Review Article

Pulmonary sarcoidosis: from clinical features to pathology-narrative review

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Abstract: Sarcoidosis is a multisystem disease with unknown causes. The prevalence of sarcoidosis that occurs worldwide is highly variable. It is pathologically characterized by the formation of non-necrotizing epithelioid cell granuloma, mainly affecting the respiratory tract and involving extrapulmonary organs including the skin, heart, extrathoracic lymph nodes, central nerves and eyes. A correct diagnosis of sarcoidosis depends on the clinical symptoms, imaging observations, and characteristic histopathological findings. This study aims to review the recent contributions of pulmonary sarcoidosis. It is based on a search of a published article and review on pulmonary sarcoidosis. PubMed, Embase and CNKI were searched for latest developments from 1977. The most common clinical symptoms of sarcoidosis include dry cough, dyspnea, and chest discomfort. The imaging manifestations of sarcoidosis can be divided into typical and atypical findings. Lymphadenopathy is a typical imaging manifestation of sarcoidosis. Sarcoidosis is also a highly variable multisystem disease with an unpredictable clinical course. Clinically encountered cases cover a wide range from asymptomatic patients with incidental findings in radiographic images to chronic progressive diseases. Corticosteroids are the most widely recommended as the first-line treatment for symptomatic or organ-threatening disease in sarcoidosis, but they are associated with substantial toxic effects. Meanwhile, for sarcoidosis, the follow-up is also an important part of the diagnosis and treatment. Pulmonary sarcoidosis needs further recognition. In this paper, the clinical features, imaging observations, pathology, and treatment modalities for pulmonary sarcoidosis are presented and discussed vis-à-vis the current dilemma in diagnosis and therapy.

Keywords: Sarcoidosis; pulmonary; granuloma; pathology; image

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Introduction

Sarcoidosis was first described in 1869, but its etiology remains unknown. The course of this disease is still difficult to predict and the treatment is often suboptimal. Sarcoidosis is a global phenomenon, but people of Nordic and African American descent are the most affected population (1-3). The prevalence of sarcoidosis is 141 for every 100,000 African Americans and 49.8 for every 100,000 Caucasians, with significant variations (4). The total incidence reported in the United Kingdom is 5 per 100,000 people (5). Japan has a morbidity rate of 1.01 per 100,000 people, which is significantly lower than that in Europe and the United States (6). There is little data available for the incidence of sarcoidosis in China. The incidence of sarcoidosis is higher in women than in men, and it is worth noting that the incidence peaks in men aged 30–50 years and women aged 50–60 years (7). The mortality rate of sarcoidosis reported in the United States is 7.6%, with main causes of death including pulmonary fibrosis, pulmonary hypertension, nervous system damage, and cardiac sarcoidosis. Although the etiology is not clear, an analysis of the diverse distribution of sarcoidosis and the ever-changing clinical outcome indicates that there may be varied pathogenic and environmental factors. Currently, there is no consensus on the pathogenesis of sarcoidosis. We search the PubMed, Embase and China National Knowledge Infrastructure (CNKI) database for latest developments of pulmonary sarcoidosis from 1977. There is no gold standard for the diagnosis of pulmonary sarcoidosis. And the main diagnostic basis is epithelial granuloma. At the same time, the diagnosis of pulmonary sarcoidosis is still an exclusionary diagnosis. Diagnosis needs to exclude other lung diseases such as tuberculosis that can cause granuloma changes. So we reviewed and analyzed the clinical features, imaging findings, pathological manifestations, current treatment status and follow-up plan of pulmonary sarcoidosis from the clinical point of view, which provided help for clinicians to further understand the disease.

We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/apm-21-344).

Imaging findings

The Scadding staging system presents an initial definition of imaging findings of sarcoidosis based on chest X-ray manifestations, but with the advent of high-resolution computed tomography (CT), this staging system needs to be revisited. High-resolution pulmonary CT is more sensitive and precise than chest radiographs in gauging lung involvement. In typical cases, high-resolution CT has diagnostic significance for suspected sarcoidosis when other diseases are excluded. Pulmonary CT manifestations in patients with sarcoidosis can be divided into typical and atypical findings.

Typical findings

Lymphadenopathy is a typical imaging manifestation of sarcoidosis (*Figure 1*) (8). More than two-thirds of patients with sarcoidosis have lymphadenopathy, especially symmetrical bilateral hilar and mediastinal lymphadenopathy.

Pulmonary nodule shadow has been found in about 15–25% of pulmonary sarcoidosis cases. Pulmonary nodules are usually round, well circumscribed, and 2–5 mm in size. Nodules tend to accumulate along bronchovascular bundles, in interlobular septa, interlobar fissures, and subpleural regions, and are characterized by distribution around the lymphatic drainage area. Pulmonary nodules in patients with pulmonary sarcoidosis are mainly distributed in the upper and middle lobes (9). Pulmonary fibrosis can be seen in 20–25% of sarcoidosis cases. Typical fibrotic changes are linear or reticular in distribution, showing changes such as interlobular septal thickening, bronchovascular distortion (traction bronchiectasis), and reduced lung volume.

Atypical findings

Atypical pulmonary CT manifestations in patients with sarcoidosis include the following: (I) asymmetric, isolated, or unilateral lymphadenopathy (particularly rare in young patients); (II) "eggshell-like" calcification or lamellar calcification or calcification of thoracic lymph nodes and microcalcification of hilar lymph nodes; (III) a pulmonary mass manifest as density shadows mainly located in the upper and middle lungs and around the bronchovascular vessels; (IV) ground glass opacity; (V) fibrocystic lesions; (VI) halos; (VII) cavity. It can be said that sarcoidosis is an excellent "imitator". Sarcoidosis can present with almost all manifestations of lung disease on imaging (10).

Pathological findings

Histopathologic features of sarcoidosis are non-

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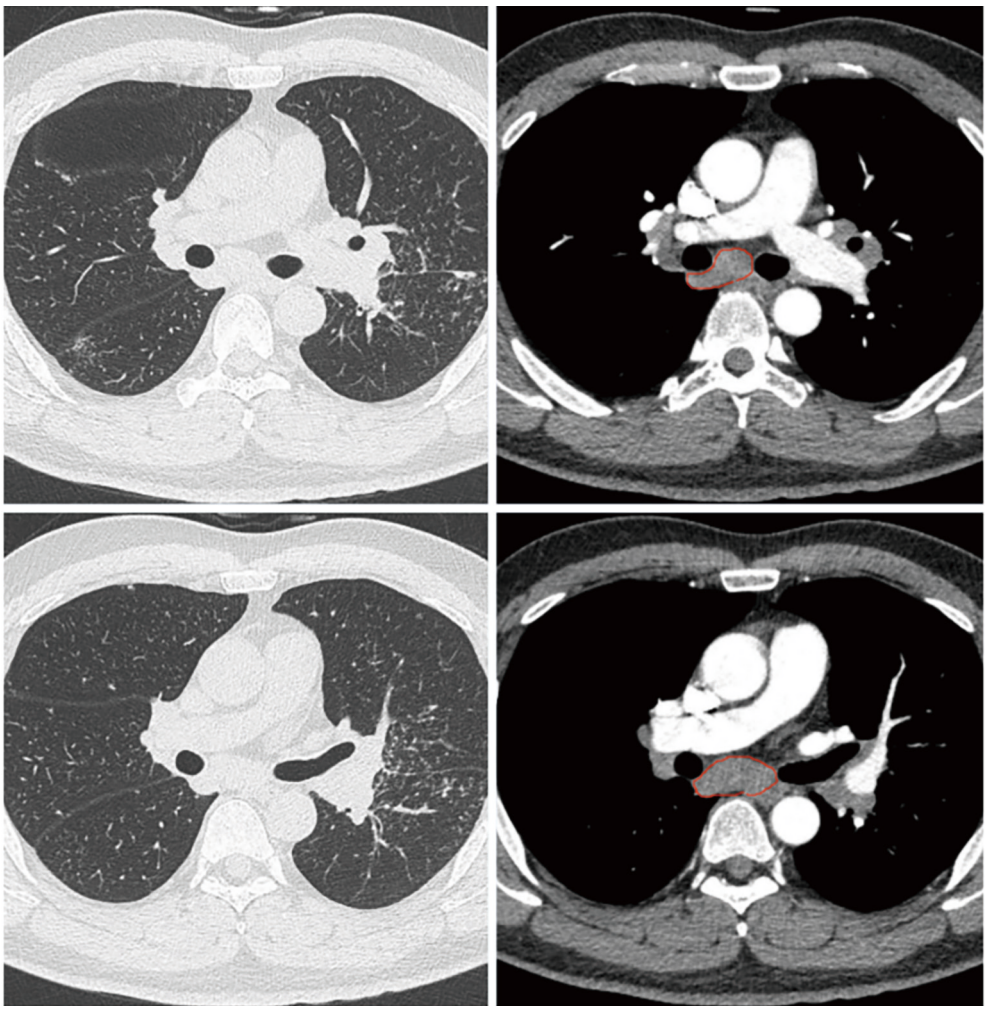

Figure 1 Typical imaging performance of pulmonary sarcoidosis (red).

necrotizing epithelioid cell granulomas, in which the cell components include epithelioid cells, giant cells, central $CD4^+$ T cells, and surrounding $CD8^+$ T lymphocytes and B lymphocytes (11). Granulomas are present around the bronchial vascular structure; hence, signs of vascular invasion can also be seen. In addition, a small amount of fibrinoid necrosis may occur in granuloma of sarcoidosis, which is not a diagnosis of exclusion.

Gross morphology of pathological specimens

In the initial stage of sarcoidosis, the gross morphology of the lung is unremarkable. However, as the disease progresses, micronodules are seen in the pleura and pulmonary parenchyma. The nodules are white and usually 1–2 mm in diameter, distributed in areas with abundant lymphatic supply such as subpleural and pleural regions, interlobular septa, and peribronchial regions (12). In advanced cases, extensive fibrotic manifestations may be present in the lungs. Long-term sarcoidosis may present as honeycomb structure or changes, and the above findings are more common. Solitary pulmonary nodules are rare in sarcoidosis, and such manifestations are common in infection-induced sarcoidosis.

Histopathology

Sarcoidosis behaves differently at different stages. At a very early stage, the pathology is mainly characterized by mild, nonspecific mononuclear inflammatory cell infiltration or alveolitis. The typical pathological manifestation of sarcoidosis, namely polynecrotic epithelial granuloma, do

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not occur until after disease progression. Sarcoidosis has a relatively uniform histological pattern. It should also be noted that histopathologically, granulomas have relatively well-defined borders with the surrounding tissue. As the disease progresses further, there are manifestations of confluent nodules.

Current studies suggest that sarcoidosis granulomas are immune granulomas formed against unknown antigens with specific cellular regulation, with $CD4^+$ T cells in the center of the granuloma and $CD8^+$ T lymphocytes and B lymphocytes in its periphery (11). Sarcoid granulomas are mostly non-necrotizing, but small lesions with central fibrinoid or eosinophilic necrosis are not uncommon. However, when there is greater necrosis, it can result in infection. More caution is required when diagnosing sarcoidosis with greater necrosis.

Sarcoidosis granulomatous inflammation is more common in the larger airways and often invades around the airway wall. It further invades the vasculature from the outside, firstly by destroying the adventitia and outer layer of blood vessels. However, vascular intimal involvement increases the possibility of necrotizing granuloma and granulomatous vasculitis. Pulmonary hypertension develops when the disease progresses and intimal involvement is prevalent. Long-term chronic sarcoidosis increases the occurrence of pulmonary fibrosis and honeycombing, with fibrosis being more common in the upper and middle lobes of the lung, which is contrary to the rule of distribution in the lower lobes of idiopathic pulmonary fibrosis.

Nonspecific cytoplasmic results, such as stellate bodies, shell-like bodies, and calcium oxalate crystals, can be seen in the histopathology of some sarcoidosis. Their incidence varies from 48% to 88% of sarcoidosis cases and from 2% to 9% of sarcoidosis granulomas (13). The presence of these inclusions may mislead pathologists into believing sarcoidosis occurs due to stimulation of exogenous foreign bodies, but recent views suggest that these bodies may be produced during cellular metabolism.

A necrotizing granuloma is clinically rare and controversial. At present, the current and relatively consistent view is that necrosis in most necrotizing sarcoidosis granulomas often coexists with vasculitis. In pathology, necrotizing sarcoidosis granuloma has the following characteristics: granulomatous pneumonitis secondary to sarcoidosis, and a certain degree of necrosis and granulomatous vasculitis, which mostly invades along the lymphatic invasion. The signs of necrosis are variable, from small fibroin-like necrotic lesions to lamellar infarct-like necrotic areas. Only cases of granulomatous pneumonitis and vasculitis without necrosis are common. It should also be emphasized that when the pathological manifestation is a necrotic granuloma and the diagnosis of sarcoidosis is considered, the possibility of infection must be excluded. The proportion of necrotic granuloma with extrapulmonary sarcoidosis is different. Pathological manifestations of extrapulmonary lesions usually include granulomas or chronic inflammation with little necrosis or vasculitis. As sarcoidosis often invades the airway, tracheoscopy and fine-needle biopsy are effective techniques for sarcoidosis biopsy (14). However, the transairway biopsy technique has an insufficient diagnostic yield for necrotizing sarcoid granulomas (15). All patients diagnosed with necrotizing sarcoidosis granulomas are diagnosed by surgical biopsy. Therefore, for special types of sarcoidosis, it might be difficult to make a diagnosis for small specimens.

In addition, sarcoidosis is even rarer, with an incidence of 1.6–4% (16). Imaging findings include multiple nodules 1–5 cm in diameter, and, like pulmonary metastases, are often associated with bilateral hilar lymphadenopathy. Pathologically, sarcoidosis shows a confluence of granulomas and fibrous tissues. Necrosis and vasculitis usually do not occur.

The diagnosis of sarcoidosis is a comprehensive analysis, during which clinicians rely on pathological results, clinical judgment, imaging examinations, microbial culture, and other data. Therefore, the discovery of nonnecrotic granuloma cannot itself confirm diagnose without more adequate clinical criteria.

Clinical features

Dry cough, dyspnea, and chest discomfort are the most common clinical symptoms of sarcoidosis, occurring in about 30–50% of patients, and are more pronounced in patients with lesions that invade the lung parenchyma or present with endobronchial lesions (17). Studies have shown a considerable delay between the onset of clinical symptoms and the diagnosis of sarcoidosis. However, when patients have extrapulmonary manifestations, such as typical skin manifestations or scleritis, the diagnosis of sarcoidosis is more likely to be noticed by clinicians. This may be because most lung symptoms are nonspecific and may be mistaken for other more common manifestations of lung disease such as asthma or chronic bronchitis. Chest examination has no specific manifestations, and clubbing fingers is not common.

A typical respiratory dysfunction is a restrictive ventilatory

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defect, with reduced dispersibility of carbon monoxide (DLCO). Studies have shown that restrictive ventilatory defects can exist in all stages of sarcoidosis. Current studies have not demonstrated a correlation with sarcoidosis severity, but continuous monitoring of lung function contributes to disease control and prognostic evaluation of sarcoidosis.

Complications

The most common complication of end-stage sarcoidosis is pulmonary hypertension. The reported prevalence ranges from 5% to 79% depending on the population studied. The factors of pulmonary hypertension include further progression of pulmonary fibrosis and hypoxemia, granulomatous inflammation of pulmonary vessels, and external pulmonary artery compression caused by mediastinal or hilar lymphadenopathy. Echocardiography is a good screening tool for pulmonary hypertension. Right heart catheterization can confirm the diagnosis and is beneficial in evaluating the severity.

Treatments

Sarcoidosis is self-limiting or has nonprogressive characteristics, and since some patients are asymptomatic, the timing, duration, and evaluation indicators of sarcoidosis treatment are not clear. Since uncontrolled granulomatous inflammation can lead to fibrosis and irreversible organ damage, the treatment of sarcoidosis aims to inhibit and limit the progression of granulomatous inflammation. The main indications for treatment are life-threatening and organ-threatening diseases, as well as unacceptable quality of life. With respect to pulmonary sarcoidosis, active initiation of treatment is recommended if patients concurrently present with the following: (I) deterioration of respiratory symptoms, especially dyspnea; (II) severe pulmonary dysfunction or deterioration of substantive function (i.e., reduction of forced vital capacity (FVC) ≥10% or DLCO decrease by 15% from baseline value); (III) major imaging progression (i.e., continuous development of cavitation or honeycombing, or significant deterioration of interstitial changes). Corticosteroids are the most commonly used treatment, but it is also necessary to recognize sarcoidosis as an incurable disease. Immunomodulators and cytotoxic drugs are commonly used in patients who do not respond to corticosteroids or are who unable to be treated with corticosteroids, or in patients who require high-dose corticosteroid therapy for the long-term (18).

In the 1999 American Thoracic Society/European Respiratory Society/World Association for Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) joint guidelines (19), corticosteroids were recommended as the first-line treatment in sarcoidosis. Although the application of corticosteroids cannot cure the disease and change the outcome of the disease, hormone therapy can alleviate granulomatous inflammation, improve lung function, alleviate the symptoms of patients, and improve the changes of pulmonary imaging. The recommended dose of prednisone is 20–40 mg/d (for at least 1 month but not more than 3 months). Intravenous methylprednisolone is used in patients with acute lung invasion and severe pulmonary dysfunction. Patients with sarcoidosis stage II and III may benefit more from hormone therapy. Steroids are recommended to be tapered to 5–10 mg/day and maintained for 1 year of treatment. However, this treatment regimen is empirical and there is little support from clinical research.

Methotrexate is a nonhormone immunosuppressant with a recommended dose of 5–15 mg/week. Methotrexate can effectively reduce hormone secretion and has a positive effect on the improvement of lung function, but it takes at least 6 months to maximize the effects of methotrexate (20). Azathioprine is similar to methotrexate and can also reduce hormone secretion and improve lung function. The main side effects are liver damage and blood cell reduction. Moreover, current data suggest that patients on azathioprine are at greater risk of infection than patients on methotrexate (21). Leflunomide, used in combination in second-line treatment of recurrent patients (22), has not received a go-ahead on its use in the current study.

Other drugs include antimalarial drugs that have been used in clinical studies for the treatment of sarcoidosis, but the results are not very satisfactory. Hydroxychloroquine with structural changes as compared to chloroquine not only has fewer side effects, but also has many immunomodulatory effects. However, the treatment of sarcoidosis by hydroxychloroquine lacks solid evidence from clinical research (23). Treatment of microbial infection has always been a suspected pathogenic factor of sarcoidosis, and the combination of broad-spectrum anti-infective drugs is helpful for improving pulmonary function and clinical symptoms in patients with pulmonary sarcoidosis (24).

Follow-up

Follow-up is an important part of the diagnosis and treatment of sarcoidosis. Patients with previously treated

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pulmonary sarcoidosis are advised to undergo a clinical assessment every 3–6 months, while untreated patients are advised to undergo assessments every 6–12 months (19). The assessment includes 3 main components: lung function, imaging findings, and positron emission tomography (PET)-CT. For lung function, the most frequently affected parameters in pulmonary sarcoidosis include reduced DLCO, and DLCO reductions can be observed in the early stages of the disease, even in asymptomatic patients. Another indicator is FVC and its combination with DLCO, which can more accurately assess disease progression. When FVC increases >10% or DLCO increases by 15%, this is considered sufficient evidence of therapeutic effectiveness. For imaging assessments, compared with chest radiographs, high-resolution computed tomography (HRCT) is more sensitive and specific in diagnosing diseases and confirming the range of involvement. A third evaluation, PET-CT, has more advantages in identifying active diseases and is used to evaluate chronic refractory sarcoidosis, especially fibrotic lung disease.

In 2019, researchers from 6 medical centers around the world discussed and refined the follow-up protocols of patients with nodules, which produced several noteworthy findings and recommendations. First, it was found that monitoring of mortality should be the main outcome measure of sarcoidosis. Second, monitoring of changes in the patient's condition should include pulmonary function tests and the soluble interleukin-2 receptor (sIL-2R) test. Pulmonary function testing is recommended to be assessed every 3–6 months according to the severity of the disease, with indicators such as FVC, forced expiratory volume in one second (FEV1), and DLCO, of which FVC is currently considered to be the best endpoint, with sIL-2R reflecting the activity of sarcoidosis better. Third, monitoring indicators during treatment in patients with sarcoidosis should include weight gain, quality of life survey of patients (assessed every 6 months), and degree of osteoporosis.

Finally, the outcome of sarcoidosis can divide into 9 levels, from spontaneous remission to continuous exacerbation. This study is important for the detailed analysis of follow-up indicators in patients with sarcoidosis to balance follow-up data in patients with global sarcoidosis (25). In another recent study, researchers assessed the feasibility of home self-evaluation in patients with sarcoidosis, using mobile phones (26). The results showed that 10 patients had good compliance and their self-evaluation did not increase their discomfort and tolerance. This follow-up method provides a new choice for the long-term treatment evaluation of patients with chronic respiratory diseases.

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Footnote

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