Eosinophilic Lung Disease

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Eosinophilic lung disease (ELD) is a group of heterogeneous clinical diseases characterized by eosinophilia in airway and (or) lung parenchyma, with or without eosinophilia in peripheral blood [1]. ELD is not an independent disease, and its diagnostic criteria are as follows: ① chest radiographs show eosinophilia in peripheral blood or CT shows abnormal lung manifestations; ② eosinophilia in lung tissue is confirmed by lung biopsy; and ③ eosinophilia is found in bronchoalveolar lavage fluid (BALF) [1, 2]. At present, there is no uniform standard for clinical classification of ELD, which can be divided into ELD with unknown etiology and ELD with known etiology and eosinophilic vasculitis (eosinophilic granulomatous polyangiitis) (see Sect. 20.3 of Chap. 20 for details). ELD with known etiology includes airway diseases (such as bronchial asthma, allergic bronchopulmonary aspergillosis, and bronchial central granuloma), autoimmune diseases, parasitic infection, drug-induced eosinophilic pneumonia, and so on. ELD with unknown etiology is idiopathic ELD, including simple eosinophilia, acute eosinophil pneumonia, chronic eosinophil pneumonia, and eosinophil syndrome [1–4].

29.1 Simple Pulmonary Eosinophilia

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29.1.1 Overview

Simple pulmonal eosinophilia (SPE) was first reported by Loeffler in 1932, so it is also called Loeffler syndrome. It is characterized by eosinophilia in blood, transient and focal lung consolidation on X-ray radiograph or CT. The course of the disease is 2–4 weeks, and the abnormal changes in imaging often disappear within 1 month.

Simple pulmonary eosinophilia can be asymptomatic and is occasionally found during X-ray examination. If there are symptoms, they are mild. The most common symptoms are cough with a small amount of sticky sputum or a small amount of lemon-colored sputum, occasionally with blood in sputum. Eosinophils can be found in sputum. In addition, other manifestations include headache, fatigue, catarrhal symptoms of upper respiratory tract, night sweats, chest pain, etc. Generally, there is no fever. If fever occurs, it is low fever. Clinical physical examination may have no signs. A small amount of dry and moist rales can rarely be heard, occasionally with percussion dullness. Symptoms and signs often disappear in a short time, rarely exceeding 2 weeks. The total number of leukocytes is normal or slightly to moderately increased, the proportion of eosinophils in blood is increased to 10–70% [2], eosinophils in sputum and bronchoalveolar lavage fluid (BALF) are increased, and IgE and IgM in blood are higher than the normal value. It should be noted that transient migratory consolidation and pulmonary eosinophil infiltration are often secondary to parasitic infection and drug reaction, while simple pulmonary eosinophilia is limited to cases with unknown etiology.

29.1.2 Pathological Manifestations

The main pathological changes are eosinophil accumulation and edema in alveolar septa and interstitial tissue, mainly involving the peripheral areas of middle lung and upper lung.

29.1.3 Imaging Manifestations

1. X-ray: Manifestations include transient and migratory patchy consolidation, and the lesions show no pulmonary

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segmental distribution but can be multiple or single lesions, with blurred edges, mostly distributed in the surrounding lung fields, and dissipate spontaneously within 1 month.

2. CT: Main manifestations are patchy lung consolidation and ground-glass opacities, which are also transient and migratory, mainly involving the periphery of the middle and upper lobes of both lungs (Fig. 29.1). Sometimes, manifestations include pulmonary nodules surrounded by ground-glass opacities [4, 5].

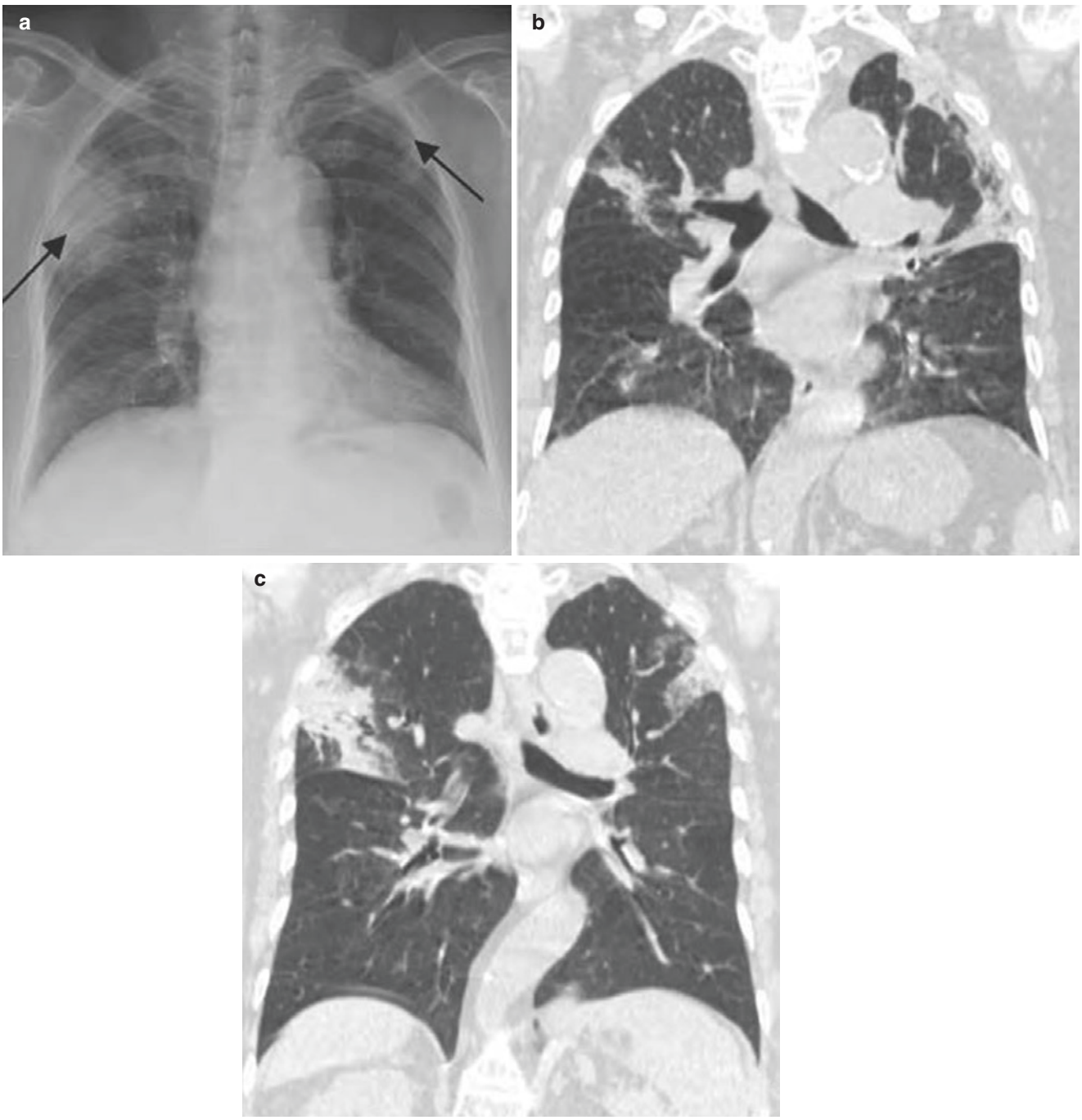

Fig. 29.1 Simple pulmonary eosinophilia. (**a** and **b**) Anterior position chest radiograph (**a**) and CT lung window (**b**) showed patchy consolidation of upper lobes of both lungs (arrow); (**c**) 1 week later, reexamination showed the consolidation of the upper lobe of the right lung significantly reduced and the new patchy consolidation of the upper lobe of the left lung, suggesting transient and migratory consolidation of the lung

29.1.4 Diagnostic Key Points

1. The clinical manifestations are mild, with eosinophilia in peripheral blood.
2. Chest radiograph or CT shows transient and migratory pulmonary consolidation distributed in periphery, and the lesions dissipate spontaneously within 1 month.
3. Clinically, parasitic infections and drug reactions need to be excluded.

29.1.5 Differential Diagnosis

1. Lung consolidation: It has no specificity on a single image. It is common in lung infection, pulmonary hemorrhage, pulmonary edema, etc. Transient and migratory consolidation areas can be found in a series of chest radiographs, which need to be differentiated from pulmonary hemorrhage and vasculitis. Mild clinical symptoms and eosinophilia in blood are helpful for the diagnosis of simple pulmonary eosinophilia.
2. Eosinophilic pneumonia with known etiology: Parasitic infection or drugs often cause transient and migratory eosinophilic pneumonia, which needs to be differentiated in combination with clinical history.
3. Chronic eosinophilic pneumonia: Simple pulmonary eosinophilia has mild clinical symptoms and shorter course of disease less than 4 weeks, while chronic eosinophilic pneumonia has severe clinical symptoms and longer course of disease.

29.1.6 Research Status and Progress

Tissue biopsy is the gold standard for the diagnosis of ELD, but it is not a routine diagnostic method at present because of the significant trauma of surgical lung biopsy, and it is mainly suitable for patients with atypical clinical manifestations and difficulty in diagnosis through comprehensive examinations such as alveolar lavage fluid examination. Detection of the content of eosinophils in alveolar lavage fluid is currently recognized as a diagnostic method. Under normal circumstances, the content of eosinophils in alveolar lavage fluid does not exceed 1%. If exceeding 5%, the disease is defined as eosinophilia but cases with 5–25% content are often nonspecific and can also be found in other interstitial lung diseases (such as idiopathic pulmonary fibrosis) besides ELD. Eosinophil count in peripheral blood is the most commonly used serological index in the diagnosis of ELD, and the absolute value of eosinophils is mostly used. Usually, the absolute value count (0.5–1.5) × 10^9/L is defined as mild increase, (1.5–5.0) × 10^9/L defined as moderate increase, and over 5.0 × 10^9/L defined as severe increase. Some scholars have suggested that the threshold value of eosinophil count in the peripheral blood for the diagnosis of ELD is >1 × 10^9/L, the threshold value of eosinophils in alveolar lavage fluid is >25%, and the diagnostic standard of alveolar lavage fluid for chronic eosinophilic pneumonia is >40% [6]. However, some acute eosinophil pneumonia may not be accompanied by increased eosinophils in peripheral blood in the early stage. Therefore, patients suspected of this disease should be examined with alveolar lavage fluid to make a definite diagnosis.

29.2 Acute Eosinophilic Pneumonia

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29.2.1 Overview

Acute eosinophilic pneumonia (AEP) is an acute febrile disease with rapidly progressed shortness of breath and hypoxic respiratory failure. Diagnosis is based on acute respiratory failure and significantly increased eosinophils in alveolar lavage fluid, but peripheral blood eosinophils may not increase in the early stage, and eosinophils may increase in the later stage of the disease [7].

AEP has no gender difference and may occur at all ages, but it is more common in young people. Most cases are idiopathic, and a few are caused by infection, drugs, or smoke inhalation, especially cigarette smoke inhalation. Typical clinical manifestations include fever and rapidly aggravated dyspnea, and some patients may have chest pain and muscle pain [5]. AEP is characterized by acute fever and respiratory failure. Misdiagnosis and inappropriate treatment can lead to high morbidity and mortality. However, AEP responds quickly to corticosteroid therapy, without recurrence. Through appropriate and timely treatment, the survival rate is close to 100% [8].

29.2.2 Pathological Manifestations

The histopathological features of AEP include massive eosinophil infiltration, acute diffuse alveolar damage (DAD), exudation and edema in alveolar space, hyaline membrane formation, but usually without granuloma and alveolar hemorrhage.

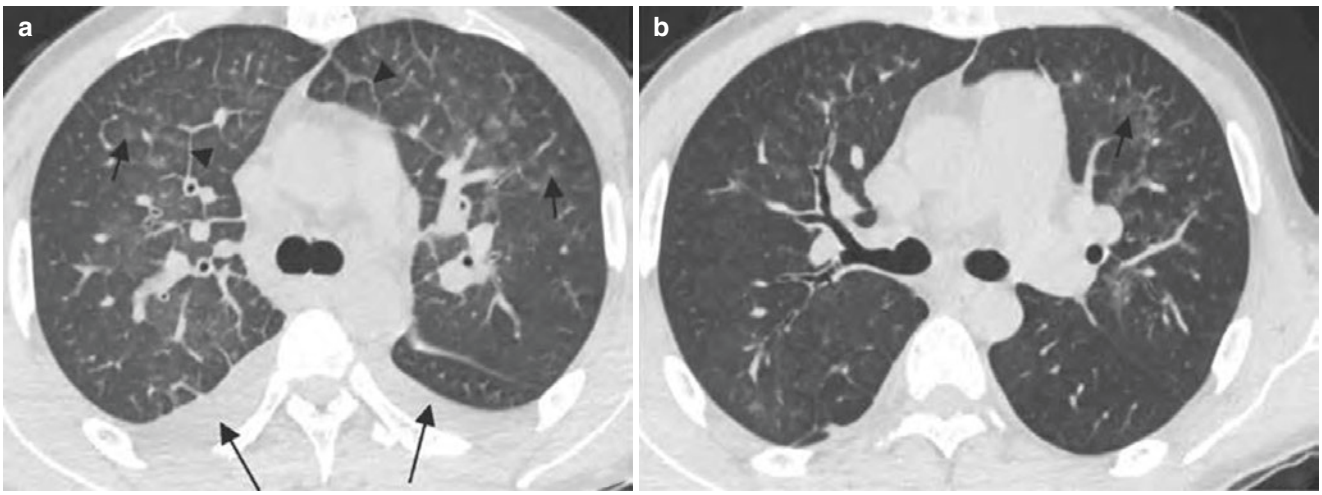

Fig. 29.2 Acute eosinophilic pneumonia. (**a** and **b**) CT lung window showed scattered patchy ground-glass opacities in both lungs (short arrow), smoothly thickened interlobular septa (tailless arrow), and a small amount of pleural effusion (long arrow)

29.2.3 Imaging Manifestations

1. X-ray: Manifestations are similar to those of venous pulmonary edema, showing diffuse reticular opacities and septal thickening (Kerley B line) in both lungs in the early stage, which further develop into diffuse pulmonary consolidation in both lungs, with pleural effusion in most patients.
2. CT: Diffuse ground-glass opacities and a small amount of consolidation in both lungs, smoothly thickened interlobular septa and a small amount of pleural effusion (Fig. 29.2). Ground-glass opacities and consolidation in most patients are randomly distributed, which is different from that of chronic eosinophilic pneumonia, rarely showing peripheral distribution [4, 6, 9].

29.2.4 Diagnostic Key Points

1. Typical manifestations are rapid progression of fever and dyspnea.
2. A large number of eosinophils (>25%) can be found in the alveolar lavage fluid.
3. X-ray chest radiograph or CT shows diffuse ground-glass opacities or consolidation of both lungs, smoothly thickened interlobular septa and a small amount of pleural effusion.
4. Hormone therapy is effective.

29.2.5 Differential Diagnosis

1. Cardiogenic pulmonary edema: It has similar imaging manifestations. Cardiogenic pulmonary edema is often accompanied by cardiac enlargement. The distribution of pulmonary edema is more influenced by gravity, which is different from AEP distribution.
2. Acute interstitial pneumonia (AIP): The imaging findings of early AIP are similar to those of diffuse alveolar damage, but the later AIP is often accompanied by lung structural destruction and fibrosis.
3. Diffuse alveolar hemorrhage: Diffuse ground-glass lesions can be found in both lungs, similar to AEP imaging, but generally not accompanied by pleural effusion. Clinical manifestations are different from those of AEP. Alveolar hemorrhage is often accompanied by nephropathy and hemoptysis.
4. Other types of eosinophil lung disease: Secondary eosinophil lung disease, caused by other factors such as drug damage or parasitic infection, needs to be excluded. Common drugs causing eosinophil lung disease include amiodarone, antidepressants, β-blockers, bleomycin, cocaine, sulfasalazine, etc. Eosinophil pneumonia caused by drugs is similar to chronic eosinophil pneumonia, and consolidation and ground-glass changes of both lungs tend to be distributed in the peripheral areas and the upper lungs. Chronic eosinophilic pneumonia has a long course of disease, and its pulmonary manifestations are mainly distributed in the peripheral areas and the upper lungs.

29.3 Chronic Eosinophilic Pneumonia

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29.3.1 Overview

Chronic eosinophilic pneumonia (CEP) is an idiopathic disease characterized by a large amount of mixed inflammatory exudate containing eosinophils in the alveolar space. The exact incidence and prevalence of CEP are still unclear, and it is more common in females, and the prevalence rate of females is twice that of males. Most of them are nonsmoking patients, and the disease may occur at all ages. The peak age of the disease is over 50 years, and the disease rarely occurs in children [10, 11]. Patients often have a history of asthma and allergic rhinitis. The disease has gradual onset, and the symptoms often last for at least 1 month before diagnosis. Typical symptoms include dry cough, shortness of breath, often accompanied by fever, weight loss, and lethargy. CEP usually has no obvious extrapulmonary infiltration.

CEP patients always have eosinophilia in alveolar lavage fluid and peripheral blood, and the proportion of eosinophils in alveolar lavage fluid is usually very high, sometimes reaching more than 40% [11].

The clinical manifestations of CEP lack specificity, such as "pneumonia" with poor anti-infection effect for a long time and "asthma" with poor response to inhaled glucocorticoid. If chest CT shows pulmonary shadows and increased eosinophils in peripheral blood, the possibility of CEP should be considered and further alveolar lavage fluid examination and lung biopsy should be performed to confirm eosinophil infiltration in the lung. In addition, known etiology and systemic diseases should be excluded before the diagnosis of CEP.

29.3.2 Pathological Manifestations

The pathogenesis of CEP is still not fully understood, and the aggregation and activation of eosinophils in lung are the key to cause lung damage. The histopathology of CEP was characterized by a high proportion of inflammatory exudation of eosinophils filling the alveolar space. Interstitial inflammatory cell infiltration usually also occurs in interstitium, but fibrosis is mild. Eosinophils and other inflammatory cell infiltration may also occur in the pulmonary vascular wall, but it is not accompanied by necrosis and thrombosis.

29.3.3 Imaging Manifestations

1. X-ray: The main manifestation is consolidation with the non-lung segmental distribution of both lungs, especially in upper lungs and periphery, which is called "reversed pulmonary edema" sign [12].
2. CT: The imaging features of typical CEP include patchy consolidation and ground-glass opacities distributed in the upper lobes and periphery of both lungs, and sometimes consolidation can be manifested as patchy masses with unclear edges. The lesions may be accompanied by interlobular septal thickening, showing "paving stone" sign (Fig. 29.3) [12–14]. A few cases may be accompanied by a small amount of pleural effusion and slightly enlarged lymph nodes in mediastinum. Cavities and emphysema are rare. Hormone therapy has a good effect on CEP, and the lesions can be absorbed 7–10 days after hormone therapy, but may recur.

29.3.4 Diagnostic Key Points

1. The onset is subacute or chronic, and half of the patients have a history of allergy and/or asthma.
2. Eosinophils in peripheral blood and alveolar lavage fluid are increased significantly.
3. Typical X-ray and CT findings are patchy consolidation and ground-glass opacities distributed around the upper lobes of both lungs.
4. Hormone therapy is effective.

29.3.5 Differential Diagnosis

1. Cryptogenic organizing pneumonia (COP): COP is also manifested as subpleural patchy consolidation, which was similar to CEP in imaging, but COP tends to be distributed in lower lung. Nodules, reticular opacities, bronchiectasis, and consolidation around bronchovascular bundles are more common in COP. COP has no eosinophilia in peripheral blood and alveolar lavage fluid.
2. Other types of eosinophilic lung disease: The clinical manifestations of simple pulmonary eosinophilia are often mild and self-limiting, and consolidation in the lungs is mostly transient. CSS patients often have systemic manifestations, such as lesions of skin and peripheral nervous system.

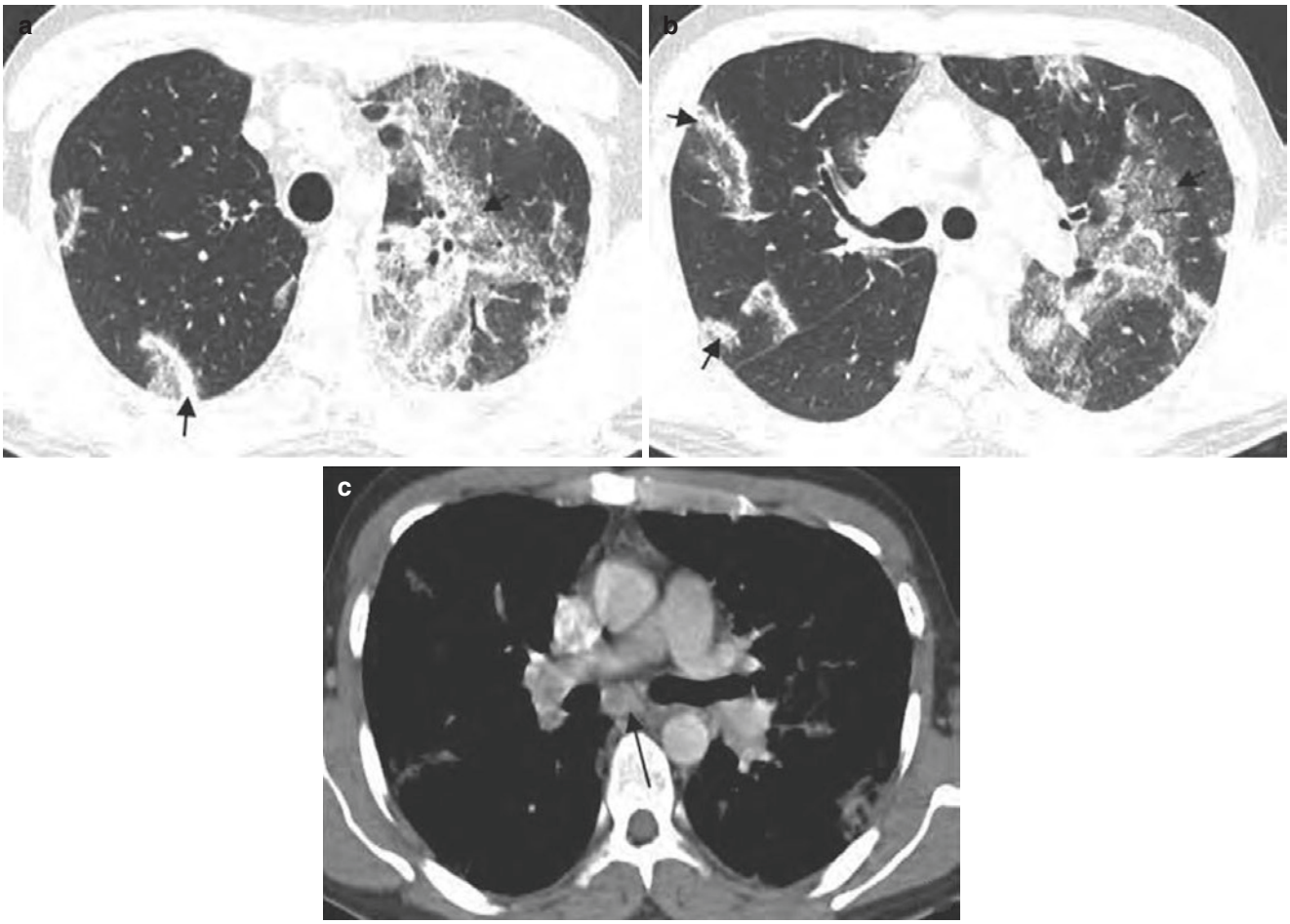

Fig. 29.3 Chronic eosinophilic pneumonia. (**a** and **b**) CT lung window showed scattered patchy ground-glass opacities and consolidation (arrow) in both lungs, especially in the upper lungs and (**c**) CT mediastinal window showed enlarged lymph nodes (arrow)

3. Pulmonary infection: CEP may be confused with pulmonary consolidation caused by infection in clinical practice, with a chronic course. The characteristics of eosinophilia in peripheral blood and pulmonary consolidation distributed in peripheral imaging are helpful to distinguish CEP from pulmonary infection.

29.4 Hypereosinophilic Syndrome

Mingming Ma and Yufeng Xu

29.4.1 Overview

Hypereosinophilic syndrome (HES) is a group of diseases with the main clinical manifestations of persistent eosinophilia in peripheral blood accompanied by organ damage or dysfunction caused by eosinophilic infiltration in tissues. Chusid et al. put forward the diagnostic criteria of HES for the first time in 1975: ① eosinophil count in peripheral blood >1.5 × 10^9/L lasting for more than 6 months; ② other causes of eosinophilia excluded; and ③ manifestation of multisystem and multiorgan damage [15]. The expert group of the 2011 Working Conference on Eosinophil Disorders and Syndromes updated the diagnostic criteria of HES as follows [16]: ① the eosinophil count in peripheral blood >1.5 × 10^9/L after two examinations (the interval more than 1 month), with or without tissue HE [definition of tissue HE: bone marrow eosinophils are more than 20% of all nucleated cells, and/or pathologists have confirmed extensive tissue infiltration of eosinophils and/or obvious eosinophil granule protein deposition, with or without eosinophil tissue infiltration]; ② high numbers of eosinophils have caused organ damage; and ③ other diseases causing organ damage have been excluded.

HES may occur at any age, mostly from 20 to 50 years, more common in males than in females [17]. Eosinophilia in HES can involve many organs and systems, and the common involved organs or systems are heart, skin, nerve, lung, and spleen [18, 19]. Because of the different organs and degrees of involvement, the clinical manifestations of patients are

also diversified. The main clinical manifestations of HES include fever, fatigue, loss of appetite, night sweat, weight loss, and other systemic symptoms. Skin abnormalities such as eczema, maculopapule, erythroderma, pruritus, and angioedema. Cardiac involvement is the main cause of death in HES patients, which can cause myocarditis, cardiomyopathy, valve disorder, and cardiovascular thrombosis. Respiratory system involvement is mainly manifested as cough, chest pain, shortness of breath, pleural effusion, etc. Some cases may have lung infarction.

29.4.2 Pathological Manifestations

The histopathological features of HES were eosinophil infiltration in lung. Eosinophil infiltration in the wall of pulmonary arterioles and occlusion of related vessels cause pulmonary infarction, and fibrosis may occur.

29.4.3 Imaging Manifestations

1. X-ray: The manifestation is nonspecific, and the initial manifestation is transient blurred opacities and consolidation. Cardiac enlargement, pulmonary edema, and pleural effusion can occur in cardiac involvement.
2. CT: The findings on CT include small nodules and patchy ground-glass opacities. The most common CT findings are bilateral ground-glass opacities, with or without consolidation (Fig. 29.4). Other manifestations include multiple small nodules with diameters ranging from several millimeters to 1 cm. Most nodules can show "halo" sign, usually distributed in peripheral areas [20]. Some cases may be accompanied by pleural effusion.

29.4.4 Diagnostic Key Points

1. The eosinophil count in peripheral blood >1.5 × 10^9/L after two examinations (interval more than 1 month).
2. Symptoms of lung involvement, such as cough, wheezing, shortness of breath, etc.
3. X-ray chest radiograph shows blurred opacities and patchy consolidation, while CT shows patchy ground-glass opacities and small nodules.
4. Cardiac involvement in patients may be manifested as enlarged cardiac shadow and pleural effusion.

29.4.5 Differential Diagnosis

1. Eosinophilic pneumonia: It is manifested as eosinophilia in peripheral blood, but it does not meet the diagnostic criteria of eosinophilia syndrome, without involvement of extrapulmonary organs.
2. Cardiogenic pulmonary edema: It is often caused by ischemic heart disease without increased eosinophils in peripheral blood. Pulmonary edema is mainly characterized by symmetrical ground-glass opacities and thickened interlobular septa, rarely with nodules.

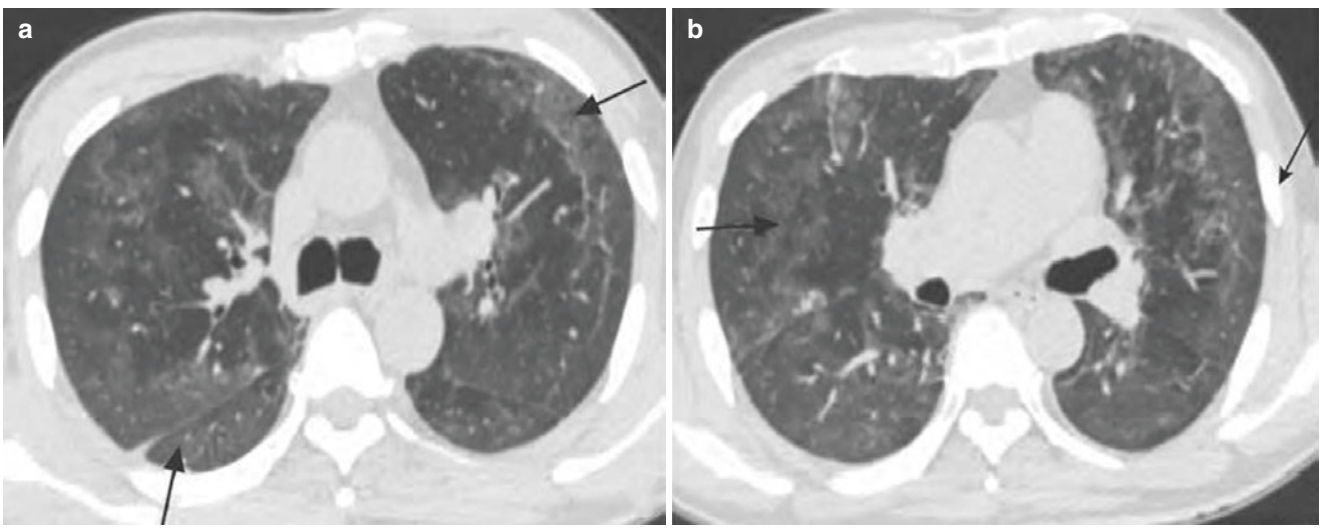

Fig. 29.4 Eosinophilia syndrome. (**a**, **b**) CT lung window showed multiple patchy ground-glass opacities in both lungs, with peripheral distribution (arrow)

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