Sarcoidosis

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26.1 Overview

Sarcoidosis is a systemic disease with unknown etiology and characterized by the formation of non-caseous necrotizing granuloma, which can involve all organs of the whole body, mostly in lung and lymphatic system, followed by eyes and skin, and a few cases may involve liver, heart, nervous system, lacrimal gland, joints, and kidney [1, 2]. Sarcoidosis has various manifestations without specificity, so its diagnosis is difficult. The diagnosis of sarcoidosis should be confirmed by combining clinical history with pathological examination, and other diseases with similar manifestations, such as tuberculosis, fungal infection, and tumor, should be excluded.

Sarcoidosis can occur at any age, mostly in 20–40 years. The prevalence and incidence of sarcoidosis are related to age, gender, race, and region, females are prone to sarcoidosis, and about 70% of patients is females aged 25–45 years [3].

The disease is usually sporadic, but a few patients show familial aggregation. The occurrence and development of sarcoidosis may be related to the following factors: ① Genetic factors: Sarcoidosis may be a polygenic genetic disease, and it is considered that HLA-A1, HLA-B8, and HLA-DR3 in human leukocyte antigen (HLA) are closely related to the pathogenesis of sarcoidosis. ② Environmental and occupational factors: Sarcoidosis often occurs in winter and spring. ③ Infectious factors: Some viruses, spirochetes, *Propionibacterium acnes*, *Mycobacterium tuberculosis*, nontuberculosis mycobacteria, and mycoplasma may induce this disease. ④ Immune factors: Th1/Th2 imbalance may be related to the pathogenesis of sarcoidosis. Most of the local helper T cells in the lesion are Th1 (CD_4^+) cells, and only a few are Th2 (CD_8^+) cells. The cellular immune function in the lesion site is enhanced, while the cellular immune function in the peripheral blood is decreased [4]. If the acute onset is accompanied by erythema nodosum or asymptomatic bilateral lymphadenectasis, it has certain self-limitation. If the onset is occult or multiple extrapulmonary injuries occur, the prognosis is poor.

The clinical manifestations of sarcoidosis vary greatly with different course, scope of involvement, and severity of disease. Most patients have mild or asymptomatic symptoms, and the common symptoms are cough with a small amount of sticky sputum, fatigue, low fever, night sweat, lack of appetite, and chest tightness. Other symptoms include hepatosplenomegaly, skin nodules, joint pain, parotid gland enlargement, peripheral lymphadenectasis, and eye lesions [5]. If sarcoidosis involves other organs, corresponding symptoms and signs may occur. Laboratory examination: There is often no abnormality in blood routine. In the active stage, the total number of leukocytes decreased, the total number of lymphocytes decreased moderately, and hemoglobin and thrombocytes decreased in a few cases. Serum angiotensin-converting enzyme (SACE) level, erythrocyte sedimentation rate, and some C-reactive proteins are increased. CD_4^+ T lymphocytes and CD_4/CD_8 increased in bronchoalveolar lavage fluid (BALF) [6].

26.2 Pathological Manifestations

Characteristic pathological changes of sarcoidosis are epithelial granuloma with clear edges, tightly arranged cells, and no caseous necrosis [4]. Typical manifestations: Epithelioid cells fuse into Langerhans giant cells, which form nodule center with multinucleated giant cells and a few lymphocytes, surrounded by lymphocyte infiltration and peripheral fibrous tissue to form nodules [7]. Electron microscope: ① there are abundant mitochondria and endoplasmic reticulum in epithelioid cells, mostly with tonofilaments and many lysosomal granules, and there are many drumstick-shaped protuberances on the cell surface with clear connection; ② giant cells are formed by fusion of multiple monocytes, and there are residual membrane-like structures

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between cells; and ③ the cytoplasm of macrophages, epithelioid cells, and giant cells contains abundant lysozyme, and epithelial cells have the strongest reaction [8].

26.3 Imaging Manifestations

The imaging manifestations of sarcoidosis are diverse, mainly including thoracic lymphadenectasis, intrapulmonary lesions, pleural lesions, and bronchial lesions, but the latter two are rare. Intrapulmonary lesions are divided into alveolar sarcoidosis, granulomatous nodules, and pulmonary fibrosis [8–10]. The common imaging methods of sarcoidosis include X-ray chest radiograph, CT, MRI, and ^{18}F-FDG PET/CT [10].

1. X-ray: Chest radiograph is the most commonly used examination method for pulmonary sarcoidosis. Bilateral symmetrical hilar lymphadenectasis and/or mediastinal lymphadenectasis are typical manifestations of pulmonary sarcoidosis on chest radiographs, mostly with clear edges and no fusion (Fig. 26.1). Intrapulmonary infiltrative changes are manifested as small nodules, patchy opacities, nodules, or masses, mainly distributed around the hilum, and more common in the upper lobes of both lungs. If the nodules are distributed along the bronchovascular bundles, manifestations are mostly the thickened bronchovascular bundles with beads-like shape. The main manifestations of pulmonary fibrosis are diffuse thickened stripe-like opacities in both lungs, distorted bronchi, and local lucency shadows. Pleural lesions may be manifested as pleural effusion; endobronchial lesions can cause bronchial stenosis and lead to lobar atelectasis.

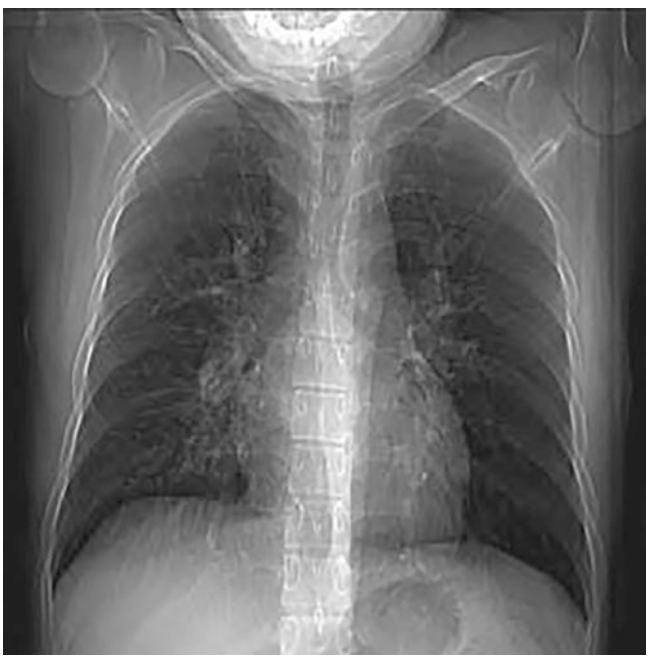

Fig. 26.1 Sarcoidosis (I). Chest radiograph showed bilateral hilar enlargement

2. CT: It is widely used in the diagnosis of pulmonary sarcoidosis, especially HRCT with high sensitivity. CT is effective for differential diagnosis of sarcoidosis, while reflecting the severity of sarcoidosis, and can find pulmonary infection lesions in time. Conventional CT plain scan, HRCT scan, or even enhanced CT scan can be used, clearly showing the scope, size, and density of lesions, but also clarifying the relationship between the lesions and adjacent structures.

   The typical CT findings of pulmonary sarcoidosis are symmetrical hilar lymphadenectasis with clear edges and uniform density (Fig. 26.2). Some patients mainly show right hilar lymphadenectasis, which can be complicated with mediastinal lymphadenectasis. Para-aortic arch space, subcarinal space, and pretracheal retrocaval space are common. Lymph node calcification is also a typical sign of pulmonary sarcoidosis, with a large scope of calcification in mostly bilateral lungs.

   Pulmonary involvement is manifested as diffuse small nodules, linear opacities, ground-glass patchy opacities, and mass opacities in both lungs (Fig. 26.3). Nodules are the most typical manifestation. The diameter of typical nodules is 1–5 mm, and the diameter of larger nodules can reach 5–10 mm, mainly distributed in subpleural area, next to interlobar fissure and around bronchovascular bundle.

   Linear opacities include septal linear opacities, non-septal linear opacities, honeycomb or cystic shadows, structural and morphological lung changes, all indicating pulmonary fibrosis, mainly in the later stage, and the resulting traction bronchiectasis can be found [11]. Ground-glass opacities reflect focal alveolar inflammation, which is mainly distributed in lobules and often absorbed after treatment. In severe cases, the lesions can develop into pulmonary interstitial fibrosis or honeycomb lung. Most of the mass opacities show hyperdensities larger than 3 cm, mainly distributed in the middle and upper lungs, with uncertain number and blurred edges. Sometimes air bronchogram can be found inside, and most of the masses are formed by further fusion of granulomatous nodules. “Air retention” is also a common sign of pulmonary sarcoidosis, which is caused by small airway stenosis. If pulmonary fibrosis occurs, traction bronchiectasis, pulmonary bullae, honeycomb lung, and other signs can be found [12]. Pleural lesions are rare on CT, mainly manifested as pleural thickening or a small amount of pleural effusion [9].
3. MRI: Compared with CT, MRI has more advantages in displaying hilar and mediastinal lymph nodes. Pulmonary

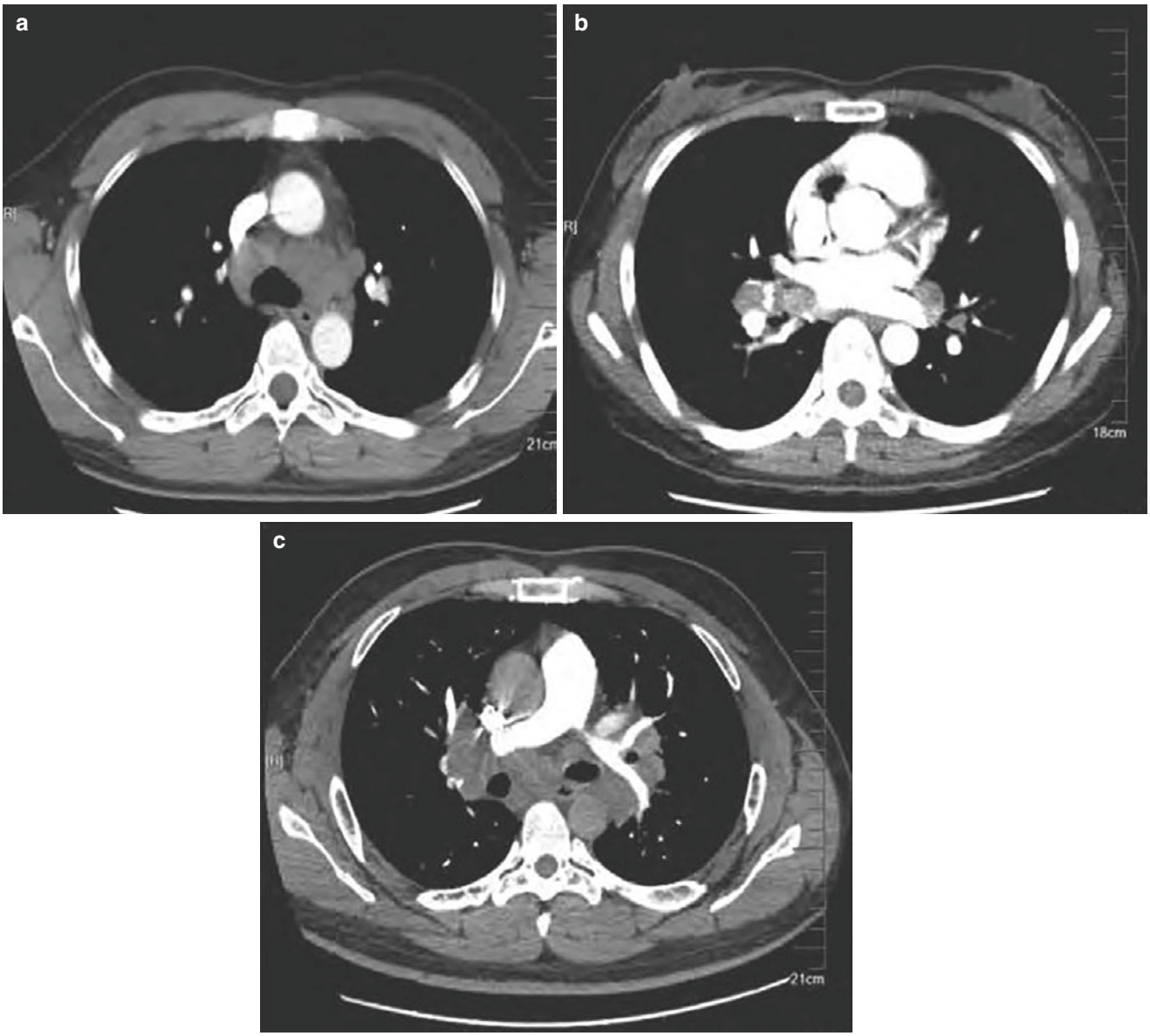

Fig. 26.2 Sarcoidosis (II). (**a**) Enhanced CT scan showed multiple enlarged lymph nodes in mediastinum and (**b** and **c**) multiple enlarged lymph nodes in bilateral hilum, with symmetrical distribution

sarcoidosis is generally examined by equipment with a field strength of 1.5 T or above. Fluid-attenuated inversion recovery (FLAIR) sequence scanning can be performed in addition to conventional scan, and enhanced scan can also be performed if necessary. Mediastinal and hilar enlarged lymph nodes usually show medium low signal intensity on T_1WI and medium high signal intensity on T_2WI. However, MRI cannot show the pulmonary changes of sarcoidosis well, so it is not used as a routine clinical examination, but MRI has better sensitivity [13].

4. PET/CT: A large number of inflammatory cells gather in sarcoidosis granuloma, with high glucose metabolism rate and high uptake rate of ^{18}F-FDG (Fig. 26.4). Many studies have shown that PET/CT can better show lung changes and lymphadenectasis in sarcoidosis [14]. PET/CT adopts SUV value to measure the metabolic activity of lymph nodes, which is very valuable for the evaluation of sarcoidosis [15]. It also has important value in differentiating sarcoidosis from lymphoma and tumor. However, PET/CT is expensive and seldom used as routine examination.

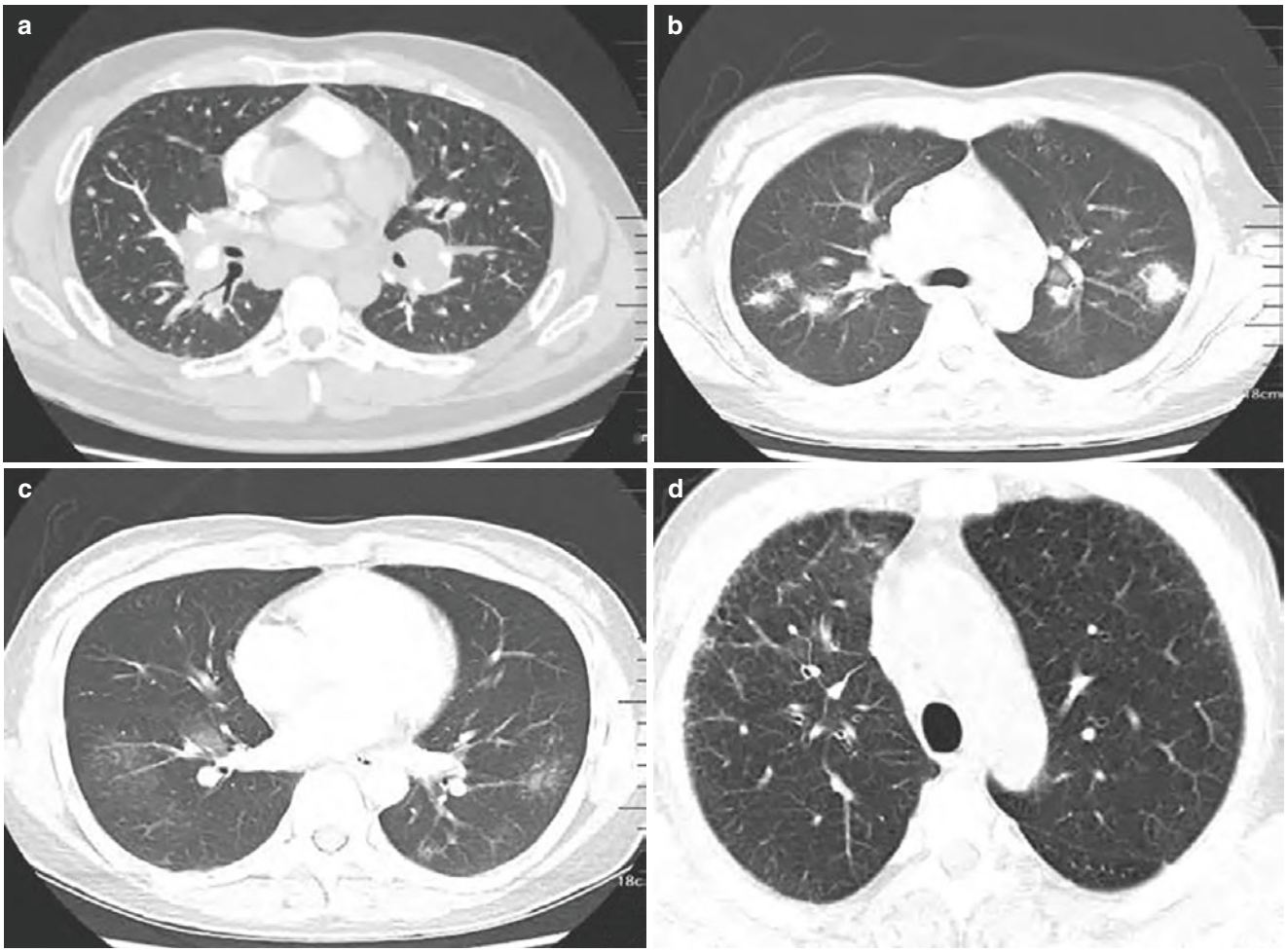

Fig. 26.3 Sarcoidosis (III). (**a**) CT lung window showed multiple small nodules in both lungs, scattered in all lobes of both lungs and distributed along bronchovascular bundles; (**b**) nodules and patchy opacities in both lungs. The large nodules need to be differentiated from metastases; (**c**) patchy lesions with blurred edges in both lungs, which are infiltrative lesions of sarcoidosis in alveoli; and (d) isolated line opacities, mostly caused by thickened interlobular septa or intralobular septa

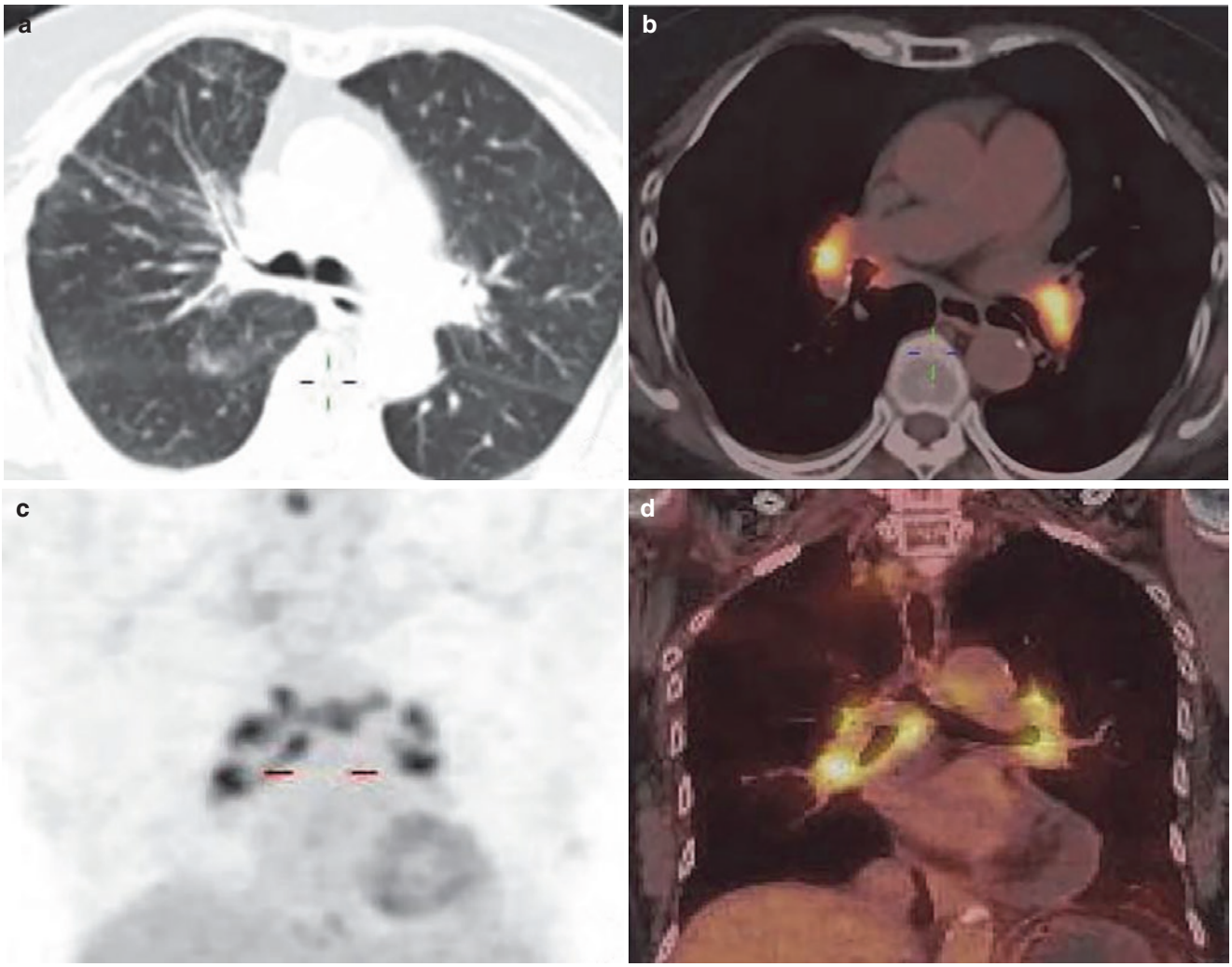

Fig. 26.4 Sarcoidosis (IV). (**a**) CT lung window showed multiple small nodules and patchy opacities in the upper lobes of both lungs; (**b**) PET/CT mediastinal window showed cross-sectional fusion image, bilateral hilar lymph node enlargement with increased FDG metabolism; and (**c** and **d**) PET/CT MIP images and PET/CT mediastinal window showed coronal fusion image, mediastinal, and bilateral hilar lymphadenectasis with increased FDG metabolism

26.4 Diagnostic Key Points

1. Typical imaging findings include hilar and mediastinal lymphadenectasis, with or without diffuse lesions in both lungs on chest radiograph and CT.
2. Respiratory symptoms are mild, accompanied by superficial lymphadenectasis and skin and eye involvement.
3. Most cases occur in young and middle-aged patients, especially females. The course of the disease is long.
4. Histopathological results should be analyzed as much as possible before diagnosis can be made.

26.5 Differential Diagnosis

1. Tuberculosis of lymph nodes: Hilar lymph node tuberculosis usually occurs in unilateral hilum; mediastinal lymph node tuberculosis is more common in the right paratracheal lymph nodes, often with calcification. Enhanced scan may show ring enhancement, and antituberculosis treatment is effective.
2. Lymphoma: Mediastinal lymphadenectasis is common, hilar lymphadenectasis is rare, and retrosternal lymphadenectasis is common. Clinical symptoms develop rapidly,

complicated with pleural effusion. Extrathoracic lymphadenectasis is common, and if intrapulmonary infiltration occurs, it deteriorates rapidly, which can be diagnosed according to the lymph node biopsy pathology.

3. Metastasis: Lymphatic metastasis of lung is manifested as hilar and mediastinal lymphadenectasis, accompanied by fibrous nodular lesions in lung, which sometimes needs to be differentiated from lymphatic metastasis of lung. The hilar lymphadenectasis of lymphatic metastasis is not as significant as mediastinal lymphadenectasis and features bilateral asymmetry. In addition, the stripe-like opacities of cancerous lymphangitis are significant and the distribution of cancerous nodules along lymphatic vessels is asymmetric and uneven in both lungs. Combined with the history and disease course of primary malignant tumor, differential diagnosis is generally not difficult. If metastases are manifested as simple hilar and mediastinal lymphadenectasis, it is difficult to differentiate. Patients' history of primary tumors can be helpful for diagnosis.
4. Lung cancer: It is manifested as nodules or masses in the lung and hilar area, and the edges and adjacent structures of the masses have their corresponding characteristics, mostly with vacuole sign, lobulation sign, burr sign, pleural depression sign, and vascular cluster sign, while air bronchogram is rare, tumor necrosis can be found in hypodensities, and mediastinal and unilateral hilar involvement is common if lymph node metastasis occurs. Pathological examination after bronchoscopy, mediastinoscopy, and mass puncture biopsy is helpful for diagnosis, but there is no obvious absorption or improvement after hormone therapy.
5. Castleman's disease: Also known as vascular follicular lymphoproliferative disease, it is a chronic lymphoproliferative disease with unknown etiology, characterized by lymphadenectasis, and it needs to be differentiated by histopathology.

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