FDG, and ^{18}F-FDG PET/CT can be used to diagnose asymptomatic bronchitis and chondritis for early diagnosis, and to evaluate the scope and activity of RP lesions [48].

19.8 Ankylosing Spondylitis

Yufeng Xu

19.8.1 Overview

Ankylosing spondylitis (AS) is a chronic inflammatory disease, which mainly invades sacroiliac joint, spinous process, paravertebral soft tissue and peripheral joints, and may be accompanied by extrarticular manifestations. In severe cases, spinal deformity and ankylosis may occur. The prevalence of AS varies from one country to another, 0.05–0.2% in Japan and 0.3% in China. The ratio of males to females is (2–3): 1. Female patients have slow onset and mild symptoms. The age of onset is usually 13–31, and the peak age is 20–30 [49].

Laboratory results of AS are usually nonspecific, and patients with active disease may have increased acute reaction including ESR and CRP. HLA-B27 is positive in most AS patients. AS is a type of spondyloarthritis (SPA). Spondyloarthritis is a group of interrelated diseases with common clinical features, related to HLA-B27, familial aggregation, involving the central axis and joints mainly of lower limbs, showing attachment point inflammation and some characteristic extra-articular manifestations. Such diseases include AS, reactive arthritis (ReA), psoriatic arthritis (PsA), inflammatory bowel disease-associated arthritis, undifferentiated spinal arthritis and juvenile spinal arthritis, among which AS is often regarded as the prototype of this group of diseases.

The onset of this disease is occult, and most patients gradually have back pain or sacroiliac pain, mainly manifested as inflammatory back pain, characterized by night pain, significant morning stiffness and relief after activities. The systemic manifestations of this disease are mild, and a few severe cases have fever, fatigue, emaciation, anemia or other organ involvement. Unilateral uveitis is the most

common extrarticular complication of AS, which occurs in 25–40% of patients. In 1941, Dunham reported pulmonary involvement of AS for the first time. The incidence of pulmonary involvement of AS varies from 1.5% to 40%, which may be related to different detection methods. Its main manifestations include fibrosis, cavitation and interstitial lung diseases in the upper lobe of the lung [50, 51]. According to the early literature, the fibrosis of upper lobe of lung is the main lung lesion, which mostly occurred in adult males, and the ratio of male patients to female patients is about 50:1. The onset is often occult, and patients with small lesion scope have no obvious clinical symptoms. If fibrosis is severe or complicated with infection, patients may have cough, expectoration, dyspnea and other symptoms. AS can involve unilateral or bilateral lungs, and most of them are unilateral or asymmetric lesions in the early stage, which progress slowly, and most cases eventually develop into bilateral upper lung lesions [52]. The pathogenesis of AS complicated with upper pulmonary fibrosis is unclear, and the reason may be related to the decreased ventilation in upper lobe of lung caused by the decrease of chest wall mobility or recurrent pulmonary inflammation. With the popularization of CT, more and more studies have found that the lung manifestations of AS patients are similar to those of other connective tissue diseases [53, 54]. According to a systematic review published in 2012, 61% of AS patients show abnormal chest, 33% patients show nonspecific interstitial changes, 6.9% patients have upper lung fibrosis, 18.1% patients have emphysema, 10.8% patients have bronchiectasis and 11.2% patients show ground-glass opacities. The most common abnormalities are thickened pleura (52%), pulmonary parenchymal fibrous stripe-like opacities (45%) and thickened interlobular septa (30%) [55].

19.8.2 Pathological Manifestations

AS mainly involves synovial joints, which is similar to rheumatoid arthritis, but the inflammatory process of AS is more dispersed and less severe than rheumatoid arthritis, generally without significant pannus formation locally. Connective tissue hyperplasia can be found locally in the involved joints, which may be accompanied by cartilage ossification and subchondral osteosclerosis, resulting in joint ankylosis. Sacroiliac joint and spine are the most frequently involved sites of AS. Joint ankylosis can occur if thoracic costal joints and thoracic vertebrae are involved, and sternal handle or sternoclavicular joint of anterior chest wall can also be involved, resulting in limited activity of thorax. Limited activity of thorax is one of the factors of lung changes in AS. The pathological features of pulmonary involvement in AS are fibrosis of upper lobe of the lung and bullae. Nonspecific pathological changes such as thickened interlobular septa, bronchial or bronchiolar inflammation and alveolar inflammation can often be found around the lower lobe of both lungs.

19.8.3 Imaging Manifestations

1. X-ray.
   (a) Pulmonary apex fibrosis: It may be unilateral and asymmetric lesions in the early stage, and gradually develop into bilateral lesions in the later stage. The lesions are manifested as thickened pleura at the apex of the lung, multiple nodular or patchy blurred opacities at the apex of the lung, which then fuse into agglomerate opacities, accompanied by cavities (Fig. 19.16a), and finally develop into fibrosis. In the advanced stage, severe fibrosis can lead to bronchiectasis and upward shift of hilar structure in the upper lung (Fig. 19.16b).
   (b) Nonspecific interstitial changes: Mostly manifested as reticular nodules in both lower lungs, with the sensitivity of chest radiograph significantly lower than that of HRCT.
   (c) Other changes: Osteosclerosis of anterior horn of thoracic vertebra ("shiny-corner" sign), "square" vertebra and vertebral fusion ("bamboo" vertebra).
2. CT.
   (a) Pulmonary apex fibrosis: Fibrous stripe-like opacities and thickened pleura in upper lobe of lung are accompanied by cavity, emphysema, bullae and bronchiectasis. Spontaneous pneumothorax may occur in a few patients.
   (b) Nonspecific interstitial changes: Mainly distributed in the peripheral part of the lower lobe of both lungs, which can be manifested as thickened interlobular septa, subpleural curvilinear shadow, ground-glass opacities and bronchiectasis.

19.8.4 Diagnostic Key Points

1. The most common and characteristic early complaints are morning stiffness and pain in the lower back.
2. X-ray radiographs show sacroiliac arthritis and MRI shows active inflammation of sacroiliac joint.
3. Serological HLA-B27 is positive, and rheumatoid factors are mostly negative.
4. The most common manifestations of AS chest involvement are: (1) Nonspecific interstitial changes, thickened interlobular septa, subpleural curvilinear shadow, etc.; (2) Fibrosis of both lung apexes, which may be accompanied by emphysema, bullae and cavity; (3) Changes of tho-

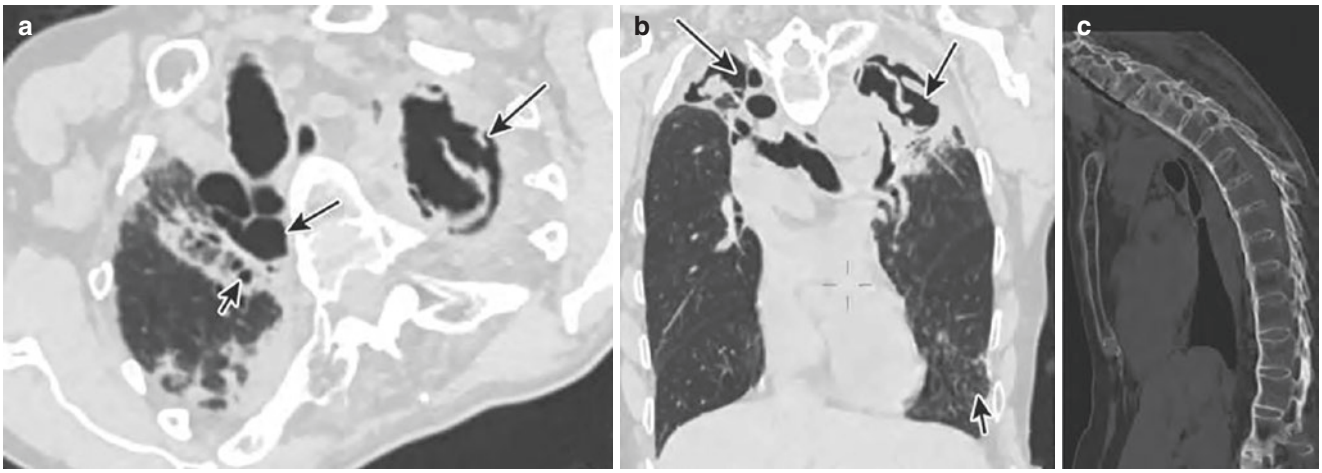

Fig. 19.16 Pulmonary changes in ankylosing spondylitis. (**a** and **b**) CT lung window showed fibrosis, multiple cavities (long arrow) and bronchiectasis (short arrow) in upper lobe of both lungs; (**b**) Pulmonary fibrosis on both upper lungs and upward shift of hilar structure; scattered pulmonary interstitial changes in lower lobe (arrow); (**c**) Sagittal reconstruction of thoracic vertebrae, calcification of anterior longitudinal ligament of thoracic vertebrae

racic vertebrae, "shiny-corner" sign, "square" vertebrae and "bamboo" vertebrae.

19.8.5 Differential Diagnosis

Pulmonary tuberculosis: Secondary pulmonary tuberculosis can be manifested as bilateral upper pulmonary fibrosis, sometimes accompanied by cavitation or calcification, which is similar to the imaging manifestations of pulmonary apex fibrosis caused by AS. Medical history and etiological examination are helpful to distinguish the two.

1. Silicosis: Simple silicosis is manifested as multiple small nodules mainly involving the upper lobe of the lung. Complex silicosis is manifested as multiple small nodules fusing into large lesions, showing progressive mass fibrosis, which usually occurs in the middle and upper lungs and gradually migrates to the hilum, sometimes accompanied by emphysema and often accompanied by eggshell calcification of hilum and mediastinal lymph nodes.

19.8.6 Research Status and Progress

Spondyloarthritis (SpA), formerly known as seronegative spondyloarthropathy, is a group of chronic inflammatory diseases with specific pathophysiological, clinical, radiological and genetic characteristics. This group of diseases includes AS, reactive arthritis, psoriatic arthritis, inflammatory bowel disease-related arthritis, undifferentiated SpA and juvenile SpA, among which AS is considered as the prototype of SpA. SpA can be divided into two types: axial Spondyloarthritis (axSpA) and peripheral Spondyloarthritis. Axial Spondyloarthritis (axSpA) includes AS and radiologically negative axial Spondyloarthritis (nr-axSpA).

Clinically, for those not meeting the diagnostic criteria of AS, the diagnostic criteria of SpA can be referred to.

19.9 Inflammatory Bowel Disease

Yufeng Xu

19.9.1 Overview

Inflammatory bowel disease (IBD) is a kind of chronic and recurrent intestinal inflammation caused by multiple causes and mediated by abnormal immunity, including ulcerative colitis (UC) and Crohn disease (CD). The worldwide incidence of IBD is increasing year by year. In North America, the incidence of UC is (2.2–19.2)/100,000, and the incidence of CD is (3.1–20.2)/100,000. The incidence of UC in developed countries in Europe is as high as 24/100,000, and the worldwide incidence of UC and CD is as high as 505/100,000 and 322/100,000. According to the epidemiological data in China, the standardized incidence of IBD in Daqing City, Heilongjiang Province is 1.77/100,000, and that in Zhongshan City, Guangdong Province is 3.14/100,000, which is lower than that in European and American countries, but with an increasing trend in recent years [56].

UC occurs most frequently in young adults. According to the statistics in China, the peak age of UC is 20–49, without obvious gender difference. The clinical manifestations are persistent or recurrent diarrhea, mucous pus and bloody stool

with abdominal pain, tenesmus and systemic symptoms of different degrees. The course of disease is mostly over 4–6 weeks. CD occurs most frequently in young people. According to the statistical data in China, the peak age of onset is 18–35, with slightly more male patients than female patients.

Clinical manifestations are diverse, including digestive tract manifestations, systemic manifestations, parenteral manifestations and complications. Digestive tract manifestations mainly include diarrhea and abdominal pain, sometimes with bloody stool. Systemic manifestations mainly include weight loss, fever, lack of appetite, fatigue, anemia, etc. [57].

There is no gold standard for the diagnosis of IBD, and it is mainly analyzed in combination with clinical manifestations, laboratory examinations, imaging examinations, endoscopic examinations and histopathological manifestations. Colonoscopy combined with mucosal biopsy is the main basis for the diagnosis of IBD. Colonoscopy shows UC lesions mostly starting from rectum, showing continuous and diffuse distribution. The endoscopic features of mild inflammatory reaction are erythema and mucosal congestion, while severe inflammatory reaction is manifested as spontaneous mucosal hemorrhage and ulcer. Recurrent attacks and long course of mucosal atrophy can lead to shape disappearance of haustra, intestinal stenosis and inflammatory polyps. Endoscopic manifestations of CD lesions are mostly discontinuous changes, and the lesion mucosa can be completely normal. Early CD endoscopy shows aphthous ulcer. With the progress of the disease, the ulcer can gradually increase and deepen in size, and fuse with each other to form longitudinal ulcer. Other common endoscopic manifestations are "cobblestone" sign, thickened intestinal wall with different degrees of stenosis, cluster polyposis hyperplasia. and so on.

Currently, IBD is considered as a systemic disease, which involves many parenteral systems at the same time, such as osteoarticular system, hepatobiliary system, skin mucosa and respiratory system, etc. More than one-third of IBD patients have parenteral manifestations, among which iritis, arthritis, skin damage and sclerosing cholangitis have been widely recognized, while pulmonary involvement is often overlooked [58]. In 1976, Kraft et al. first reported 6 cases of UC patients with unexplained chronic bronchitis, bronchiectasis and chronic obstructive pulmonary disease. Since then, there have been more reports worldwide about IBD involving lungs [59–61]. Some studies suggest that 40–60% of IBD patients have clinical or subclinical lung lesions to some extent, and pulmonary involvement is more common in UC than CD [61]. Pulmonary involvement can occur at any stage of IBD without any symptoms or signs. Therefore, IBD-related lung diseases can be occult without significant respiratory symptoms, or have nonspecific respiratory symptoms such as cough, expectoration or shortness of breath. IBD pulmonary involvement may include the involvement of airway, pulmonary parenchyma, pulmonary vessels and pleura, among which airway involvement is the most common.

19.9.2 Pathological Manifestations

Pulmonary abnormalities in IBD patients are mainly divided into two types, namely IBD-related lung disease and opportunistic infection. Currently, the mechanism of lung injury in IBD patients is not clear, and the possible pathogenesis includes [58]: (1) Both lung and gastrointestinal tract originate from foregut in embryonic period and have similar immunological characteristics; (2) Intestinal lymphocytes migrate to the lungs through the circulatory system; (3) Immune complexes caused by intestinal inflammation are deposited in respiratory system. The lung injury of IBD patients is not only related to IBD disease itself, but also may be induced by long-term use of IBD therapeutic drugs, such as 5-aminosalicylic acid (mesalazine, sulfasalazine), azathioprine, etc., all of which lead to adverse reactions causing lung injury.

Although IBD has a wide range of onset ages, respiratory symptoms are more likely to occur in patients over 40 years old, and most of them are female UC patients. Airway is the most often involved site of IBD, which can be involved at any level. Many diseases can occur, including bronchiectasis, tracheal stenosis, chronic bronchitis, asthma and chronic obstructive pulmonary disease, among which bronchiectasis is the most common pathological change. IBD is less likely to involve small airways, and small airway damage usually occurs in younger IBD patients and in the earlier stage. Bronchiolitis is the most common pathological changes, and cellular bronchiolitis is the most common type. Other rare pathological changes include follicular bronchiolitis, bronchiolitis obliterans and diffuse panbronchiolitis.

The incidence of IBD involving lung parenchyma is low, and its pathological manifestations are diverse, including organizing pneumonia, interstitial pneumonia and eosinophilic pneumonia. IBD is often accompanied by lung infection or drug-induced lung injury.

Pulmonary venous thrombosis (PVT) is the most common pulmonary vascular disease in IBD, and the prevalence of thromboembolic diseases in IBD patients is 3–4 times higher than that in normal people. Pulmonary vasculitis in patients with IBD is rare. Wegener's granulomatosis, Churg–Strauss syndrome and microscopic polyvasculitis and other pulmonary vasculitis changes are reported in IBD patients [62, 63].

Serosal involvement in IBD is manifested as pleural effusion and pericardial effusion.

19.9.3 Imaging Manifestations

1. X-ray.
   (a) Airway lesions: Airway involvement is the most common, with different levels of airway involvement showing different manifestations. Tracheal involvement is manifested as tracheal stenosis. Bronchial involvement is manifested as thickened wall and bronchiectasis.
   (b) Pulmonary parenchymal lesions: Parenchymal involvement includes interstitial pneumonia, which is manifested as reticular opacities in the lower field of both lungs. Organizing pneumonia or eosinophilic pneumonia is manifested as patchy consolidation of both lungs.
2. CT: HRCT is of great value in the diagnosis of asymptomatic IBD-associated lung diseases.
   (a) Airway lesions: Bronchiectasis is the most common imaging manifestation of IBD [63, 64]. Tracheal and bronchial inflammation can also be manifested as concentric wall thickening and luminal stenosis with or without mucus impaction (Fig. 19.17).
   (b) Small airway lesions: Such lesions are rare. Bronchiolitis is mainly manifested as thickened bronchiolar wall, centrilobular nodules, "tree-in-bud" sign, hyperinflation and "mosaic" sign, etc.
   (c) Pulmonary parenchymal lesions: IBD-related pulmonary parenchymal lesions are rare, and organizing pneumonia is the most common type of pulmonary parenchymal lesions, manifested as multiple patchy consolidation or ground-glass opacities distributed under pleura or along bronchovascular bundles, mostly distributed in the middle and lower lungs. Uncommon pulmonary parenchymal lesions are eosinophilic pneumonia and nonspecific interstitial pneumonia (NSIP). Eosinophilic pneumonia is manifested as migratory patchy consolidation or ground-glass opacities, while nonspecific interstitial pneumonia is manifested thickened subpleural interlobular septa, reticular opacities and ground-glass opacities in both lower lobes of the lung. It is worth noting that lung infection and drug-induced lung injury are the more common pulmonary parenchymal lesions in IBD patients.
   (d) Vascular lesions: IBD-related thoracic vascular lesions are rare. Patients with IBD may have chest CT changes of ANCA-related vasculitis, such as Wegener's granulomatosis, Churg–Strauss syndrome and microscopic polyvasculitis, which are manifested as pulmonary nodules with or without cavities, patchy ground-glass opacities and other changes. Because of the high incidence of venous thrombosis in IBD patients, attention should be given to serious complications such as acute pulmonary embolism.
   (e) Serosal lesions: Such lesions are rare, manifested as pleural effusion and pericardial effusion.

19.9.4 Diagnostic Key Points

1. Persistent or recurrent diarrhea, mucous pus and bloody stool with abdominal pain and systemic symptoms of different degrees.
2. Colonoscopy combined with mucosal biopsy is the main basis for the diagnosis of IBD.
3. Common chest manifestations of IBD: Airway changes, bronchiectasis, chronic bronchitis and bronchiolitis.

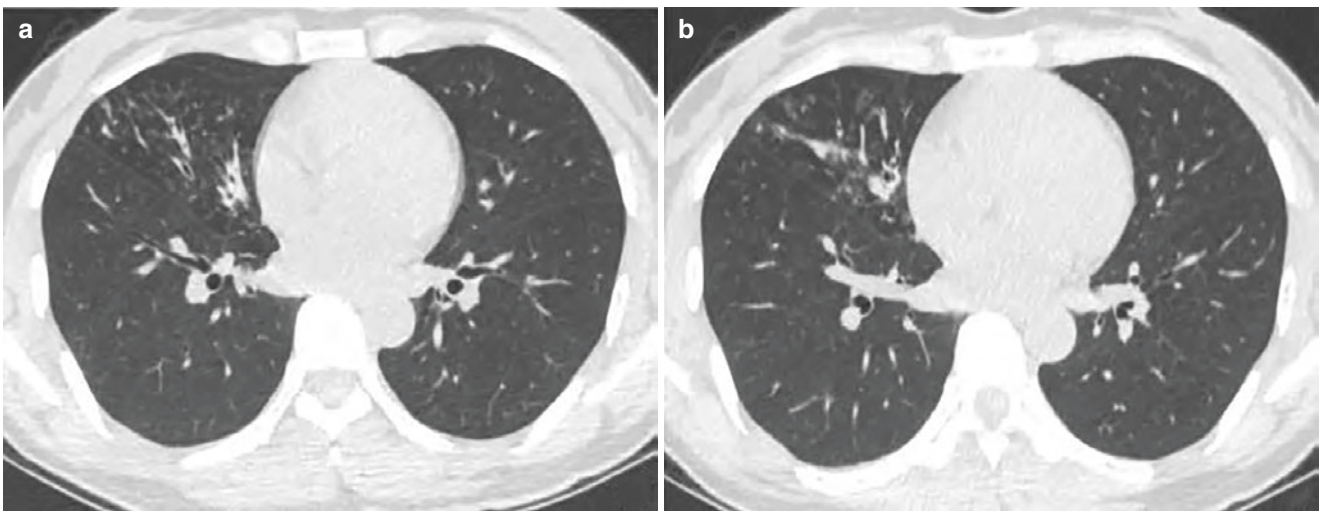

Fig. 19.17 Pulmonary involvement in ulcerative colitis. (**a**) CT lung window showed thickened bronchial wall and dilated lumen in the middle lobe of right lung; (**b**) Mucus impaction may occur in some bronchial lumens

4. Uncommon chest manifestations of IBD: Organizing pneumonia, nonspecific interstitial pneumonia, vasculitis and pleural effusion.

19.9.5 Differential Diagnosis

1. Acute tracheobronchitis: It is common in viral infection, manifested as thickened tracheobronchial wall, and the degree of lesion is generally less severe than airway inflammation caused by IBD.
2. Bronchiectasis: It is the most common manifestation of IBD involving the lungs, which needs to be differentiated from other diseases causing bronchiectasis.
3. Pulmonary infection: IBD is often accompanied by various pulmonary infections, including community-acquired pulmonary infection or opportunistic pulmonary infection. Typical pulmonary infection can be clearly diagnosed, and some pulmonary infections need to be differentiated from organizing pneumonia. Serological and clinical manifestations are of certain value for differentiation.
4. Drug-induced lung injury: Long-term use of IBD drugs may also induce lung injury, such as mesalazine, sulfasalazine and azathioprine. Among drug-induced lung injury, eosinophilic pneumonia is the most common, followed by interstitial pneumonia. Lung injury can be alleviated after drug withdrawal. Clinically, it is sometimes difficult to distinguish whether the lung injury of IBD is induced by drugs or just the extraenteral manifestations of IBD.

19.9.6 Research Status and Progress

The relationship between IBD and lung injury is very complex, and lung injury can occur in any stage of IBD. Currently, there is no special treatment method for lung injury caused by IBD disease. The only solution is to evaluate the lung imaging changes and lung function of IBD patients in time, thus finding lung abnormalities as early as possible, intervening early, avoiding or delaying the progress of lung injury, controlling disease activities, and choosing a correct and reasonable treatment scheme for IBD. Besides, attention should be given to the possible pulmonary complications and secondary pulmonary infections caused by drugs. Abnormal pulmonary function in IBD is not uncommon, mainly manifested as obstructive ventilation dysfunction and decreased diffusion function. Obstructive ventilation dysfunction is usually characterized by the decrease in forced expiratory volume in 1 s, the decrease in forced expiratory volume and maximum expiratory flow, and the increase in functional residual capacity (FRC) and residual volume (RV). The correlation between the pulmonary dysfunction of IBD patients and the inflammatory activity of IBD is still controversial.

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