Vasculitis

20

Ke Wang and Yufeng Xu

20.1 Microscopic Polyangiitis

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20.1.1 Overview

Microscopic polyangiitis (MPA) is a kind of systemic vasculitis, which mainly involves small vessels, including arterioles, capillary arteries, capillaries, capillary venules, and medium-sized arteries. MPA most often invades the kidneys, lungs, and skin. MPA is the most common cause of pulmonary hemorrhage-nephritis syndrome.

The most common clinical manifestation of MPA is rapidly progressive glomerulonephritis (over 90%). Other manifestations include hemoptysis (10–30%), gastrointestinal involvement (such as melena and abdominal pain), peripheral nerve or central nervous system involvement, cutaneous purpura, nodules or livedo reticularis, hypertension, heart failure, pericarditis, arrhythmia, etc.

MPA is a kind of antineutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. The most common ANCA-associated vasculitis is granulomatosis with polyangiitis (GPA) and MPA. MPA is mostly positive for MPO-ANCA, while GPA is mostly positive for PR3-ANCA. However, GPA and MPA overlap in symptoms, signs, and serological manifestations of ANCA. According to the standard definition of Chapel Hill Consensus Conference [1], the difference between MPA and GPA lies in whether granuloma exists in pathological manifestations. If so, it is diagnosed as GPA, and if not, it is diagnosed as MPA. However, due to sampling errors, the diagnosis of granuloma may be missed, so this classification method is not very accurate. Some literatures have proposed to classify diseases according to serological characteristics, such as PR3-ANCA diseases and MPO-ANCA diseases. Studies have shown that the classification according to serological characteristics has more prognostic significance than MPA and GPA classification [2].

20.1.2 Pathological Manifestations

The pathological manifestations of MPA include the involvement of large, medium, and small vessels, as well as arteries and veins. Pulmonary involvement is often manifested as non-capillary inflammation. The common manifestations of renal involvement are mild focal and segmental glomerulonephritis, diffuse necrotizing glomerulonephritis, and crescent glomerulonephritis. The difference between MPA and GPA is that MPA has no granulomatous changes.

20.1.3 Imaging Manifestations

Lung is the common site involved by MPA. The manifestations of MPA involving the lungs are various. Generally speaking, the two common manifestations that have great influence on prognosis are alveolar hemorrhage and pulmonary interstitial lesions. Interestingly, the common manifestations of MPA involving the lungs are different in different countries. Previous textbooks and most European and American literatures emphasized diffuse alveolar hemorrhage in MPA involving the lungs, but in recent years, more Japanese literatures reported that pulmonary interstitial lesions were more common imaging manifestations for Japanese. Furuta et al. have compared the clinical manifestations and prognosis of MPA in Europe and Japan [3]: (1) Compared with Japanese patients, British patients are younger and the proportion of MPO-ANCA positive and serum creatinine increase is lower and (2) the manifestations of organ involvement are different. The most obvious difference is that Japanese patients mostly show interstitial lesions

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or even interstitial fibrosis (37.1% in Japan and 17.0% in Britain), while British patients mainly show alveolar hemorrhage (10.6% in Japan and 20.4% in Britain), and respiratory tract involvement is more common in Japanese patients (52.5% in Japan and 34.7% in Britain).

For Chinese patients, there is still a lack of large-scale multiple center clinical trial. Qu et al. retrospectively counted the chest CT manifestations of 66 MPA patients [4], found that 65.2% of the patients had chest abnormalities, and claimed that diffuse alveolar hemorrhage was more common in the MPA active stage, while interstitial lesions and pulmonary fibrosis were common in the stable stage.

In 2016 and 2019, two reports of multiple center clinical trial were published in Japan [5, 6], which retrospectively and prospectively counted the chest CT manifestations of MPA patients. According to such studies, the chest CT manifestations of MPA patients are shown in Tables 20.1 and 20.2 [5, 6].

Table 20.1 Incidence of interstitial lesions in 144 MPA patients

Interstitial lesion	Number of patients	Type of interstitial lesion	Number of patients
Interstitial lesions occurred	74	Showing UIP manifestation	28
		Showing possible UIP manifestation	17
		Showing no UIP manifestation	29
No interstitial lesions occurred	70		

Table 20.2 Incidence of different chest imaging signs in MPA patients

Imaging signs	Incidence (%)
Pulmonary parenchymal lesion	99
Ground-glass opacity change	62
Reticular change	61
Thickened interlobular septa	61
Consolidation	34
Honeycomb change	34
Thickened bronchovascular bundle	22
Stripe-like opacities	15
Nodules	13
"Halo" sign	1
Airway lesion	99
Bronchiolitis	83
Thickened bronchial wall	66
Bronchiectasis	48
Cystic bronchiectasis	11
Pleural lesion	79
Thickened pleura	51
Pleural effusion	39
Pleural calcification	6
Emphysematous change	56
Emphysema	43
Cystic lesion	20
Others (previous inflammation, lymph node calcification, atelectasis, and mediastinal emphysema)	50

1. Pulmonary interstitial lesions: The most common pulmonary interstitial lesions in MPA patients are usual interstitial pneumonia (UIP), which occurs in about 39% of MPA patients [5]. Typical chest CT manifestations of UIP are triad signs of thickened interlobular septa, "honeycomb" change, and traction bronchiectasis (Fig. 20.1). Lung changes in UIP show gradient distribution, and lesions are mostly distributed in the lower lung and periphery. Typical UIP can show ground-glass opacity change, but it is not the main manifestation.

   Other imaging manifestations that are not typical in UIP are also common in MPA patients, including ground-glass opacity change, thickened bronchial wall, consolidation, and hyperintensities around honeycomb lung. Ground-glass opacity change may indicate that the disease is in active stage [6]. The hyperintensities around honeycomb lung is more common in MPO-ANCA positive patients, which may indicate inflammatory cell infiltration and lymphatic follicles in pathology [7].

   Emphysematous change is another common manifestation, and emphysema or cystic change may occur in about half of the patients. Combined pulmonary fibrosis and emphysema (CPFE) occurs in about 18% of the patients [5]. Whether the occurrence of CPFE in MPA patients indicates worse prognosis is still inconclusive.
2. Diffuse alveolar hemorrhage (DAH): Patients with DAH usually have clinical manifestations of hemoptysis. The most common imaging manifestations are diffuse ground-glass opacity changes in both lungs with or without consolidation (Fig. 20.2). More consolidation indicates more alveolar hemorrhage, and the possibility of blood components and exudation in alveolar space in a short time is relatively high. Multiple ground-glass lobular core solid nodules or ground-glass nodules in both lungs are also manifestations of DAH, and nodules mostly show blurred edges. Thickened interlobular septa and reticular change may occur in the hemorrhage area, and "paving stone" sign may occur, suggesting accumulated pulmonary interstitial fluid and cell infiltration, and granuloma hyperplasia and fibrosis may occur in the later stage. Kida et al. found that the risk of DAH in MAP patients is related to previous airway lesions, but not to previous interstitial lesions [8].
3. Airway lesions: There are few reports of airway lesions in MPA patients, mainly because many airway lesions are secondary to interstitial lesions or alveolar hemorrhage and many manifestations overlap with each other (Fig. 20.3), making it difficult to distinguish. Yamagata et al. used latent class modeling to divide MPA into three categories according to the chest imaging manifestations of patients, one of which is mainly characterized by airway lesions [6]. Thickened airway wall and bronchiolitis are the most common manifestations. The prognosis of such patients is relatively good and the therapeutic effect

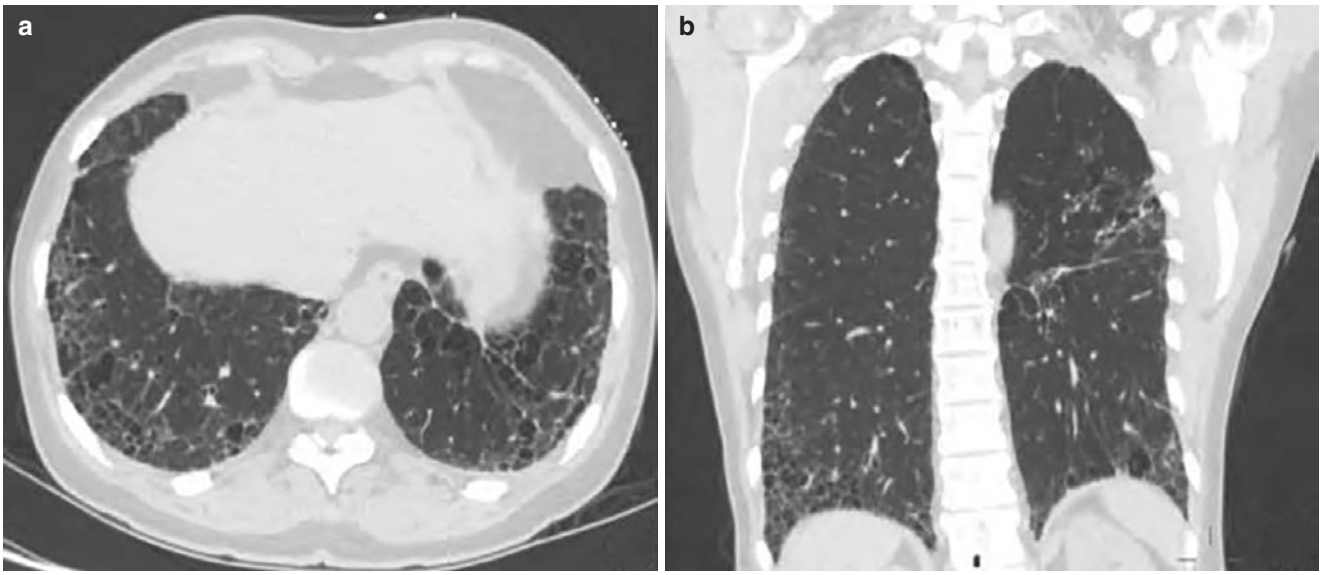

Fig. 20.1 Microscopic polyvasculitis (pulmonary interstitial lesion). (**a**) CT lung window showed thickened subpleural interstitium in lower lobes of both lungs, with "honeycomb" changes and (**b**) coronal images showed that the lesions were mainly in the lower lobes of both lungs, accompanied by traction bronchiectasis, which was consistent with the usual interstitial pneumonia

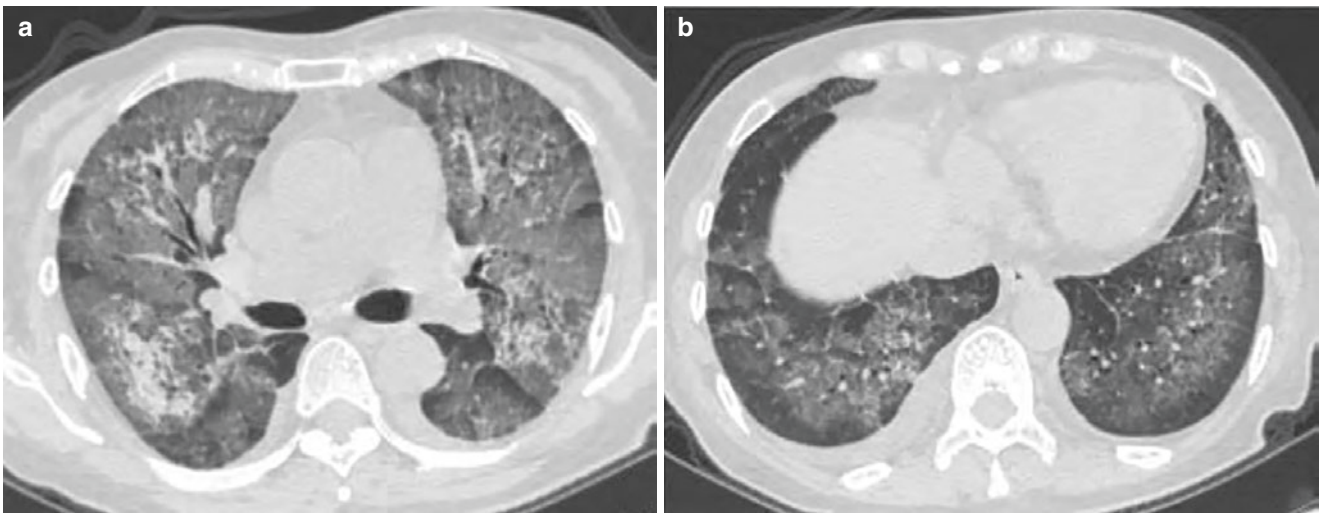

Fig. 20.2 Microscopic polyvasculitis (diffuse alveolar hemorrhage). (**a**, **b**) CT lung window showed multiple ground-glass opacity changes with patchy consolidation in both lungs, especially in the middle and inner zones of both lungs, with less involvement in the outer zone and slightly thickened interlobular septa

is significant, suggesting that this kind of airway lesion may be related to MPA disease activity. In addition, some studies have shown that bronchiectasis is related to the positive anti-MPO antibody [9].

4. Pleural lesions: Pleural thickening, pleural effusion, and pleural calcification are common pleural lesions in MPA which are often complicated with other manifestations. Pleural imaging manifestations have no significant specificity.

20.1.4 Diagnostic Key Points

1. Pulmonary hemorrhage-nephritis syndrome is common in patients with acute progressive glomerulonephritis and alveolar hemorrhage as typical manifestations, and pulmonary involvement alone is rare.
2. Bilateral diffuse ground-glass opacity changes or consolidation of air cavity is most common in the lung.

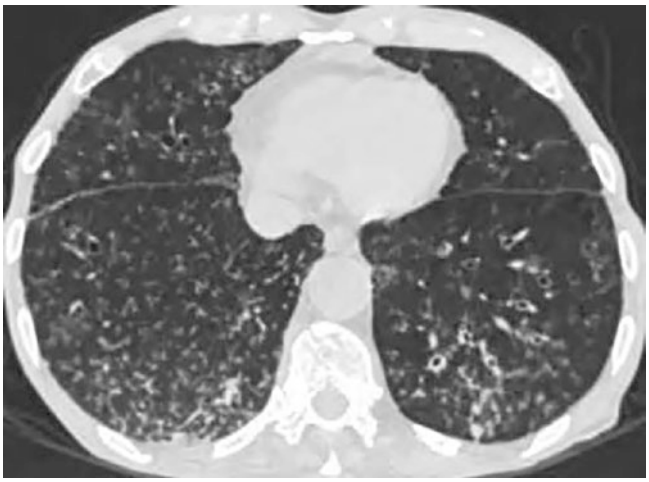

Fig. 20.3 Microscopic polyvasculitis (airway lesion). CT lung window showed multiple centrilobular nodules in both lungs, some of which were solid nodules, some of which were ground-glass opacity nodules, and multiple thickened bronchial walls

20.1.5 Differential Diagnosis

The pulmonary imaging manifestations of MPA are lack of specificity. In addition to the reference of imaging manifestations, clinical manifestations, laboratory examination, and even histological examination may be more important key points for differential diagnosis.

1. Goodpasture syndrome: It is caused by anti-GBM antibody, with crescent glomerulonephritis and pulmonary hemorrhage as the main manifestations, and its diagnosis basis is the direct or indirect detection of anti-GBM antibody. The typical manifestation of the lung is diffuse alveolar hemorrhage, which can eventually lead to interstitial fibrosis if repeated hemorrhage occurs. This disease can be complicated with granulomatosis with polyangiitis and MPA.
2. Granulomatosis with polyangiitis (GPA) is a systemic vasculitis associated with MPA, and both are related to ANCA. GPA is mainly related to PR3-ANCA, while MPA is mainly related to MPO-ANCA. Pathologically, GPA is a necrotizing granulomatous inflammation. However, MPA has no granulomatous inflammation, which mainly affects small blood vessels. In imaging, GPA often involves the airway and the manifestations are mostly nodules and cavities in the lungs, sometimes including interstitial lesions and alveolar hemorrhage, which are less common. However, MPA has a significantly higher risk of interstitial lesions and DAH, and airway lesions and pulmonary nodules are rare.

20.1.6 Research Status and Progress

At present, the imaging studies on MPA involving lung are still mainly focused on the statistics and summary of imaging manifestations. In recent years, two reports of multiple center clinical trial in Japan have suggested that MPA lung manifestations may be more common in pulmonary interstitial lesions [5, 6], while for other Asians, there is no large-scale multiple center clinical trial at present, which may be the future research direction. Currently, the classification of ANCA-related systemic vasculitis is still being gradually studied and updated, so the imaging manifestations corresponding to different serological classifications may be the future research direction. In terms of imaging technology, MPA pulmonary involvement still mainly depends on chest CT and there are few studies on the application of other imaging technologies. Renal involvement has been evaluated by MRI in some studies [10].

20.2 Granulomatosis with Polyangiitis

Ke Wang and Yufeng Xu

20.2.1 Overview

Granulomatosis with polyangiitis (GPA), also known as Wegener's granulomatosis or ANCA-associated granulomatous polyvasculitis, is a necrotizing granulomatous polyvasculitis, with unknown etiology at present. In January 2011, the American College of Rheumatology (ACR), the American Society of Nephrology, and the Council of the European League Against Rheumatism recommended that "Wegener's granulomatosis" be renamed as "granulomatosis with polyangiitis" [11].

Typical clinical manifestations of granulomatosis with polyangiitis include upper airway diseases (rhinitis and paranasal sinusitis), lower respiratory diseases (tracheal or pulmonary lesions), and glomerulonephritis (progressive renal failure). Other systems or organs and manifestations that may be involved include joints (myalgia, joint pain, and arthritis), eyes (conjunctivitis, scleritis, and uveitis), skin (blisters, purpura, and subcutaneous nodules), nervous system (multiple mononeuritis, cranial nerve abnormalities, extraocular myoparalysis, tinnitus, and hearing loss), heart (pericarditis, myocarditis, and conduction system abnormalities), gastrointestinal tract, lower urogenital tract (including prostate or ureter lesions), parotid gland, thyroid gland, liver or breast, etc.

The incidence rate of the disease is similar between male and female patients, and the age range of onset is wide from 8 to 99 years, but the age of 40–50 years is the high incidence age of the disease. The incidence rate of granulomatosis with polyangiitis is low, and the incidence rate abroad is about 5/100,000 [12].

Granulomatosis with polyangiitis is a kind of ANCA-related polyvasculitis. Some patients of granulomatosis with polyangiitis are ANCA negative (such as localized granulomatosis with polyangiitis), but about 85% of the patients of granulomatosis with polyangiitis is ANCA positive. PR3-ANCA is positive in 80–90% of the patients of ANCA positive granulomatosis with polyangiitis, and MPO-ANCA is positive in other patients. ANCA-associated vasculitis also includes microscopic polyvasculitis. There are many overlapped symptoms, signs, and ANCA serological manifestations between granulomatosis with polyangiitis and microscopic polyvasculitis. The main differentiation point is whether granuloma occurs in pathological manifestations. If granuloma occurs, it is granulomatosis with polyangiitis.

20.2.2 Pathological Manifestations

Granulomatosis with polyangiitis involves small arteries, small veins and capillaries, and occasionally large arteries. Its pathological manifestations are characterized by inflammation of vascular wall, mainly invading upper respiratory tract, lower respiratory tract, and kidney. It usually begins with focal granulomatous inflammation of nasal mucosa and lung tissue and gradually progresses to diffuse necrotizing granulomatous inflammation of blood vessels. Clinical manifestations often include rhinitis and paranasal sinusitis, lung lesions, and progressive renal failure.

20.2.3 Imaging Manifestations

1. Nodules and masses: Pulmonary nodules and masses are the most common imaging manifestations of granulomatosis with polyangiitis. Most of them are multiple lesions, often involving both lungs, and the number of lesions is usually less than 10, which can fuse into larger masses. The common shape of nodules or masses is oval in a size of 2–4 cm, with clear or blurred edges (Fig. 20.4). "Halo" sign is a relatively specific manifestation of granulomatosis with polyangiitis. "Halo" sign refers to the ground-glass opacities around the nodule, and its pathological manifestation corresponds to pulmonary parenchymal hemorrhage around the nodule, and its occurrence rate is about 15% (Fig. 20.5). The distribution of nodules has no speciality, which can be beside bronchovascular bundle, subpleural, etc., and the lobular core distribution is rare.

   Cavity formation is another imaging manifestation of granulomatosis with polyangiitis, which can be found in about 50% of the patients. Cavities are more common in nodules or masses larger than 2 cm, mostly being thick-walled cavities, with irregular and rough inner edge and burrs on outer edge. There may be necrotic debris in the cavities, but the gas–liquid plane is rare. If the cavity becomes larger rapidly or there is a gas–liquid plane, it may indicate hemorrhage or complication with infection.
2. Ground-glass opacity foci and consolidation: Such lesions of pulmonary parenchyma often indicate hemorrhage, which may or may not be accompanied by nodules. Its manifestations are various, some of which are wedge-shaped consolidation in the periphery, which may be caused by pulmonary infarction or airway involvement (Figs. 20.6 and 20.7). Some patients show diffuse ground-glass opacity changes, mainly distributed around the hilum of the lung, without subpleural involvement. Some patients might show "paving stone" sign. Cavities may occur in the consolidation, showing "reversed halo" sign. At first, "reversed halo" sign was considered as a specific manifestation of organizing pneumonia, but later studies showed that this sign can be observed in many diseases including granulomatosis with polyangiitis. "Reversed halo" sign in granulomatosis with polyangiitis may indicate local organizing changes after pulmonary parenchymal hemorrhage.
3. Airway lesions: Subglottic trachea, main bronchus, and segmental/subsegmental bronchus can all be involved. Typical tracheal involvement is localized in subglottic trachea, which can involve vocal cords. The airway wall is annular smooth or irregularly thickened, and cartilage and membrane are involved, with tracheal luminal stenosis. Segmental/subsegmental bronchial involvement is characterized by localized or longer segmental involvement, thickened bronchial wall, luminal stenosis, lumen obstruction, and consolidation/atelectasis of distal lung. Distal airway involvement is manifested as thickened bronchovascular bundle and bronchiectasis.
4. Pleural changes: Pleural thickening may occur, manifested as pleural effusion, but pneumothorax is rare.
5. Mediastinal changes: Lymphadenectasis may occur in 15% of the patients. It is often accompanied by pulmonary parenchymal lesions, which indicates infection or malignant tumor.

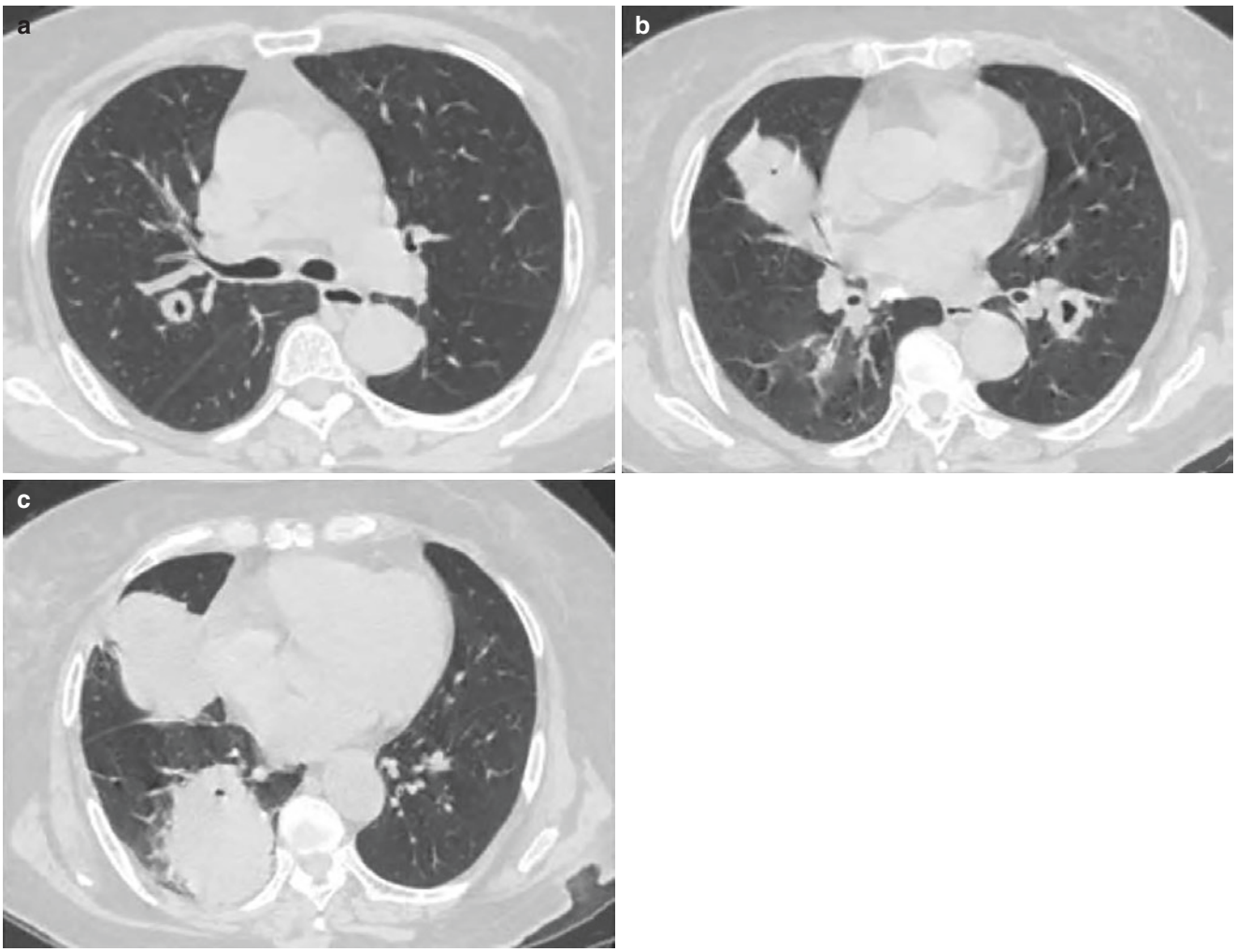

Fig. 20.4 Granulomatosis with polyangiitis (I). (**a**–**c**) CT lung window showed multiple soft tissue opacity nodules and masses in both lungs, some of which were large, mostly located beside bronchial vascular bundle, with clear edges, with thick-walled cavities inside, and the inner surface of the cavity wall was smooth and clear

6. Disease evolution: The typical manifestation of granulomatosis with polyangiitis features "migratory relapse", indicating the constantly evolved disease. If treated, the lesions in the pulmonary parenchyma can begin to improve within 1 week and completely or partially disappear within 2–6 weeks. Recurrence is common in the previous lesion area, often involving the airway.

20.2.4 Diagnostic Key Points

1. Multiple cavitary nodules and airway stenosis occur in the lung.
2. Airway involvement is characterized by localized circumferential thickened airway wall with luminal stenosis, involving tracheal membrane and cartilage, sometimes involving bronchus and distal airway.
3. The most common manifestation of pulmonary involvement is multiple nodules, which may be accompanied by cavity formation, localized or diffuse consolidation, and ground-glass opacity changes.
4. Typical triad signs can be found in clinical practice: sinus, lung, and kidney lesions, with positive PR3-ANCA.

20.2.5 Differential Diagnosis

According to the different involved sites and manifestations of granulomatosis with polyangiitis, it needs to be differentiated from different diseases.

1. *Nodule, mass lesion*.
   (a) Metastases: Most of them are multiple lesions in both lungs and randomly distributed. Some metastases

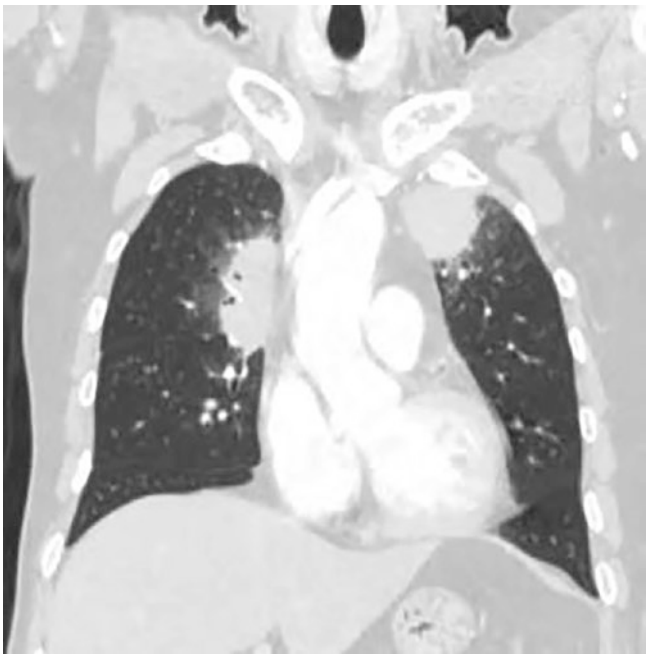

Fig. 20.5 Granulomatosis with polyangiitis (II). CT lung window showed soft tissue opacity nodules and masses in the upper lobe of both lungs, with ground-glass opacities at the edges, showing "halo" sign

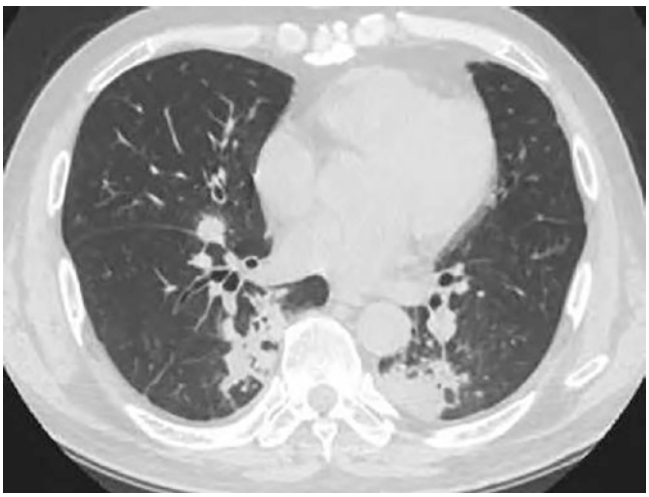

Fig. 20.7 Granulomatosis with polyangiitis (IV). CT lung window showed irregular patchy consolidation under pleura and around bronchovascular bundles of both lungs

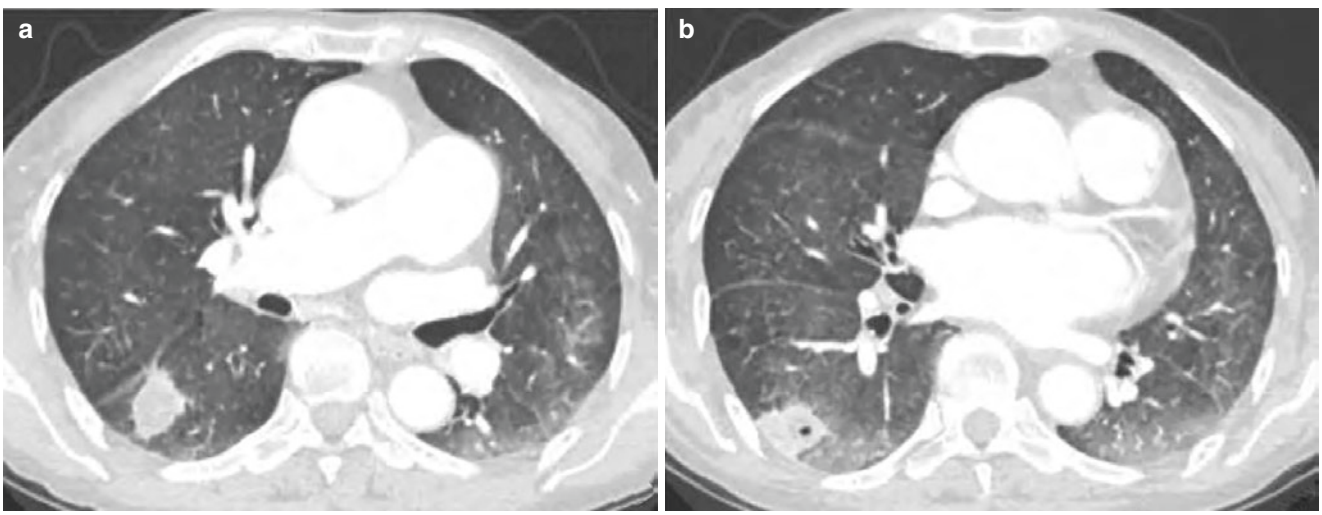

Fig. 20.6 Granulomatosis with polyangiitis (III). (**a** and **b**) CT lung window showed multiple soft tissue opacity nodules in both lungs, mostly located under pleura; diffuse multiple ground-glass opacity changes in both lungs, especially in the middle and inner zones of both lungs

may also have cavities. Squamous cell carcinoma and sarcoma are common. Metastases have clear edges and different sizes.

(b) Sarcoidosis: Multiple lesions in both lungs, distributed along lymphatic vessels, with small nodules ranging from 2 to 10 mm, generally without cavities.

(c) Inflammation: Various manifestations include single and multiple lesions, which can be distributed along blood vessels or bronchus. Typical manifestations show "tree-in-bud" sign, consolidation, and reactive lymphadenopathy.

(d) Rheumatoid nodules: Lesions are common in bilateral lower lungs, often small, mostly under pleura, with cavities. It is sometimes difficult to distinguish from inflammatory necrotic nodules.

2. *Consolidation*.

(a) Inflammation: Acute course of disease, mostly distributed along lobes and segments, or with patchy distribution. "Tree-in-bud" sign is common, but cavity is rare.

(b) Aspiration pneumonia: Showing acute course of disease, lesions are more common in the lower lobes, with "tree-in-bud" sign, and cavity is rare.

(c) Organizing pneumonia: Showing chronic course of disease, the disease can be manifested as migratory lesions, mostly consolidation or stripe-like ground-glass opacities distributed along bronchial vascular bundles, with "reversed halo" sign and mild bronchial traction and dilation.

(d) Mucinous adenocarcinoma: Single or multiple lesions show chronic course. Ground-glass opacity foci and consolidation may occur, often with "halo" sign, accompanied by lymphadenectasis.

3. *Airway lesion*.

(a) Recurrent polychondritis: diffuse or localized airway involvement, mostly in the larynx and above the trachea. The characteristic is that the cartilage part of trachea is involved, but the membrane part is not involved. It is often accompanied by other cartilage tissue involvement, including ears, nose, throat, and peripheral joints.

(b) Tracheobronchial amyloidosis: Most of them are manifested as nodular thickening of tracheal and bronchial walls with luminal stenosis. Membrane and cartilage are involved. Calcification/ossification of lumen wall is common.

(c) Acquired tracheal stenosis: Patients have a history of endotracheal intubation and other operations in the past, showing funnel-shaped stenosis centered on the operation site, and the length is mostly less than 2 cm.

20.2.6 Research Status and Progress

1. Study on imaging and clinical correlation of pulmonary involvement in granulomatosis with polyangiitis: Currently, most studies on pulmonary involvement in granulomatosis with polyangiitis still focus on clinical manifestations, especially imaging manifestations when different serological results overlap with other autoimmune diseases, but most of these studies are case reports. With the continuous updating of the concept of ANCA-related systemic vasculitis, there may be large-scale studies with more samples in the future.
2. PET/CT is helpful in identifying the nature of nodules. Many studies have reported that PET/CT is used to differentiate lung cancer from inflammatory nodules (such as granulomatosis with polyangiitis involving solid nodules in the lungs) [13].
3. MRI is mainly used in the diagnosis of granulomatosis with polyangiitis outside the lungs, including central nervous system, orbit, breast, and kidney.
4. Imaging information technology: With the continuous development of imaging information technology, many studies have reported the related technologies applied for differential diagnosis of pulmonary nodules [14].

20.3 Eosinophilic Granulomatosis with Polyangiitis

Ke Wang and Yufeng Xu

20.3.1 Overview

Eosinophilic granulomatosis with polyangiitis (EGPA) is also known as Churg–Strauss syndrome (CSS) or allergic granulomatosis with polyangiitis. In 1994, Chapel Hill Consensus Conference further clearly put forward the definition of EGPA, that is, eosinophil-rich and granulomatous inflammation involving respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels associated with asthma and eosinophilia [15]. At present, it is believed that the pathogenesis of EGPA may be vascular wall injury and eosinophil infiltration mediated by antineutrophil cytoplasmic antibody (ANCA). Genetic factors may also play a role.

Clinically, it is a multisystem disease mainly manifested as chronic sinusitis, asthma, and significant eosinophilia in peripheral blood. The average onset age of EGPA is 40, and EGPA rarely occurs in those over 65 years old and children, and there is no difference in gender. EGPA can involve all

systems of the whole body, the most common organ involved is lung, followed by skin and other organs such as cardiovascular system, digestive system, urinary system, and central nervous system. Clinically, this disease includes three stages:

(1) Prodromal stage often occurs in patients of 20–40 years old, manifested as atopic dermatitis, allergic sinusitis, and asthma. (2) Eosinophilia stage has clinical manifestations including eosinophilia in peripheral blood and eosinophilic infiltration in tissues and organs. The lung and digestive tract are most commonly involved, and about 40% of the patients have pulmonary lesions, asthma, and eosinophilia in peripheral blood before systemic vasculitis. (3) Vasculitis period has multisystem medium and small vasculitis in patients at the age of 30–50 years, often accompanied by vascular and extravascular granuloma, which is often life-threatening. Systemic symptoms such as fever, weight loss, and fatigue often indicate the occurrence of vasculitis.

Asthma is the main clinical feature of EGPA, which can be found in most patients and may occur 8–10 years earlier than vasculitis. For asthma patients with poor control of moderate dose inhaled glucocorticoid, EGPA should be suspected. Some patients may have other pulmonary abnormalities, including lung consolidation, pleural effusion, nodules, and alveolar hemorrhage.

Once EGPA is diagnosed, it is necessary to evaluate the involvement of respiratory system, kidney, heart, gastrointestinal tract, and peripheral nerves in detail and determine the type according to the involved sites. Cases meeting the diagnostic criteria of EGPA but only with respiratory system involved (including ears, nose, and throat) are classified as localized type. Those with two or more organs involved are classified as systemic type [16].

Laboratory examination shows significant eosinophilia in peripheral blood or bronchial lavage fluid. In acute stage, erythrocyte sedimentation rate is increased rapidly and IgE is increased significantly. ANCA is positive in most patients in acute stage, which can turn negative quickly after the disease remission.

20.3.2 Pathological Manifestations

The main pathological manifestations of EGPA include the following four types, which often do not occur at the same time: (1) eosinophil infiltration; (2) significant and extensive necrosis; (3) eosinophil and giant cell vasculitis, mainly involving small arteries and veins; and (4) interstitial and perivascular necrotic granuloma.

Asthmatic bronchitis, eosinophilic pneumonia, extravascular granuloma, and vasculitis (arteries, veins, and capillaries can be involved) may occur in the lung. Sometimes, inflammation can extend along pleura or interlobular septa. Granuloma of EGPA, also known as allergic granuloma, is characterized by central necrotic eosinophils, surrounded by a palisade-like structure composed of histiocytes and multinucleated giant cells. In addition, diffuse alveolar hemorrhage and capillary vasculitis can be found in the lungs.

EGPA is a kind of vasculitis involving small and middle arteries, and its histopathological manifestations vary in different stages of the disease [17]. No obvious vasculitis occurs in the early stage of vasculitis, only showing eosinophils infiltration in tissues. During vasculitis, the inflammation of vascular wall is mainly nondestructive inflammatory infiltration, while necrotizing vasculitis is rare. In the later stage of vasculitis, the lesions of vascular wall heal, which is similar to organizing emboli, but can be complicated with extensive destruction of elastic layer of vascular wall, at which time eosinophils can disappear.

20.3.3 Imaging Manifestations

1. Intrapulmonary manifestations: The most common imaging manifestation of EGPA is patchy consolidation or ground-glass opacities in both lungs (86.7%) [18], which is also the main imaging manifestation different from that of asthma (Figs. 20.8 and 20.9). Lesions are usually distributed symmetrically in both lungs, with no obvious difference among upper lobe, middle lobe, and lower lobe. Peripheral distribution is more common (50%), and peribronchial distribution or patchy random distribution can also be found. Lung consolidation is mostly caused by eosinophils infiltrating alveolar wall and alveolar space, and granuloma may occur, but may not be accompanied by vasculitis. Consolidation and

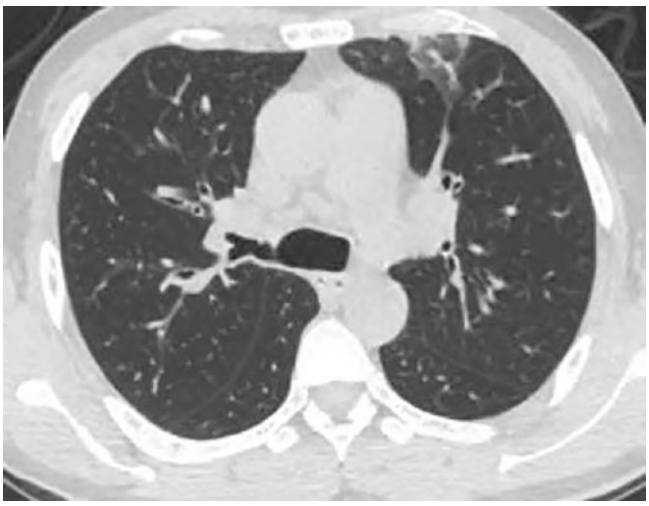

Fig. 20.8 Eosinophilic granulomatosis with polyangiitis (I). CT lung window showed patchy ground-glass opacity foci under the pleura of the upper lobe of the left lung, accompanied by small patchy consolidation, mild thickening of bilateral bronchial wall

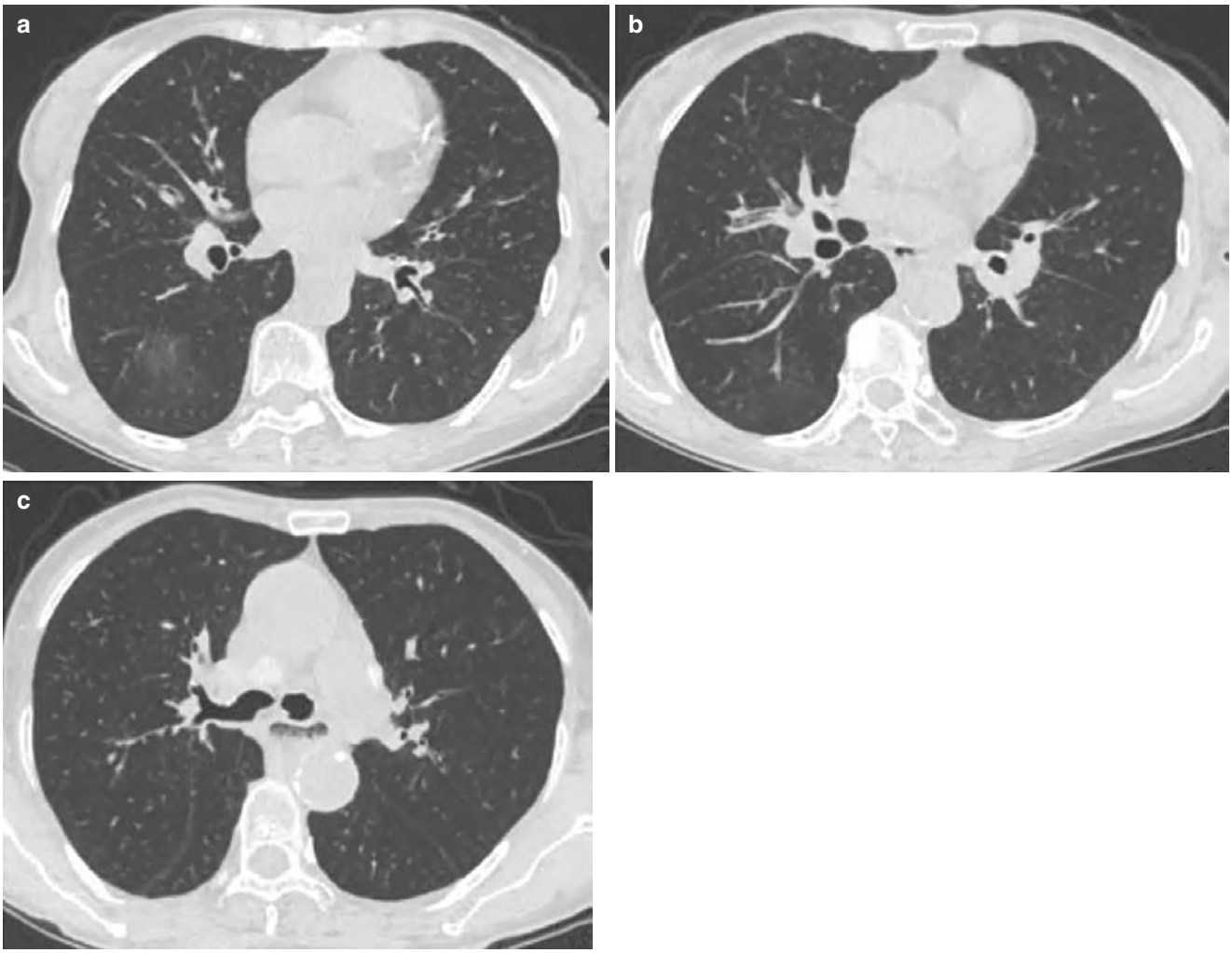

Fig. 20.9 Eosinophilic granulomatosis with polyangiitis (II). (**a**) CT lung window showed patchy ground-glass opacity foci in the lower lobe of the right lung with blurred edges; (**b**) diffuse and mild thickening of bilateral bronchial wall; and (**c**) diffuse multiple centrilobular nodules in both lungs

ground-glass opacity foci in lung can be transient. It is mentioned in literature that EGPA patients have "reversed halo" sign (50%) [19]. Opposite to "halo" sign, "reversed halo" sign means that the center is ground-glass opacity foci, surrounded by consolidation. Thickened interlobular septa and intralobular septa is another common manifestation (Fig. 20.10), which can occur in about 50% of patients, and may be related to pulmonary edema, eosinophil infiltration, and fibrosis secondary to heart involvement.

2. Airway involvement: Multiple small nodules (<10 mm) are an important imaging manifestation of EGPA (Figs. 20.9 and 20.10), which can be found in almost all patients [19], with "tree-in-bud" sign, and there is no obvious specificity in horizontal distribution and vertical distribution. These nodules may be caused by eosinophils infiltrating bronchioles and capillaries. Randomly distributed nodules are also common manifestations. Other manifestations include bronchiectasis and thickened bronchial and bronchiolar walls (Figs. 20.9 and 20.10). Bronchial wall thickening (66%) [20] may be related to eosinophil infiltration, and other manifestations may be related to asthma.
3. Other manifestations: Unilateral or bilateral pleural effusion may occur in 10–50% of the patients. Pleural effusion may be related to left heart failure and pleural eosinophil infiltration caused by myocardial involvement. Lymphadenectasis may occur in a few patients.

20.3.4 Diagnostic Key Points

1. There are many diagnostic criteria for EGPA worldwide, and the two most commonly used ones are American

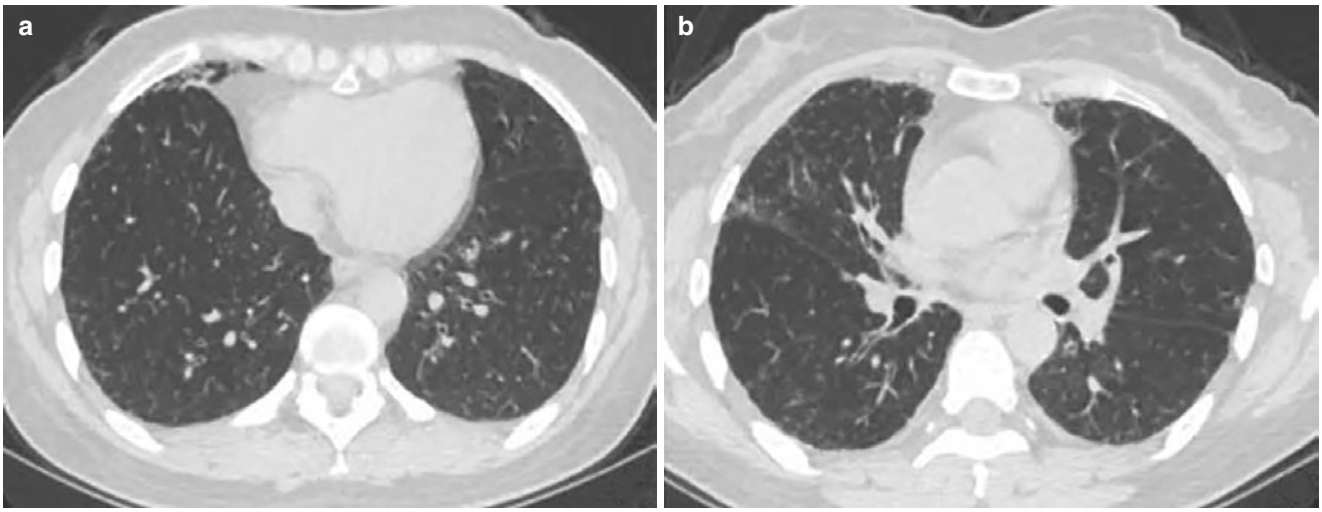

Fig. 20.10 Eosinophilic granulomatosis with polyangiitis (III). (**a**, **b**) CT lung window showed diffuse thickening of bronchial wall in both lungs, accompanied by multiple centrilobular nodules and slightly thickened bilateral subpleural interlobular septa

College of Rheumatology (ACR) criteria [21] and Lanham criteria [22].

(a) ACR criteria include 6 items, and meeting 4 items or more can confirm the diagnosis of EGPA, with a diagnostic sensitivity of 85% and a specificity of 99.7%; these six items are as follows: asthma (wheezing symptoms or expiratory wheezing sounds); the proportion of eosinophils over 10%; mononeuropathy (single or multiple) or polyneuropathy; migrant or transient intrapulmonary lesions found on imaging; paranasal sinus lesions; and extravascular eosinophil infiltration found by biopsy.

(b) Lanham criteria include three items; meeting all items can confirm the diagnosis of EGPA. These three items include: asthma; peripheral blood eosinophil count $\geq 1.5 \times 10^9$/L; and vasculitis with more than 2 extrapulmonary systems involved.

2. Thoracic imaging is characterized by transient symmetrical patchy consolidation or ground-glass opacity lesions in both lungs, mostly in peripheral distribution and accompanied by airway lesions (centrilobular nodules, bronchiolectasis, and wall thickening).

20.3.5 Differential Diagnosis

Asthma in patients who have consolidation or ground-glass opacity changes in the periphery of both lungs needs to be differentiated from the following diseases.

1. Simple pulmonary eosinophilic infiltration (Löffler syndrome): The imaging manifestations are migratory consolidation in the lungs, which changes rapidly and even has significant imaging changes every day, and usually disappears spontaneously within 1 month [23]. The lesions are mainly manifested as ground-glass opacity changes or consolidation, with blurred edges, mainly distributed in peripheral, middle, and upper lobes. This disease is a benign disease of unknown cause, which may be related to parasites, ABPA, and drugs. Most of the cases require no specific treatment, and respiratory symptoms can be alleviated.
2. Chronic eosinophilic pneumonia: It has long-term consolidation in the lung, is more common in the upper lobe and periphery, and can be migratory (the lesions occur alternately in different areas). The consolidation density of chronic eosinophilic pneumonia is often uniform, while the peripheral consolidation of EGPA is often distributed along lobules, and centrilobular nodules in ground-glass opacity foci are often found [23]. Chronic eosinophilic pneumonia often has occult onset, showing asthma and chronic sinusitis, accompanied by eosinophilia in peripheral blood and bronchoalveolar lavage fluid, but other systems are not involved. Hormone therapy can take effect quickly and often recurs after drug withdrawal.
3. Cryptogenic organizing pneumonia (COP): It can also be manifested as peripheral consolidation or ground-glass opacity foci, and solid changes are common, mainly located around bronchovascular bundle, showing patchy and nodular masses. About 20% of the patients may have "reversed halo" sign, which is more common than that of EGPA patients. It may be accompanied by bronchiectasis, but bronchiectasis is mostly confined to consolidation

and ground-glass opacity foci. Lymphocytes are predominant in COP bronchoalveolar lavage fluid, while eosinophils are predominant in that of EGPA.

20.3.6 Research Status and Progress

It is not uncommon for EGPA to involve the heart, which is one of the serious manifestations of EGPA and the most important cause of death in EGPA patients [24]. After the diagnosis of EGPA, it is generally recommended to perform electrocardiogram and echocardiography for preliminary evaluation, regardless of symptoms of cardiac involvement. In recent years, cardiac MRI has become a highly valuable imaging method for diagnosing EGPA cardiac involvement, as well as monitoring and evaluating treatment effect [25]. Cardiac MRI T_2WI can detect myocardial edema sensitively, and late gadolinium enhancement (LGE) can evaluate myocardial necrosis and fibrosis. T_2-mapping and T_1-mapping can also be used to quantitatively and accurately assess myocardial edema and fibrosis.

20.4 Behcet's Disease

Ke Wang and Yufeng Xu

20.4.1 Overview

Behcet's disease, also known as Behcet's syndrome (BS), is a chronic, recurrent, and systemic disease with vasculitis as its basic pathological manifestation. Its main clinical features are recurrent oral and genital ulcers, ophthalmia, and skin damage, which may involve joints, blood vessels, digestive tract, and nervous system [26].

In Japan, Korea, China, Iran, Iraq, Saudi Arabia, and other countries, the incidence rate of Behcet's disease is 13.5–35 patients per 100,000 people. The incidence rate is lower in American and Nordic countries. The incidence rate of males is similar to that of females. Young and middle-aged people aged 20–40 are more likely to be affected.

The common clinical manifestations of Behcet's disease are recurrent mucosal and skin ulcers (common in 2/3 patients), often accompanied by pain. Oral ulcer is diffuse and occurs many times, which may affect eating. Genital ulcer is the most specific lesion of Behcet's disease, which is similar in appearance to oral ulcer, with obvious pain, often showing scar formation. Vascular diseases (about 1/3 of patients) and central nervous system diseases (10–20% of patients) are also common clinical manifestations. Vascular diseases are caused by vasculitis, involving arteries and veins. Neurological diseases include parenchymal diseases and nonparenchymal diseases. Parenchymal diseases involve brain stem, spinal cord, and cerebral hemisphere and may be multiple lesions. Nonparenchymal diseases include cerebral venous thrombosis, intracranial hypertension, acute meningeal syndrome, and rare stroke caused by arterial thrombosis or aortic dissection. Kidney, joint, heart, and gastrointestinal tract can also be involved.

The most common site involved by Behcet's disease is pulmonary vessels, and aneurysm involving the proximal branches of pulmonary arteries is the most common pulmonary vascular lesion in Behcet's disease, which is not common in other diseases. Hemoptysis is the most common symptom, and other symptoms include cough, dyspnea, fever, and pleurisy. Pulmonary artery thrombosis can be complicated with pulmonary aneurysm or occurs alone. In addition, venous thrombosis is also a common manifestation, such as superior vena cava thrombosis and inferior vena cava thrombosis. Apart from vasculopathy, patients may have pulmonary embolism, pulmonary infarction, pulmonary hemorrhage, pleural effusion, Bronchial stenosis, pulmonary abscess, obstructive airway lesions, and pulmonary fibrosis can also be found in Behcet's disease.

20.4.2 Pathological Manifestations

Histological examination of Behcet's disease often shows vasculitis, but not in every patient. The classic pathological manifestations of Behcet's disease are necrotizing Leukocyte fragmentation, peripheral vasculitis obliterans, and venous thrombosis, involving blood vessels of various diameters, including capillaries, veins, and arteries, and lymphocyte infiltration in vascular walls. Cell infiltration usually occurs around blood vessels. There are neutrophils and CD_4^+ T lymphocytes in vasa vasorum and perivascular area. The significant leukocyte fragmentation vasculitis may show endothelial swelling, erythrocyte extravasation, and fibrinoid necrosis of vascular wall. Thrombosis is also a common manifestation.

20.4.3 Imaging Manifestations

According to the pathological basis of Behcet's disease, it is characterized by extensive involvement of arteries and veins of various diameters. Koc et al. counted the involvement of different blood vessels in 728 patients (Table 20.3) [27]. Behcet's disease involving the lungs can lead to pulmonary aneurysm, pulmonary artery thrombosis, pulmonary parenchymal lesion, and so on. The incidence rate of Behcet's disease involving lungs varies in different studies. For Chinese population, Fei et al. retrospectively counted 796 Chinese Behcet's disease patients and 12.8% of them had vascular involvement [28]. Among the patients with vascular involvement, pulmonary artery involvement accounted for about 23.2%, which was the third most common artery involvement site.

1. Aneurysm: Pulmonary aneurysm is the most common manifestation of arterial involvement. The studies of Seyahi et al. have shown that about 72% of patients with arterial involvement has pulmonary aneurysm [29]. Patients with pulmonary aneurysms often have different degrees of hemoptysis. Arteries can show cystic, fusiform, or tubular dilatation, and the lung can be involved bilaterally/unilaterally. The main pulmonary artery and branches of each lobe can be involved, and the inferior lobe artery is most commonly involved (Fig. 20.11). Aneurysms are often complicated with arterial thrombosis. Patients with aneurysm or arterial thrombosis are more likely to have hemoptysis and complication with extrapulmonary vascular involvement [30]. Compared with patients without pulmonary aneurysm, patients with pulmonary aneurysm have a significantly higher probability of involvement of extrapulmonary large vessels, such as deep vein thrombosis, aneurysm, or vascular occlusion [30].
2. Pulmonary thrombosis: It is another common manifestation of pulmonary involvement, and about 28% of patients has pulmonary artery embolism alone [29]. Different from the common pulmonary thrombosis caused by deep venous thrombosis of lower limbs with route along the blood flow to pulmonary artery, the pulmonary thrombosis of Behcet's disease is mostly in situ thrombosis secondary to pulmonary vasculitis and thrombosis occurs in the inflammatory reaction area of vascular wall. During the follow-up visit of patients with pulmonary aneurysm, the probability of complication with thrombosis is increasing. However, aneurysms gradually occur in many patients with pulmonary artery thrombosis alone during the follow-up visit.
3. Pulmonary parenchymal lesion: It is often complicated with pulmonary aneurysm and pulmonary artery thrombosis or occasionally occurs alone. On the one hand, pulmonary parenchymal lesions may be related to the involvement of large vessels, such as pulmonary infarction and pulmonary hemorrhage secondary to pulmonary thrombosis/pulmonary aneurysm. On the other hand, it may also be related to local small blood vessel involvement. The manifestations of Behcet's disease involving pulmonary parenchyma are not specific, including pulmonary nodules, consolidation, ground-glass opacity

Table 20.3 Occurrence of vasculopathy in 728 patients with Behcet's disease

Vasculopathy	Number of patients
Venous disease	
Deep vein thrombosis	221
Subcutaneous thrombophlebitis	205
Superior vena cava occlusion	122
Inferior vena cava occlusion	93
Intracranial venous thrombosis	30
Budd-Chiari syndrome	17
Other venous occlusion (such as subclavian vein, iliac vein, portal vein, renal vein, etc.)	24
Arterial disease	
Pulmonary artery occlusion or aneurysm	36
Aortic aneurysm	17
Arterial occlusion or aneurysm of limbs	45
Other arterial occlusion or aneurysm (such as iliac artery, subclavian artery, renal artery, carotid artery, etc.)	42
Right ventricular thrombosis	2

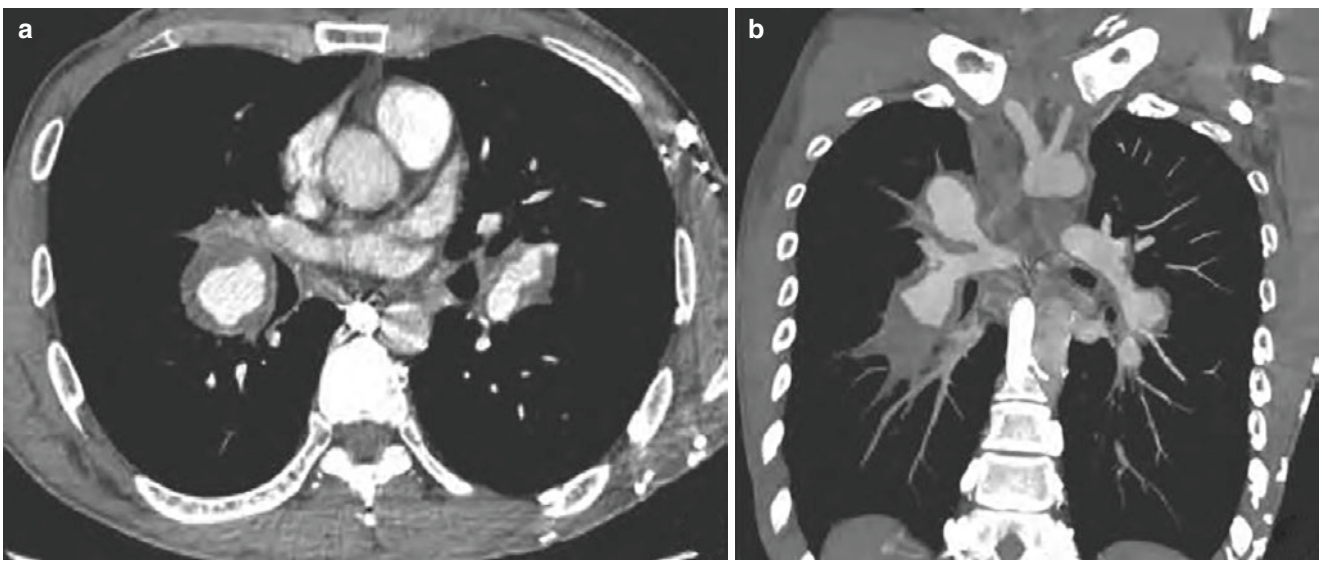

Fig. 20.11 Behcet's disease (I). (**a** and **b**) CT pulmonary angiography (CTPA) in cross section (A) and maximum intensity projection (MIP) in the coronal plane (B) of CTPA showed multiple irregular aneurysm-like dilatations and mural filling defects in both pulmonary arteries

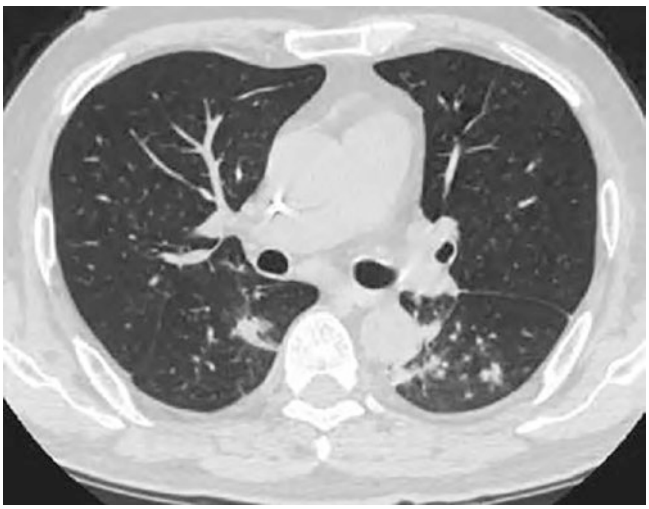

Fig. 20.12 Behcet's disease (II). CT lung window showed multiple solid nodules and patchy consolidation in the lower lobes of both lungs, some with clear edges and some with blurred edges

changes, cavities, interstitial changes, etc. (Fig. 20.12). Solid nodules often occur in the acute stage and are related to pulmonary artery involvement. About 85% of patients with pulmonary artery involvement may have nodular lesions [29]. Nodules are mostly bilateral, more common in the lower lobes, the peripheral area, or subpleural area of the lung, and its pathology is infarction, necrosis, organizing inflammation, and necrotizing granulomatous inflammation. Nodules can be absorbed in 2–3 weeks. Some patients have pulmonary cavity lesions, mostly thin-walled, with clear edges, common in the lower lobes of both lungs, which can be accompanied by the gas–liquid plane, sometimes secondary to nodules or consolidation. Ground-glass lesions may be related to alveolar hemorrhage.

Patients with pulmonary parenchyma involvement alone but no pulmonary vascular involvement mostly have mild clinical manifestations and relatively good prognosis and treatment effect.

4. Other lesions: Bilateral pleural effusion may be related to superior vena cava thrombosis, which is more common in patients with pulmonary aneurysms and often accompanied by pulmonary nodules. Some patients may have a small amount of pericardial effusion and mediastinal lymphadenectasis, which can improve with treatment.

20.4.4 Diagnostic Key Points

1. The diagnosis of Behcet's disease is mainly based on typical clinical manifestations, such as recurrent oral ulcer, genital ulcer, skin and eye lesions, etc. According to the requirements of the International Behcet's Disease Research Group in 1990, the diagnosis of Behcet's disease must meet the following criteria:
   (a) Recurrent oral ulcer (at least 3 onsets within 12 months).
   (b) Any two items of the following are also required: (1) recurrent genital ulcer; (2) ocular lesions (anterior/posterior uveitis, vitreous opacity, and retinal vasculitis); (3) skin lesions (erythema nodosum lesions, papular pustular lesions, and folliculitis lesions); and (4) acupuncture test positive.
2. According to pulmonary imaging manifestations, the diagnostic points of Behcet's disease are as follows:
   (a) Pulmonary macroangiopathy is the most common manifestation different from that of other vasculitis, and pulmonary aneurysm is the most common. Lesions are often complicated with pulmonary artery thrombosis, which mostly occurs locally in vasculitis or occurs alone. Large veins may also be involved, such as superior vena cava thrombosis and inferior vena cava thrombosis.
   (b) Pulmonary parenchymal lesions are not specific and may be complicated with pulmonary macroangiopathy or occur alone. Pulmonary parenchymal lesions include pulmonary nodules or consolidation, ground-glass opacity changes, interstitial lesions, and so on.

20.4.5 Differential Diagnosis

1. Hughes–Stovin syndrome: It is a rare disease characterized by multiple pulmonary aneurysms accompanied by peripheral venous thrombosis but has no typical clinical manifestations of Behcet's disease. The formation of pulmonary aneurysm in Hughes–Stovin syndrome is caused by weak pulmonary artery wall.
2. Takayasu arteritis: It can also involve pulmonary artery, which is mainly manifested as thickened pulmonary artery wall and luminal stenosis, and pulmonary aneurysm is rare.

20.4.6 Research Status and Progress

1. PET/CT: Many studies have used PET/CT to evaluate systemic vascular involvement and inflammatory response in patients with Behcet's disease. Studies have shown that compared with CTA, PET/CT can show the change of curative effect 4 weeks in advance [31].
2. MRI: Mainly used in Behcet's disease with nervous system involvement. Some newly discovered and summarized MR features (such as Bagel sign) have high

diagnostic specificity for spinal cord involvement in Behcet's disease [32]. In addition, some new MR techniques are gradually applied to the study of nervous system involvement in Behcet's disease, such as diffusion tensor imaging (DTI) to show pyramidal tract involvement in Behcet's disease patients [33].

20.5 Polyarteritis Nodosa

Ke Wang and Yufeng Xu

20.5.1 Overview

Polyarteritis nodosa (PAN) is a non-granulomatosis with polyangiitis characterized by segmental inflammation and necrosis of small and medium arteries. PAN mainly invades small and medium muscular arteries, showing segmental distribution. The etiology is unknown, which may be related to infection (viral infection and bacterial infection), drugs, and injected serum, especially hepatitis B virus (HBV) infection, and immunopathological mechanism plays an important role in the disease [34]. The incidence of PAN is low, ranging from 2 to 23 patients per million people. This disease is more common in middle-aged or elderly people, and its incidence rises with age, reaching its peak at 60. There are slightly more male patients, and the ratio of males to females is about 1.5:1. Children can also be affected.

The clinical manifestations of PAN are usually multisystem involvement, affecting almost all organs. Pulmonary involvement is relatively rare and can be accompanied by systemic symptoms such as fatigue, weight loss, weakness, fever, joint pain, and so on. Common manifestations: (1) Skin manifestations, including erythema, purpura, livedo reticularis, ulcer, and bullae. (2) Renal manifestations. Kidney is the most commonly involved organ. Renal artery stenosis causes glomerular ischemia, leading to renal inflammation or necrosis. In severe cases, renal infarction may occur, and some patients have perirenal hematoma due to rupture of renal aneurysm. Hypertension is also a common manifestation of renal involvement. (3) Nervous system, mostly manifested as asymmetric mononeuropathy. (4) Gastrointestinal manifestations. Mesenteric artery inflammation can lead to intermittent or continuous abdominal pain, which is more common after meals, accompanied by nausea, vomiting, black stool, bloody or nonbloody diarrhea, and gastrointestinal hemorrhage. (5) Coronary artery manifestations, coronary artery stenosis, or occlusion can lead to myocardial ischemia and even myocardial infarction. (6) Others. Muscles, reproductive system, and eyes can also be involved.

Imaging manifestations usually include middle arterial dilatation, aneurysm, or arterial stenosis and obstruction. On CT, renal artery is the most commonly involved site, while pulmonary artery is rarely involved.

20.5.2 Pathological Manifestations

Pathological manifestations of PAN include middle arterial segmental transmural inflammation without involvement of veins. Cell infiltration involves polynuclear leukocytes and monocytes. The destruction involves the elastic layer of vascular wall, often causing aneurysms. Granulomatous lesions do not occur in this disease. Otherwise, it suggests other diagnoses.

20.5.3 Imaging Manifestations

Pulmonary involvement is rare in PAN, most of which are recorded in case reports [35, 36] and a few case reviews [37]. The lung manifestations mentioned in earlier reports in the past include bronchial aneurysm, pulmonary arteritis, diffuse alveolar hemorrhage, pulmonary interstitial lesions, bronchiolitis obliterans, organized pneumonia, and pleural effusion. With the change of classification criteria, most of them should be classified as allergic granulomatosis with polyangiitis. Diffuse alveolar hemorrhage is the most frequently reported pulmonary manifestation in PAN. In some cases, bronchial artery involvement causing aneurysms has been reported, but CT is rarely used for diagnosis, and most of them are diagnosed by angiography.

1. Alveolar hemorrhage: It is usually manifested as consolidation of air cavity or ground-glass opacity change, which is common in the middle and inner zones of the lung, middle lobe, and lower lobe, but rare in the upper lobe. With the evolution of the disease, the imaging manifestations are different, initially showing nodular or patchy ground-glass opacity foci, and then gradually showing thickened consolidation of interlobular septa (Fig. 20.13). In patients with simple alveolar hemorrhage, the lesions can be gradually absorbed in 7–14 days, but the prognosis of PAN complicated with alveolar hemorrhage was poor in case reports.
2. Pulmonary artery involvement: It is rare, and bronchial artery involvement is more common [38], which is similar to middle artery involvement in other parts of the body, showing aneurysm formation. It has been reported that the middle pulmonary artery can also be involved [39]. Patients with pulmonary artery involvement often have vascular involvement at other locations.

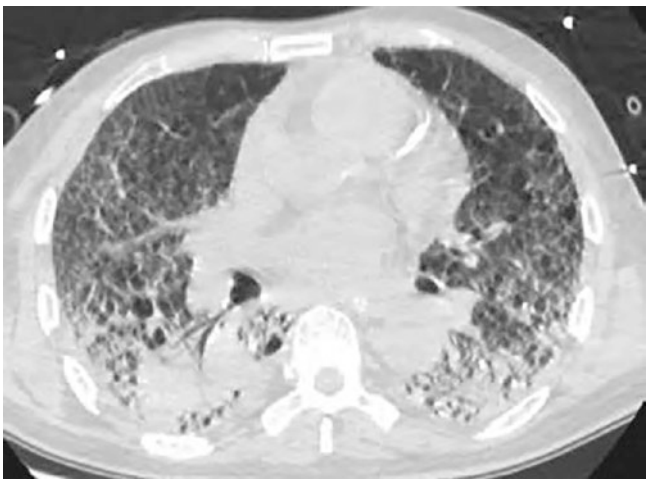

Fig. 20.13 Polyarteritis nodosa. CT lung window showed patchy consolidation and ground-glass opacity foci in both lungs, and bronchoalveolar lavage suggested alveolar hemorrhage

20.5.4 Diagnostic Key Points

1. Multisystem involvement is mainly manifested as middle artery involvement, such as renal artery, superior mesenteric artery, and hepatic artery, causing related symptoms.
2. Pulmonary involvement is rare. Otherwise, it is often manifested as alveolar hemorrhage.

20.5.5 Differential Diagnosis

PAN mainly needs to be differentiated from other vasculitis. Pulmonary involvement is rare in PAN, and patients with alveolar hemorrhage need to be diagnosed in combination with clinical manifestations.

1. Granulomatosis with polyangiitis and microscopic polyvasculitis: Both are ANCA-related systemic vasculitis, mostly with ANCA positive. The pulmonary manifestations include nodules, consolidation, ground-glass opacity changes, interstitial lesions, and so on. Alveolar hemorrhage is more common in microscopic polyvasculitis, which needs to be differentiated in combination with other clinical manifestations and serological indexes.
2. Eosinophilic granulomatosis with polyangiitis: The typical manifestations include asthma, eosinophilia in peripheral blood, and vasculitis. Lung imaging manifestations include ground-glass opacity changes and airway lesions.

20.5.6 Research Status and Progress

Because the pulmonary involvement of PAN is rare, most of the related literatures are just case reports. In recent years, some new imaging technologies have been applied to the imaging of other systems in PAN. Takei et al. used MR scan of lower extremity muscle to diagnose the muscle involvement in PAN [40]. Schollhammer et al. used ^{18}F-FDG PET/CT imaging to diagnose PAN earlier [41].

20.6 Takayasu Arteritis

Ke Wang and Yufeng Xu

20.6.1 Overview

Takayasu arteritis (TA) refers to the primary chronic inflammation of the aorta of unknown origin, which mainly involves the aorta and its main branches and can lead to luminal stenosis. TA was more common in young Asian women, the ratio of males to females is 1:(1.5–1.9), and the onset age is often less than 40 years.

On the one hand, the clinical manifestations are nonspecific symptoms, such as low fever, malaise, weight loss, fatigue, etc. The nonspecific symptoms mainly occur in the early stage of the disease. On the other hand, in vasculitis and chronic stage, patients have vascular involvement and stenosis. Typical manifestations include weakened pulse or claudication of limbs, asymmetric blood pressure of limbs, vascular murmur of aorta and/or its main branches, elevated systolic/diastolic blood pressure, etc. According to the different locations of involved blood vessels, patients may also have different manifestations of organ involvement, such as skin erythema, hemorrhage, positive nervous systemic sign for lesion localization, digestive tract ischemia, etc. The patient's condition is often recurrent, with the alternating of each stage.

The Guidelines for Diagnosis and Treatment of Takayasu Arteritis published by Chinese Rheumatology Association in 2011 divides TA into four types according to the lesion site, including brachiocephalic artery type, thoracoabdominal aortic type, extensive type, and pulmonary artery type [42]. Because of the stenosis or occlusion of carotid artery and vertebral artery, brain ischemia can occur in brachiocephalic artery type. Thoracoabdominal aortic type can involve renal artery and iliac artery and then cause hypertension, intermittent claudication, and other symptoms. Extensive type refers to multiple lesions, which have the characteristics of the above two, mostly causing serious condition. Pulmonary artery type refers to the lesions complicated with pulmonary artery involvement, which can be manifested as palpitation, shortness of breath, cardiac insufficiency, and so on.

According to the diagnostic criteria of European Alliance of Associations for Rheumatology (EULAR) and Paediatric Rheumatology European Society (PRES) in 2006, digital

subtraction angiography (DSA), CT, or MR angiography indicating the abnormalities of aorta and main branches are necessary conditions for diagnosing TA [43]. In addition, any one of the following five criteria is also required: weakened pulse of limbs or claudication; asymmetric blood pressure of limbs (blood pressure difference more than 10 mmHg); vascular murmur of aorta and/or its main branches; increased systolic blood pressure/diastolic blood pressure (>95th percentile); and increased biochemical indexes (ESR or CRP) in the acute stage. Therefore, the imaging examination is very important for the diagnosis of Takayasu arteritis.

20.6.2 Pathological Manifestations

The etiology of TA is not clear, and it is believed that TA may be related to HLA complex, infection, cellular and humoral immune-mediated tissue damage, and so on. TA mainly involves aorta and its main branches, and the whole thickness of artery can be involved in histopathology. In the acute inflammation stage, the adventitia of artery is characterized by vasa vasorum inflammation. Lymphocyte infiltration occurs in the media of artery. Mucopolysaccharide deposition, infiltration of smooth muscle cells, and fibroblasts occur in the intima of artery. Such lesions and inflammation together lead to thickened artery wall. During the fibrosis healing stage, the elastic fibers of arterial wall are broken, which leads to stenosis and obstruction of arterial lumen. Pulmonary artery involvement in this disease is rare, usually secondary to systemic Takayasu arteritis, rarely showing solitary lesion, and pulmonary artery involvement usually indicates the later stage of this disease.

20.6.3 Imaging Manifestations

1. X-ray: Chest radiograph can provide little information, mainly some nonspecific manifestations of aortic lesions, such as irregular contour of descending aorta, linear calcification of aortic wall, dilation of aortic arch, enlarged cardiac shadow, sparse lung markings, and so on.
2. *CT*.
   (a) Thickening of vascular wall: The typical performance of TA is centripetal thickening of vascular wall, and the thickness may be up to several millimeters. Calcification of vascular wall is another manifestation, and about 1/3 patients can have calcification of vascular wall. On plain CT scan, the density of thickened vascular wall is higher than that of lumen. Enhanced scan shows typical "double ring" sign on the vascular wall [44] (Fig. 20.14). "Double ring" sign is more common in venous stage, manifested as the inner layer showing ring-shaped slightly low enhancement, while the outer layer showing relatively high enhancement. The central low-enhancement layer may correspond to edematous intima, while the outer high-enhancement layer corresponds to active inflammatory media and adventitia. In the acute inflammatory stage, delayed enhancement can be found in the vascular wall, so delayed phase of scan is necessary for the diagnosis of Takayasu arteritis.
   (b) Change of vascular diameter: Luminal stenosis is the most common manifestation, and about 90% of patients with Takayasu arteritis has arterial luminal stenosis [44] (Fig. 20.15). Thoracic and abdominal segments

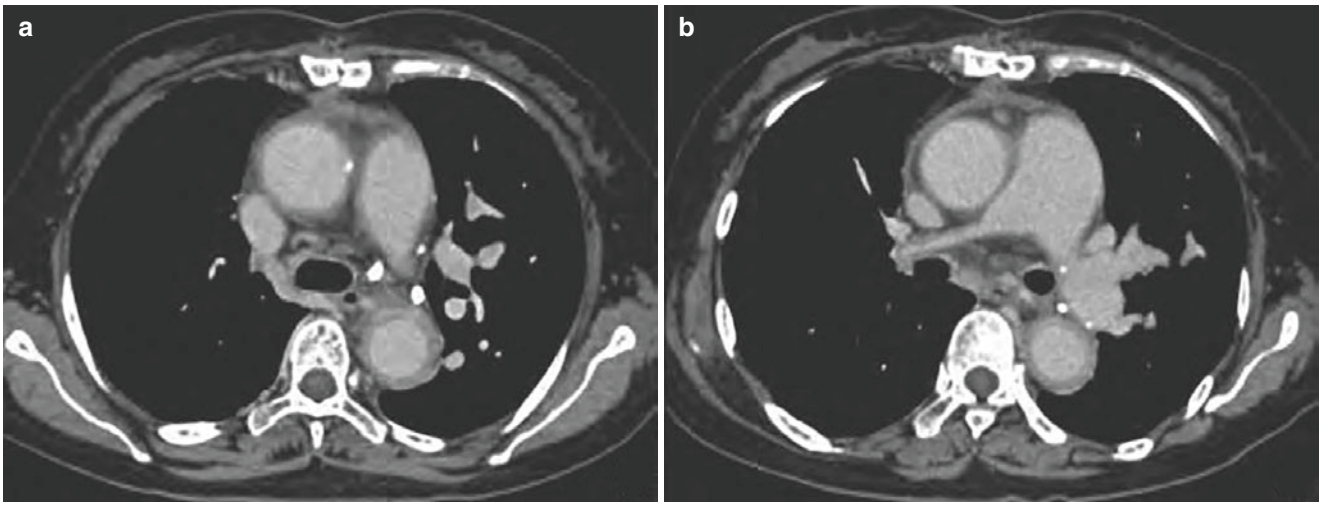

Fig. 20.14 Takayasu arteritis (I). (**a**) CT-enhanced scan in the delayed phase showed the significantly thickened arterial wall, some with calcification. "Double ring" sign was found in the wall, the inner ring was thin-line ring with low enhancement, and the outer ring was thicker with relatively high enhancement, showing delayed enhancement and (**b**) the lumen of the right pulmonary artery was significantly narrowed, with thickened wall, showing delayed enhancement

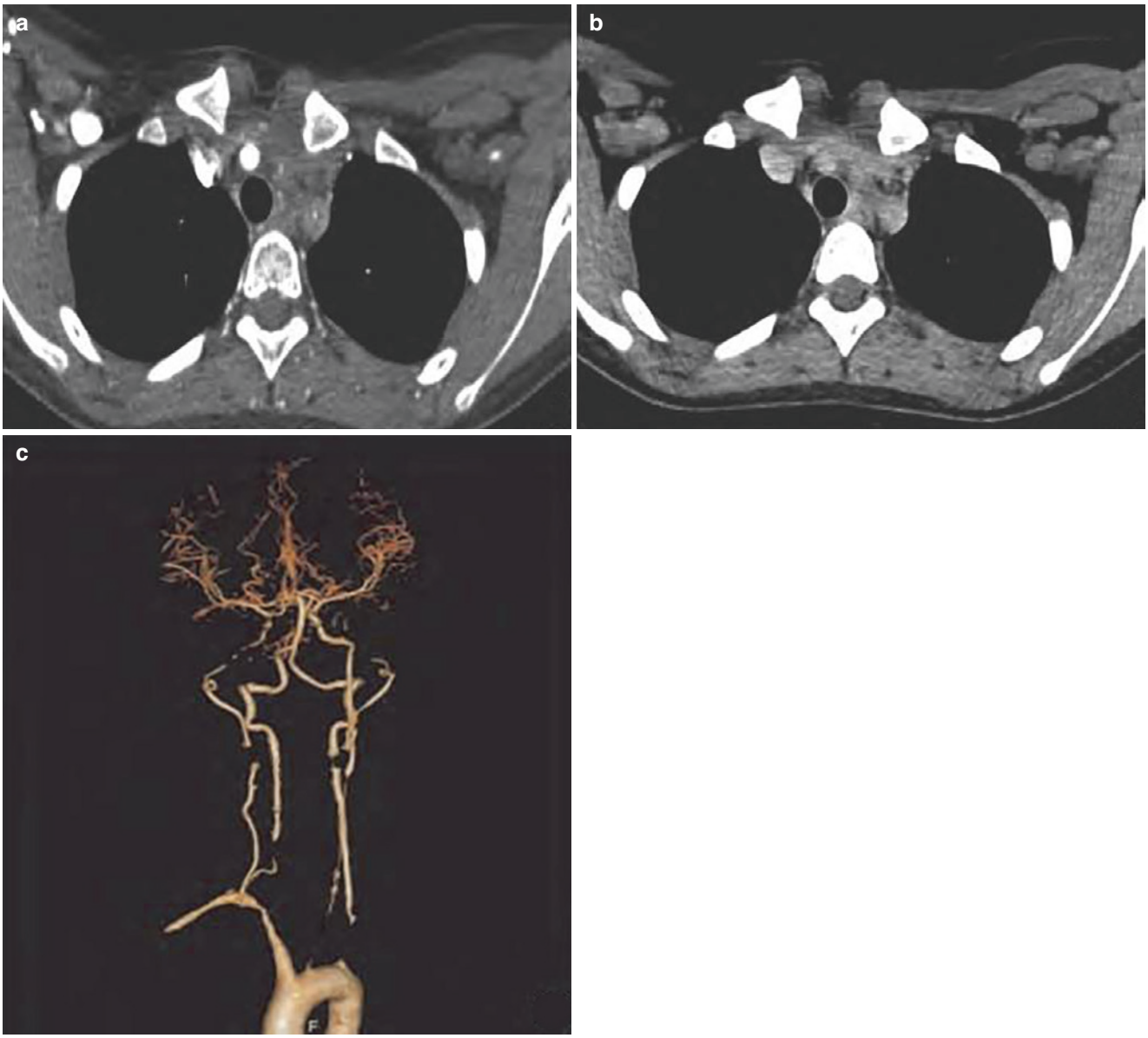

Fig. 20.15 Takayasu arteritis (II). (**a**) CT-enhanced scan in the arterial phase showed the significant circumferential thickening of the left common carotid artery wall and left subclavian artery wall; (**b**) the scan in delayed phase showed the delayed enhancement of the vascular wall; and (**c**) coronary virtual reality (VR) images showed multiple severe stenosis and occlusion of brachiocephalic trunk, right common carotid artery, right subclavian artery, left common carotid artery, left subclavian artery, and bilateral vertebral artery lumens

are the most common sites of aortic luminal stenosis. Subclavian artery, carotid artery, and renal artery are the most common stenosis sites of aortic branches. Segmental dilatation, luminal occlusion, and aneurysms can also be found, but relatively rare. Luminal dilatation and aneurysms are more common in ascending aorta and abdominal aorta, and such patients should be alert to arterial rupture. Thrombosis may occur in arterial lumen with stenosis or occlusion, and multiple collateral circulation may occur in some patients.

(c) Pulmonary artery involvement: Takayasu arteritis rarely involves pulmonary artery, usually complicated with arteritis in other sites, indicating the later stage of the disease. Pulmonary artery involvement is similar to aortic involvement, showing luminal stenosis or atresia, which mostly occurs in segmental or subsegmental arteries and rarely occurs in lobar arteries or main pulmonary arteries (Fig. 20.16). In the early stage, the vascular wall may be thickened and enhanced, while in the later stage, the vascular wall may show calcification and luminal stenosis or atresia.

3. MRI: In recent years, MRI has more application in the diagnosis of Takayasu arteritis. The most commonly used MRI sequences include fat suppression sequence T_2WI, fat suppression sequence T_1WI, enhanced T_1WI, and three-dimensional MRA. Among them, fat suppression sequence T_2WI

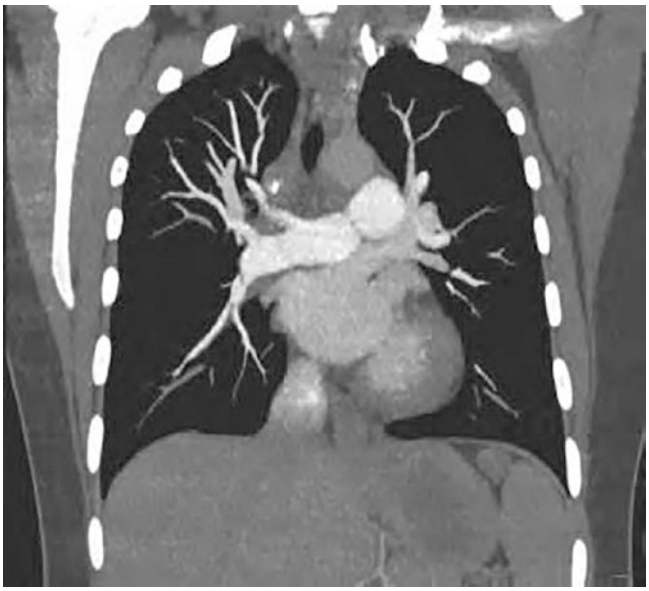

Fig. 20.16 Pulmonary artery involvement in Takayasu arteritis. Coronal CTPA MIP showed severe stenosis at the origin of the right inferior lobe artery

is used to show thickened vascular wall and edema, manifested as fat suppression sequence T_2WI. Plain scan and enhanced T_1WI are used to show the thickened vascular wall and enhancement. Three-dimensional MRA is used to show the stenosis or dilation of vascular lumen. Compared with CT, MRI is sensitive to acute lesions and can better show edema of vascular wall, with high resolution of soft tissue. In addition, MR plain scan can show thickened vascular wall and lumen stenosis or dilatation, without using contrast agent, which is more advantageous for patients with contraindication of contrast agent application.

20.6.4 Diagnostic Key Points

1. The involved blood vessels are usually large arteries, and the common involved parts are aorta and its main branches. Pulmonary arteries can be involved, but it is relatively rare.
2. The imaging manifestations are thickened vascular wall, edema, and enhancement. Lumen stenosis is common, lumen dilatation, and aneurysm is rare.
3. The diagnosis can be made according to epidemiological characteristics (more common in Asian young female patients) and clinical manifestations (blood pressure asymmetry, intermittent claudication, great vessel murmur, etc.).

20.6.5 Differential Diagnosis

1. Behcet's disease: Arteries and veins can be involved, often showing aneurysm formation, arterial stenosis, and arteriovenous thrombosis. Pulmonary aneurysm is the most common manifestation, mostly complicated with pulmonary artery thrombosis. However, TA aneurysm and arterial thrombosis are rare, veins are not involved, and pulmonary vascular involvement is relatively rare.
2. Atherosclerosis: The imaging manifestations are multiple thickened arterial walls, mostly showing uneven thickening or eccentric thickening. The density of vascular wall is uneven, with calcified plaque, mixed plaque, and atherosclerotic plaque. Atherosclerosis can involve all levels of arteries, which is common in middle-aged and elderly people. However, the thickened vascular wall in TA mostly shows uniform and circumferential thickening. Although calcification can be found, there is no atherosclerotic plaque. In addition, TA mainly involves aorta and its branches and the branches of aorta mostly start to be involved near the aorta. TA is common in young and middle-aged Asian female patients.
3. Pulmonary embolism: Patients often have a history of venous thrombosis of lower limbs and hypercoagulable state caused by various reasons. Pulmonary artery filling defect is the typical manifestation in imaging. Central filling defect can be found in the acute stage, and eccentric filling defect can be found in the chronic stage. Pulmonary artery trunk and branches can be involved, and thickened pulmonary artery wall is rare. However, pulmonary artery involvement in TA is rare, which is manifested as thickened pulmonary artery wall and corresponding segment stenosis, mostly accompanied by involvement of aorta and its branches.

20.6.6 Research Status and Progress

1. PET/CT: It is very meaningful to evaluate disease activity [45]. In the active phase, monocytes and macrophages of arterial wall uptake ^{18}F-FDG, which can show the extent and degree of inflammation. Some studies have shown the degree of inflammation and its relationship with corresponding inflammatory indexes by quantitative methods [46]. The application of new PET imaging agents can show specific inflammatory cell infiltration in vascular wall [47].
2. MRI and PET/MRI: MRI has become an important method for the diagnosis and reexamination of TA. T_1WI can provide anatomical information, T_2WI can show edema of vascular wall, and enhanced scan can show inflammatory activity of vascular wall. Thickening and delayed enhancement of arterial wall indicate disease activity. Currently, the research focus is mainly on the evaluation of inflammatory activity by MR, the optimized MRI sequence and technology, etc. In addition, PET/MRI has higher soft tissue resolution and lower radiation dose and can quantitatively measure the inflammatory response

of vascular wall, attracting more and more researchers in this study direction [48].

3. Ultrasound: More and more studies have applied contrast-enhanced ultrasound (CE-US) to help the diagnosis of TA. Enhanced ultrasound uses microbubbles as contrast agent to show the changes of blood supply, which can show the boundary of vascular lumen more clearly, while showing the enhancement of vascular wall, and its signal intensity may be related to inflammatory activity [49].

20.7 Antiglomerular Basement Membrane Antibody-Mediated Disease

Ke Wang and Yufeng Xu

20.7.1 Overview

Antiglomerular basement membrane (GBM) antibody-mediated disease is an immune-related disease caused by the emergence of antibodies against GBM lamina propria in patients. Glomerulonephritis is the main manifestation of this disease, which is often complicated with pulmonary hemorrhage. Clinical symptoms include glomerulonephritis and pulmonary hemorrhage. Without anti-GBM antibody, it is called Goodpasture syndrome. With positive anti-GBM antibody, it is called Goodpasture disease.

Anti-GBM antibody-mediated disease is rare, less than one case per million people, but the proportion of rapid progressive glomerulonephritis or crescent glomerulonephritis caused by anti-GBM antibody-mediated disease can reach 20% [50]. Among younger patients, the disease is slightly more common in men than in women, while among older patients, the number of female patients is slightly dominant. The main clinical manifestations of patients are glomerulonephritis and pulmonary hemorrhage. The disease may have occult onset and gradually progress. It may also progress rapidly, and the disease can be very severe within a few days. About 60–80% of the patients show lung and renal involvement, 20–40% of the patients show renal involvement only, and less than 10% of the patients shows pulmonary involvement only [50]. The common manifestations of pulmonary involvement are shortness of breath, cough, and hemoptysis, and iron deficiency anemia may occur in patients with long-term hemorrhage. The common manifestations of renal involvement are hematuria, proteinuria, odynuria, renal pain, hypertension, edema, and so on. Systemic symptoms are rare, mainly including fatigue, fever, arthralgia, weight loss, lack of appetite, and so on. Systemic symptoms are mostly complicated with other vasculitis.

Serological examination can detect anti-GBM antibodies in serum, and patients with high antibody titer usually have rapid disease progression. However, serological examination is not completely reliable, and the diagnosis of most cases still needs to be confirmed by renal biopsy. Renal biopsy is an important method to diagnose anti-GBM antibody-mediated diseases.

Anti-GBM antibody-mediated disease is often complicated with other vasculitis, such as granulomatosis with polyangiitis and microscopic polyvasculitis, so it is necessary to detect ANCA.

20.7.2 Pathological Manifestations

The main target of anti-GBM antibody is type IV collagen fibers. The antibody recognizes type IV collagen α-3 (IV) NC1 chain on basement membrane, activates immune response, and causes tissue damage. Anti-GBM antibody can recognize different epitopes of α-4 (IV) NC1 and α-5 (IV) NC1 in addition to α-3 (IV) NC1 chain [51]. Recognition of different epitopes may be related to the prognosis of diseases.

Typical manifestations of renal involvement: Crescent glomerulonephritis can be found in microscopic examination. Immunofluorescence analysis shows that IgG is linearly deposited along glomerular capillaries and occasionally along distal convoluted tubules.

Not all patients have pulmonary involvement. Pulmonary involvement is related to smoking, pulmonary infection, and interstitial lesions [52]. On the one hand, these injury factors may induce the expression of related epitopes; on the other hand, it may be due to the injury of alveolar capillaries that anti-GBM antibodies contact with antigens in the alveolar basement membrane.

20.7.3 Imaging Manifestations

Pulmonary involvement of anti-GBM antibody-mediated disease is manifested as diffuse alveolar hemorrhage (DAH). Chest radiographs mostly show multiple exudation shadows in both lungs, especially in inner zone and around hilum. However, a large proportion of patients with alveolar hemorrhage show negative chest radiographs, especially in the initial stage of onset, and the negative rate can reach 20–50%. Therefore, chest CT examination is important for patients with anti-GBM antibody-mediated disease.

The diagnosis of chest CT alveolar hemorrhage is related to the course of disease [53] (Fig. 20.17). Initial consolidation of the air cavity and ground-glass opacity changes are the only

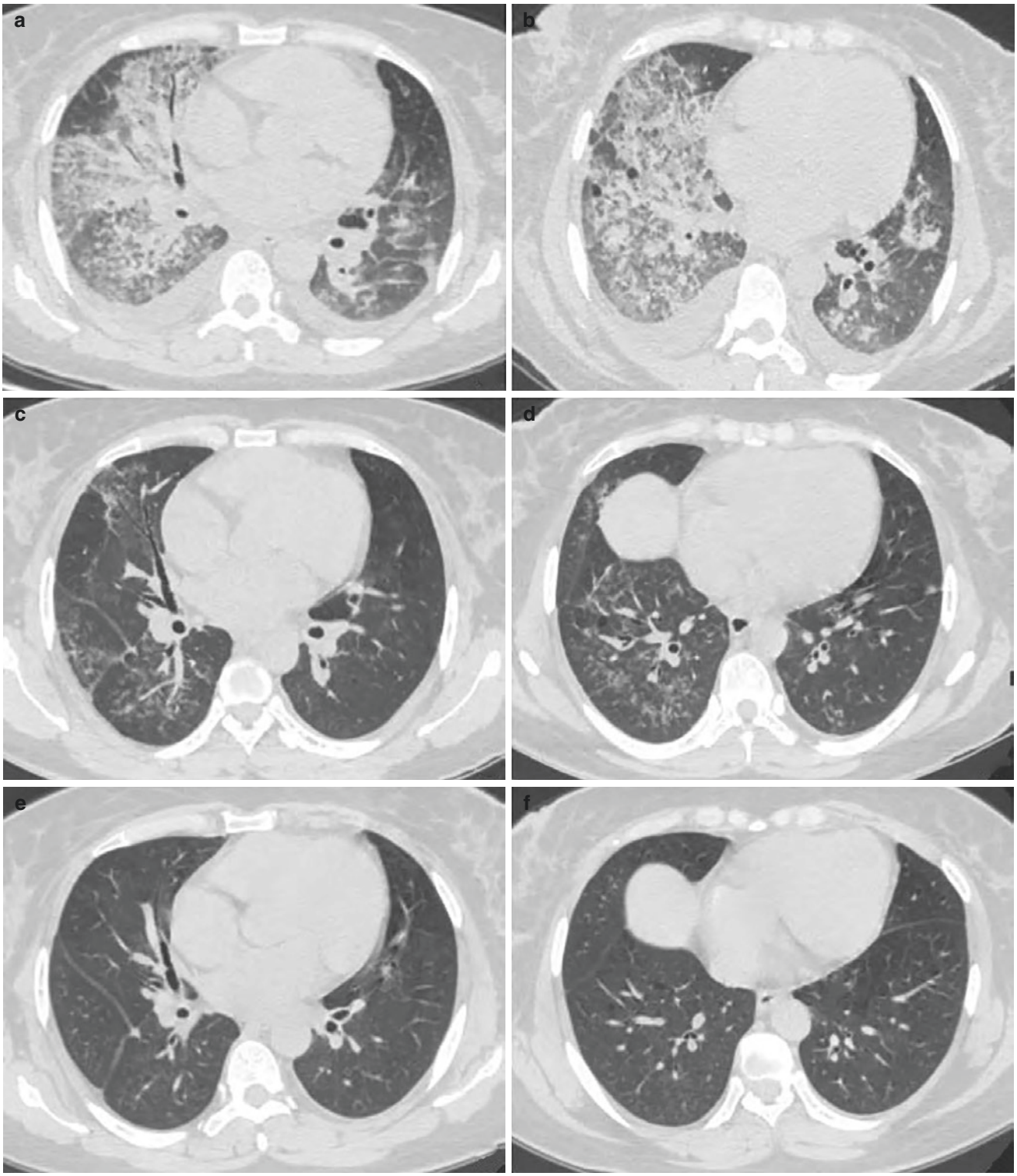

Fig. 20.17 Anti-glomerular basement membrane antibody-mediated disease. The patient, a 46-year-old female, had hemoptysis. (**a** and **b**) 3 days after the onset, CT lung window showed diffuse ground-glass opacity changes and consolidation in both lungs, accompanied by thickened interlobular septa, some of which showed "paving stone" changes, especially in the middle and inner zones of both lungs, and a small amount of pleural effusion on both sides; (**c** and **d**) 2 weeks after the onset, reexamination showed ground-glass opacity changes and consolidation mostly absorbed, a little residual stripe-like opacities and interstitial thickening; and (**e** and **f**) the lesions of both lungs disappeared 1 month after onset

manifestations, which can be manifested as multiple patchy opacities, dotted opacities, or air cavity nodules. Most of them are bilateral and symmetrically distributed, mainly in the lower lung and around the hilum, and the apex of the lung is rarely involved [54], showing gas-filled bronchi shadows. About 48 h after onset, lobules and intralobular septa gradually become thickened. Interstitial thickening can overlap with ground-glass opacity changes, and then "paving stone" changes occur. About 7–14 days after onset, consolidation, ground-glass opacity changes and interstitial thickening can gradually be absorbed. Pleural effusion may occur in some patients in the course of disease. Patients with chronic and recurrent hemorrhage may eventually develop pulmonary fibrosis.

20.7.4 Diagnostic Key Points

The diagnosis of anti-GBM antibody-mediated disease requires the detection of positive anti-GBM antibody in serum or kidney. For patients without contraindications, it is recommended to perform renal biopsy and diagnose according to the typical manifestations of renal biopsy, which prompts whether the disease is in active stage.

Chest CT examination provides evidence for pulmonary involvement of the disease. First of all, patients with pulmonary involvement often have the clinical manifestation of hemoptysis. The main imaging findings are diffuse alveolar hemorrhage. Typical manifestations are bilateral symmetrical consolidation and ground-glass opacity changes with involvement of lower lung and inner zone. The lesions can be absorbed in 7–14 days.

20.7.5 Differential Diagnosis

Chest CT diagnosis and differential diagnosis of anti-GBM antibody-mediated diseases should include the following two aspects. First of all, diffuse alveolar hemorrhage should be identified and diagnosed on CT. After that, the etiology of alveolar hemorrhage should be analyzed.

1. Diffuse alveolar hemorrhage: Different imaging manifestations of diffuse alveolar hemorrhage require different differential diagnosis. Ground-glass opacity changes should be differentiated from pulmonary edema, infection, and tumor. Centrilobular nodules should be differentiated from infection, tumor, hypersensitivity pneumonitis, interstitial lesions, and edema. Thickening of interlobular septum should be distinguished from edema, pulmonary interstitial disease, proliferative, or neoplastic lesions of lymphatic system. The most common and confusing ones are pulmonary edema and pulmonary infection.
   (a) Pulmonary edema: It is also often manifested as ground-glass opacity changes, consolidation, and interlobular septal thickening. The ground-glass opacity changes and consolidation of pulmonary edema are generally distributed along gravity. In addition, cardiac pulmonary edema usually shows cardiac enlargement and pleural effusion, but these two manifestations are rare in diffuse alveolar hemorrhage. Pulmonary edema has rapid onset and regression and can significantly progress/subside in 1–3 days. The duration of diffuse alveolar hemorrhage is relatively long, and the absorption period is 7–14 days.
   (b) Lobular pneumonia: It is often manifested as ground-glass opacity changes, patchy consolidation, and centrilobular nodules, which overlap with diffuse alveolar hemorrhage, and viral infection is the most common. Pulmonary infection is mainly unilateral, and both lungs can be involved, but most of the lesions are asymmetric. However, diffuse alveolar hemorrhage generally causes bilateral involvement, mostly with diffuse and relatively symmetrical distribution. Pulmonary infection is often accompanied by thickened adjacent bronchial wall, which is rare in diffuse alveolar hemorrhage. The absorption of pulmonary infection is slightly slower than that of diffuse alveolar hemorrhage.
2. Etiology identification: Vasculitis, autoimmune diseases, drugs, idiopathic pulmonary hemosiderosis, etc. can cause diffuse alveolar hemorrhage. Differential diagnosis is mainly based on other imaging manifestations and clinical manifestations of the chest. Pulmonary involvement of anti-GBM antibody disease has less other manifestations except alveolar hemorrhage. The typical clinical manifestation is pulmonary hemorrhage-nephritis syndrome. Other common diseases mostly have other lung manifestations and other multisystem involvement.
   (a) Granulomatosis with polyangiitis: Lower airway involvement is common. Multiple nodules are common in the lungs, which can be accompanied by necrotic cavities.
   (b) Lupus erythematosus: Pleural effusion and pericardial effusion are common, and respiratory muscles are involved in severe cases.
   (c) Churg–Strauss syndrome: Pulmonary lesions are mostly migratory and distributed in the periphery.
   (d) Drugs: The anticoagulant effect of drugs and thrombocytopenia induced by drugs are the most common causes, and the lesion degree is milder than that of anti-GBM antibody, often complicated with symptoms of hemorrhage in other parts.

20.7.6 Research Status and Progress

The studies of anti-GBM antibody-mediated disease mostly focus on the pathogenesis rather than the traditional imaging technology research, and most of them are case reports.

In recent years, texture analysis has been used to diagnose and differentiate diffuse alveolar hemorrhage. Kloth et al. used CT texture analysis to differentiate and diagnose viral interstitial pneumonia, Pneumocystis jirovecii pneumonia, and diffuse alveolar hemorrhage in the early stage of the disease, which are all manifested as ground-glass opacity changes with interstitial lesions [55]. The application of texture analysis or radiomics in disease diagnosis may be a development trend in the future.

20.8 Idiopathic Pulmonary Hemosiderosis

Ke Wang and Yufeng Xu

20.8.1 Overview

Idiopathic pulmonary hemosiderosis (IPH) is a rare disease, common in children, characterized by recurrent diffuse alveolar hemorrhage. Idiopathic pulmonary hemosiderosis can be diagnosed after excluding other possible causes of alveolar hemorrhage. In patients with idiopathic pulmonary hemosiderosis, long-term repeated alveolar hemorrhage can eventually lead to hemosiderin deposition and pulmonary fibrosis.

Idiopathic pulmonary hemosiderosis can occur at any age, but 80% cases occur in children and usually occur before the age of 10 years. For adults, the onset age is mostly 20–40 years.

The clinical manifestations of idiopathic pulmonary hemosiderosis are related to the course of the disease. Acute onset may be characterized by acute hemoptysis and dyspnea, while chronic onset may be characterized by fatigue, anemia, and progressive exertional dyspnea. Sometimes anemia may be the only manifestation. Dyspnea, cough, and hemoptysis are common in children. Fever is also a common manifestation. Long-term anemia may affect the growth and development of children, and some patients may have liver and spleen enlargement. For adults, hemoptysis, exertional dyspnea, and fatigue are more prominent symptoms and acropachia may occur in some patients. The simultaneous occurrence of both idiopathic pulmonary hemosiderosis and celiac disease is called Lane–Hamilton syndrome, which may be related to the autoimmune response to milk.

The exact etiology of idiopathic pulmonary hemosiderosis is still unknown. At present, it is thought to be related to autoimmunity. Immune complexes are found in plasma of some patients, and most patients have other autoimmune diseases within 10 years after onset. In addition, it may be related to genetic factors, environmental exposure (such as secondhand smoking, fungi, etc.), and Down syndrome.

20.8.2 Pathological Manifestations

The lung tissue of idiopathic pulmonary hemosiderosis during acute alveolar hemorrhage usually shows that the alveolar cavity is filled with blood, accompanied by free hemosiderin and macrophages containing hemosiderin. Prussian blue staining is used to show hemosiderin in and around alveolar macrophages. Idiopathic pulmonary hemosiderosis may cause thickened alveolar septa and type II pulmonary cell hyperplasia.

In the advanced stage of the disease, due to the deposition of hemosiderin and different degrees of fibrosis and consolidation, the lungs show brown appearance in general pathology. Pulmonary interstitial fibrosis and collagen deposition are the pathological features in the chronic stage.

Idiopathic pulmonary hemosiderosis has no histological or immunohistochemical evidence of capillary inflammation, compared with other alveolar hemorrhage-related diseases, such as granulomatosis with polyangiitis, microscopic polyvasculitis, and systemic lupus erythematosus. In idiopathic pulmonary hemosiderosis, there was no neutrophils and nuclear dust infiltration in alveolar septa and immunofluorescence staining shows no immune complex in lung tissue.

20.8.3 Imaging Manifestations

The imaging manifestation of idiopathic pulmonary hemosiderosis is diffuse alveolar hemorrhage. In the acute stage, chest CT shows consolidation of air cavity and ground-glass opacity changes, which can be patchy and dotted, or manifested as multiple air cavity nodules, mostly with bilateral distribution (Fig. 20.18). Consolidation may occur, mainly around the lower lungs and hilum, and lung apex involvement is rare. Gas-filled bronchi shadows can be found, suggesting that alveoli are full of blood. During the gradual absorption of consolidation, the lobules and interlobular septa become gradually thickened, and the thickening of interstitium can overlap with the ground glass-like density change, followed by the “paving stone” changes. Pleural effusion may occur in some patients in the course of disease. Chronic and repeated hemorrhage may eventually lead to pulmonary fibrosis.

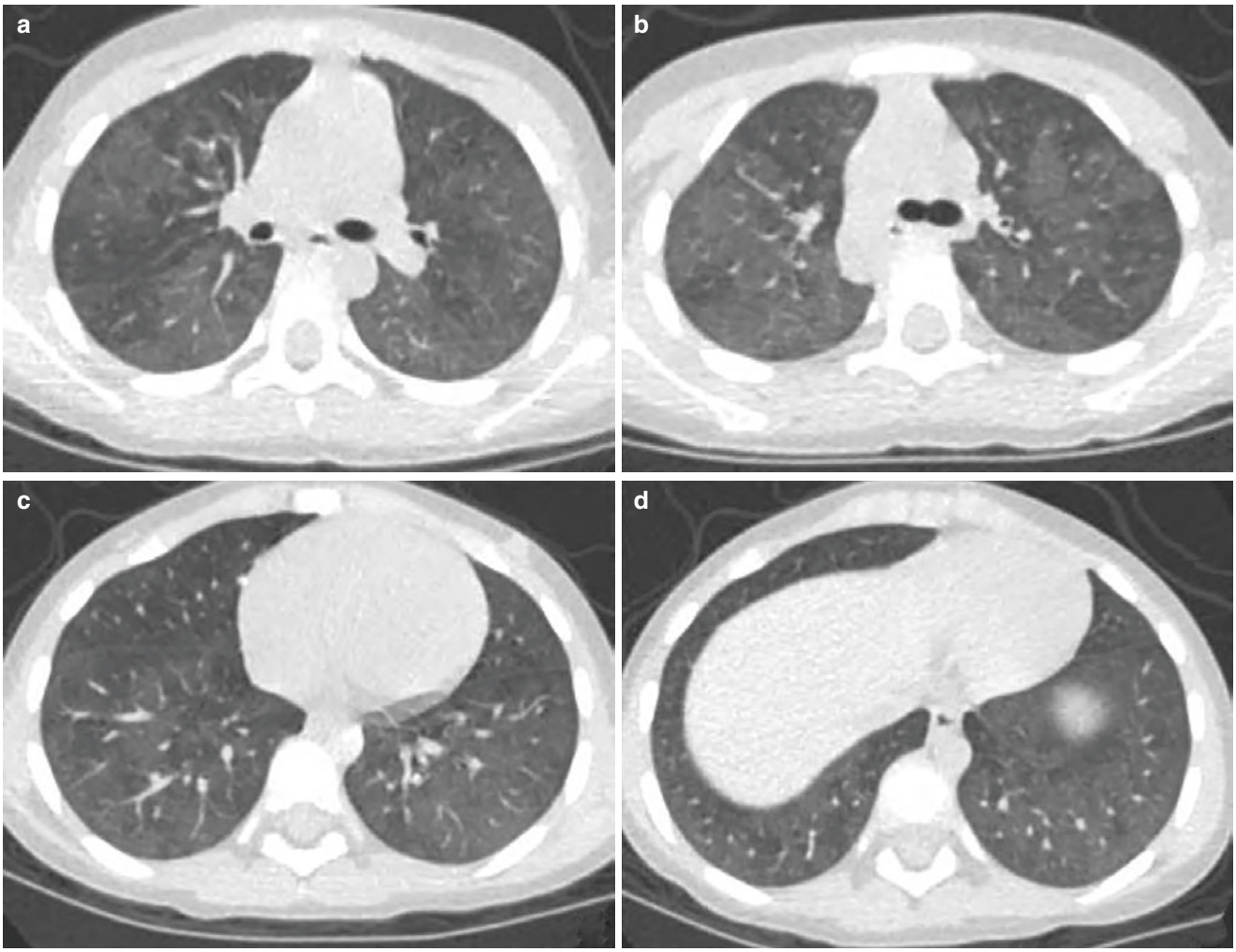

Fig. 20.18 Idiopathic pulmonary hemosiderosis. The children patient is a 3-year-old female. (**a**–**d**) CT lung window showed diffuse patchy ground-glass opacity changes in both lungs, with centrilobular nodules and mild interstitial thickening in some areas

20.8.4 Diagnostic Key Points

The diagnosis of idiopathic pulmonary hemosiderosis is exclusive. For patients with alveolar hemorrhage, the disease can be diagnosed as idiopathic pulmonary hemosiderosis after excluding other factors. Therefore, the diagnosis of idiopathic pulmonary hemosiderosis includes two aspects: first diagnosis of alveolar hemorrhage and then etiological diagnosis.

1. Diagnosis basis of alveolar hemorrhage: Patients have typical clinical manifestations such as hemoptysis, cough, and dyspnea. CT shows multiple ground-glass opacity changes and consolidation in both lungs, especially in the middle and inner zones. Interstitial thickening may occur over time. Iron deficiency anemia occurs. Macrophages containing hemosiderin are found in bronchoalveolar lavage fluid or biopsy specimens.
2. Except for other causes of alveolar hemorrhage: Vasculitis, connective tissue diseases, infection, drugs or poisons, blood system diseases, etc. are common causes of alveolar hemorrhage, especially for the diagnosis of adult idiopathic pulmonary hemosiderosis. Serological examination, biopsy, and other techniques should be used to exclude the possibility of alveolar hemorrhage caused by other secondary factors.
3. This disease is common in children, and some cases can be complicated with celiac disease.

20.8.5 Differential Diagnosis

This disease should mainly be differentiated from other alveolar hemorrhage-related diseases, including vasculitis, autoimmune diseases, drug side effects, etc. [56]. Differential diagnosis is mainly based on other imaging manifestations

and clinical symptoms of the chest. Idiopathic pulmonary hemosiderosis is common in children. Alveolar hemorrhage, iron deficiency anemia, and fever are common symptoms. According to literature, some cases may be complicated with celiac disease, but there are no other systems involved [57].

1. Anti-GBM antibody-mediated disease: It is manifested as pulmonary hemorrhage-nephritis syndrome and alveolar hemorrhage, which is difficult to distinguish from idiopathic pulmonary hemosiderosis according to chest imaging manifestations alone. However, idiopathic pulmonary hemosiderosis has no renal involvement, with negative anti-GBM antibody, which is common in children.
2. Granulomatosis with polyangiitis and microscopic polyvasculitis: Multiple nodules and cavities are common in the lungs of granulomatosis with polyangiitis, and alveolar hemorrhage and interstitial lesions are common in microscopic polyvasculitis. Granulomatosis with polyangiitis and microscopic polyvasculitis are ANCA-related systemic vasculitis, while idiopathic pulmonary hemosiderosis features negative ANCA.
3. Churg–Strauss syndrome: Asthma is common in clinical practice. Besides airway involvement, ground-glass opacity changes often occur in pulmonary lesions, which are mostly migratory and distributed in the periphery.
4. Drug side effects: The anticoagulant effect of drugs and drug-induced thrombocytopenia are the most common causes, and such cases are often complicated with symptoms of hemorrhage in other parts.

20.8.6 Research Status and Progress

In recent years, most of the researches on idiopathic pulmonary hemosiderosis focus on pathogenesis, early diagnosis, and treatment. Studies have shown that the occurrence of idiopathic pulmonary hemosiderosis is related to Down syndrome [58]. More evidence of immune-mediated mechanism has also been found [59].

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