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CASE REPORT

Sarcoidosis Stage II: a Case Report and Review of the Literature

Xuebo Yan [1], Shu Fang [1, 2], Tong Wang [3], Huimei Wu [1], Zifeng Jiang [1], Lei Fang [1], Xiaoyun Fan [1], Yanbei Zhang [1], Jiong Wang [1]

[1] *Department of Geriatric Respiratory and Critical Care, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China*
[2] *School of Biomedical Engineering, Anhui Medical University, Hefei, Anhui Province, China*
[3] *General Medicine Department, The Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui Province, China*

SUMMARY

Background: **Sarcoidosis is a systemic granulomatous disease of unknown origin characterized by non-caseous necrotizing epithelial cell granuloma that affects the lung and lymphatic system. Sarcoidosis mainly occurs in young and middle-aged people, usually manifested as bilateral hilar lymph node enlargement, lung infiltration, and eye and skin lesions. Sarcoidosis has a high natural remission rate, but patients with progressive imaging or pulmonary function accompanied by significant clinical symptoms or extrapulmonary lesions need to be treated.**
Methods: **The sarcoidosis patient had received a 3-month methylprednisolone treatment which significantly improved clinical manifestations including cough and sputum, and extrapulmonary presentation, such as skin nodules and enlargement of parotid glands.**
Results: **A 52-year-old female reporting repeated cough and sputum, with scattered skin rashes and nodules on the extremities, accompanied by nasal congestion, enlargement of abdominal and retroperitoneal lymph nodes and parotid glands was studied. Computed tomography (CT) showed miliary nodules diffusely distributed in both lungs, multiple enlarged lymph nodes in mediastinum, bilateral enlarged hilar lymph nodes, and right pleural effusion. Bronchoscopy with lung biopsy showed granuloma formation, special staining including acid resistance was negative, but signet ring cell carcinoma and tuberculosis cannot be excluded. Biopsy of a skin nodule also showed granulomatosis. PET-CT reported all considered as inflammatory lesions, with a high possibility of tuberculosis. Based on all the information, we confirmed the diagnosis of sarcoidosis stage II. She was then successfully treated with a steroid monotherapy, which resulted in a satisfactory clinical outcome without serious complications.**
Conclusions: **Clinical manifestations of this patient are unspecific. Based on the pathological finding, clinical and radiological manifestation, and evidence of no alternative diseases, sarcoidosis stage II is diagnosed. Treatment with a steroid was of benefit in this sarcoidosis patient.**
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Correspondence:
Assistant Professor Jiong Wang, MD, PhD
Department of Geriatric Respiratory and Critical Care
The First Affiliated Hospital of Anhui Medical University
Jixi Street 218
230000 Hefei, Anhui Province
China
Phone: +86 0551-62922807
Email: wangjiong7286@163.com

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KEY WORDS

sarcoidosis, stage II, cough and sputum, bronchoscopy with lung biopsy, computed tomography, case report

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown origin characterized by non-caseous necrotizing epithelial cell granuloma that affects the lung and lymphatic system [1]. Sarcoidosis mainly occurs in young and middle-aged people, usually manifested as bilateral

hilar lymph node enlargement, lung infiltration, and eye and skin lesions. Liver, spleen, lymph node, salivary gland, heart, nervous system, muscle, bone, and other organs may also be involved [1,2]. In 1887, British physician Hutchinson first described sarcoidosis. In the 1940s and 1950s, Swedish physician Lofgren described sarcoidosis in detail. Due to sarcoidosis involving all systems of the body, clinical manifestations are also complex and diverse, more than 90% of patients have lung involvement, no obvious symptoms and signs can be found, some patients have coughing with sputum; systemic symptoms lack specificity [1,2]. The etiology of sarcoidosis is not clear. Some scholars believe that infection is the cause of sarcoidosis [3,4], but there is no definite evidence. Genetic factors may also play a role. Human leukocyte antigen may be related to the susceptibility to sarcoidosis [5,6], but there is still some controversy. Angiotensin-converting enzyme gene polymorphism may be associated with sarcoidosis. A proposal for major criteria includes non-caseating granulomas and lack of acid-fast bacilli on biopsy [1,2,7]. Tuberculosis and primary pulmonary malignancy, which share many clinical features, are the major differential diagnosis in sarcoidosis [4].

Currently, no firm guidelines exist on whether, when, and how treatment should be started. Patients with risk of severe dysfunction or irreversible damage to major organs, risk of death, or the presence of incapacitating, constitutional symptoms should be treated immediately [1,2]. In other words, patients with progressive imaging or pulmonary function accompanied by significant clinical symptoms or extrapulmonary lesions need to be treated [1,2]. We present one case of a female sarcoidosis patient with repeated cough and sputum, multiple extrapulmonary manifestations including scattered skin rashes and nodules on the extremities, nasal congestion, and enlargement of abdominal and retroperitoneal lymph nodes and parotid glands. She was successfully treated with a steroid monotherapy immediately and follow-up. The approval from the hospital ethical committee was obtained for the study.

CASE PRESENTATION

Chief complaints

Repeated cough and sputum for 10 months.

History of present illness

Patient has recently noticed scattered skin rashes and nodules on the extremities, nasal congestion, and enlargement of abdominal and retroperitoneal lymph nodes and parotid glands.

History of past illness

She denied any history of disease.

Physical examination upon admission

Clinical examination revealed multiple unequal-sized slight red rashes and nodules scattered on the skin of the extremities, which did not fade when pressed. The diameter of the biggest one was about 10 millimeters. The skin of bilateral parotid gland region is red. Hand poor-mobility 4 cm * 3 cm parotid gland was touched under red skin on each side. A hard and movable, bean-sized subcutaneous lymph gland was located on left mandibular submandibular region. Congestion of nasal mucosa and moderate edema of lower limbs were observed. There were no obvious dry-wet rales or other positive signs in the lungs. Multiple small and medium-sized lymph nodes were touched in the inguinal region with moderate mobility.

Laboratory testing

Blood routine, liver function, renal function tests and serum sodium, potassium, creatinine, magnesium, calcium in urine and blood were all within normal limits. Blood tumor biomarker tests were negative. Tuberculin skin test, sputum stains for acid fast bacilli were all negative. Serological tests for antinuclear antibodies, rheumatoid factors, and antineutrophil cytoplasmic antibodies were within normal limits. In addition, there was no angiotensin test because it was not available at the hospital. Arterial blood gas analysis at room air revealed pH 7.38, PaO_2 83 mmHg, and $PaCO_2$ 37 mmHg. The pulmonary function test revealed mild restrictive ventilatory impairment and moderate functional abnormality of small airways.

Imaging examination

High-resolution computed tomography (CT) scan of the chest showed miliary nodules diffusely distributed in both lungs, multiple enlarged lymph nodes in mediastinum, bilateral enlarged hilar lymph nodes, and a small amount of right pleural effusion (Figure 1). ^{18}F-fluorodeoxyglucose PET: 1. Multiple miliary and nodular lesions in both lungs with fine calcification, slight increase in FDG metabolism, multiple lymph nodes in hilum, mediastinum, porta hepatis, and retroperitoneum (around pancreatic head) and bilateral inguinal region, slight increase in FDG metabolism, all considered as inflammatory lesions, with a high possibility of tuberculosis; 2. Abnormal increase in symmetrical FDG metabolism in bilateral parotid glands and left submandibular gland, delayed FDG metabolism slightly increased, considered as inflammatory lesions; 3. right pleural effusion. Bronchoscopy with lung biopsy and biopsy of a skin nodule on the lateral side of the left thigh were performed.

Multidisciplinary expert consultation

Jie Chen, MD, Professor, Department of Pathology; Geng-tian Sun MD, Professor, Department of Pathology.

The bronchial gland goblet cells were atypical hyperplasia, and some cells were in a cluster and like signet-ring.

The signet-ring cell carcinoma cannot be excluded. A little bronchial mucosa showed chronic inflammation and giant cell granuloma can be seen in the lamina propria. Special stains including acid resistance, hexamine silver, mucus carmine, and periodic acid-Schiff were negative. A diagnosis of sarcoidosis was considered morphologically, but tuberculosis should be excluded clinically (Figure 2A). Biopsy of a skin nodule also showed isolated giant cell granuloma in dermis. A diagnosis of sarcoidosis was considered morphologically, but tuberculosis should be excluded clinically (Figure 2B).

Final diagnosis

Sarcoidosis stage II.

Treatment

The patient was therefore started with intravenous methylprednisolone 80 mg/day for 1 day, then 60 mg/day for 3 days. Considering the possible side effects of the drug, we then reduced the dosage to 16 mg twice daily taken orally for 1 month. The patient was discharged on a tapering schedule of methylprednisolone 12 mg/day for 1 month, then 8 mg/day for 1 month, and 4 mg/day for 1 month.

Outcome and follow-up

After 1 month of treatment with methylprednisolone, the patient's repeated cough and sputum was significantly alleviated. Scattered skin rashes and nodules on the extremities, nasal congestion, and enlargement of abdominal and retroperitoneal lymph nodes and parotid glands were all improved. Improvement of small airways function to mild functional abnormality was observed. CT scan also showed significant improvement (Figure 3), and miliary nodules diffusely distributed in both lungs, multiple enlarged lymph nodes in mediastinum, bilateral enlarged hilar lymph nodes, and a small amount of right pleural effusion were all resolved gradually. During the treatment with steroids, the main side-effect was hypertension, which was resolved by antihypertensives. No significant adverse side-effects were observed. The repeat chest CT scan revealed almost normal findings after 3 months (Figure 4).

DISCUSSION

Sarcoidosis is a systemic granulomatous disease, which was recognized more than one hundred years ago, but the cause of sarcoidosis is still unclear [1]. The initial presentations, varying with race, gender, and age, are atypical, diverse, unusual and misleading [8-10]. The manifestations usually included persistent cough, skin [11] or eye presentation, and peripheral lymph nodes, erythema nodosum [12,13], systemic symptoms such as fatigue [14], and incidental abnormal chest radiograph. Diagnosis was difficult and might be delayed, because persistent nonspecific respiratory symptoms and rare manifestations often did not prompt the need for a chest radiograph [1,2]. This patient initially showed repeated cough and sputum for 10 months, accompanied by scattered skin rashes and nodules on the extremities, nasal congestion, and enlargement of parotid glands. Because the presentations were atypical and not severe, she did not see the doctor until abnormalities were found by routine physical examination of chest CT. After admission, enlargement of abdominal and retroperitoneal lymph nodes was found. Sarcoidosis was diagnosed after hospitalization in our hospital 2 months later, and the cause was unknown.

The diagnosis of sarcoidosis depended on the pathological finding of non-caseating granulomas, clinical and radiological manifestation, and evidence of no alternative diseases [1,2]. The pathological finding of sarcoidosis is usually non-caseating granulomas [15], which are not specific for sarcoidosis [1,2]. Main differential diagnose was tuberculosis, which can also cause granulomas, but usually with necrosis and acid resistance staining was positive [4,16]. A granulomatous reaction can be also found in the pathological finding of lymphoma [17] and epithelioid tumors such as lung cancer [18]. Positive pathological results, clinical and radiological manifestation need to support each other. None of them was specific enough to be thought diagnostic for sarcoidosis [1, 2]. Mediastinoscopy or bronchoscopy can be used to approach the enlarged lymph nodes and lung for biopsy [19-22]. Characteristic findings identified on chest CT scans were mediastinal and bilateral hilar lymphadenopathy or diffuse pulmonary micronodules, lung disease with upper lobe predominance, peribronchial irregularities, and subpleural micronodules, strongly supporting the diagnosis of sarcoidosis [1,2]. According to chest CT signs, sarcoidosis can be classified into four stages, including stage I (lymphadenopathy alone), stage II (pulmonary infiltration with lymphadenopathy), stage III (pulmonary infiltration without lymphadenopathy), and stage IV (pulmonary fibrosis) [1,2]. ^{18}F-FDG positron emission tomography (PET) can be used to accurately assess an uncommon localization and inflammatory activity in suspected sarcoidosis patients [23-25]. For this case report, chest CT scan of the female patient showed diffuse miliary nodules in both lungs, multiple enlarged lymph nodes in mediastinum, bilateral enlarged hilar lymph nodes, and a small amount of right pleural effusion. ^{18}F-FDG PET/CT showed inflammatory activity in multiple micronodules in both lungs, multiple lymph nodes in hilum, mediastinum, porta hepatis, and retroperitoneum (around pancreatic head) and bilateral inguinal region, bilateral parotid glands and left submandibular gland. Both bronchoscopy with lung biopsy and biopsy of a skin nodule showed giant cell granuloma. Therefore, considering clinical features, pathological findings, and imaging tests, sarcoidosis stage II was diagnosed.

For this sarcoidosis patient, a 3-month methylprednisolone treatment significantly improved clinical manifestations including cough and sputum, and extrapulmo-

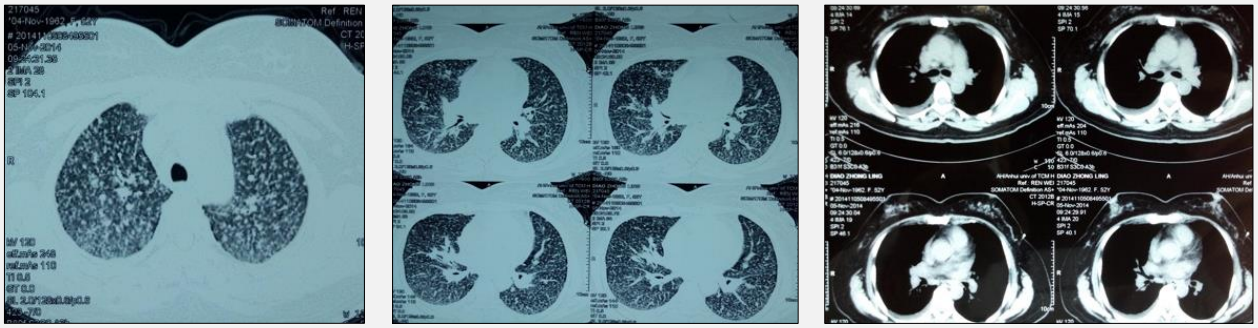

Figure 1. Chest CT scan showed miliary nodules diffusely distributed in both lungs, multiple enlarged lymph nodes in mediastinum, bilateral enlarged hilar lymph nodes, and a small amount of right pleural effusion.

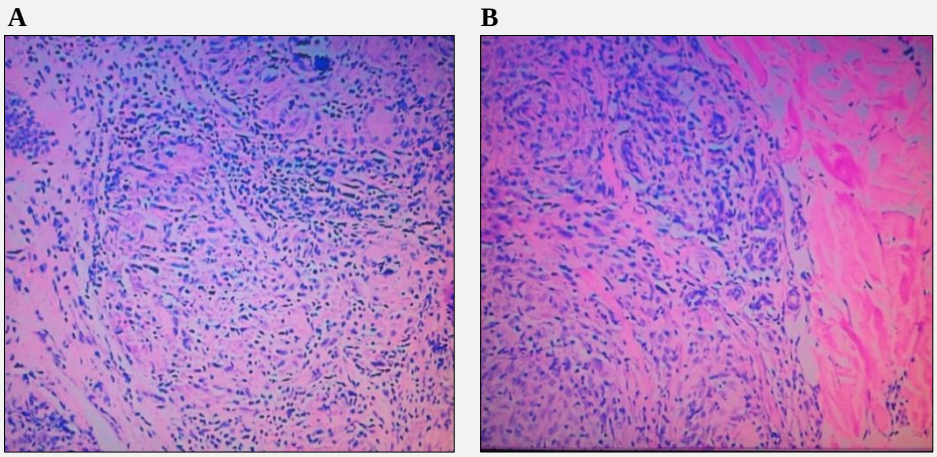

Figure 2. A: Pathology of bronchoscopy with lung biopsy: Several small pieces of broken mucosa. Granulomatous structure formed by epithelioid cells aggregated mainly by multinucleated giant cells was found in the focal interstitium. Blue-stained calcified crystalline bodies were seen in some multinucleated giant cells, interstitial fibrosis with lymphocyte and eosinophil infiltration was considered as granulomatous inflammation. B: Biopsy of a skin nodule on the lateral side of the left thigh: Granulomatous structure consisting of epithelioid cell proliferation and multinucleated giant cell reaction was seen in the dermis. Granulomatous inflammation was considered.

nary presentation, such as skin nodules and enlargement of parotid glands. Chest radiographic abnormalities were all resolved completely. No significant adverse side-effects were detected, except hypertension, which was resolved by antihypertensives. Sarcoidosis has a high natural remission rate and systemic treatment was not necessary for many patients. No treatment is needed for patients without symptoms or with mild pulmonary dysfunction and stable condition. Patients with progressive imaging or pulmonary function accompanied by significant clinical symptoms or extrapulmonary lesions should be considered with systemic therapy [2]. Corticosteroids were widely used to treat sarcoidosis, even though long-term benefit were not clear. It had been reported that the use of a 3-month corticosteroid treatment was of benefit in sarcoidosis patients with persistent chest parenchymal disease on radiography [26], but no serious pulmonary symptoms. This benefit persisted for 5 years after treatment was ended [27].

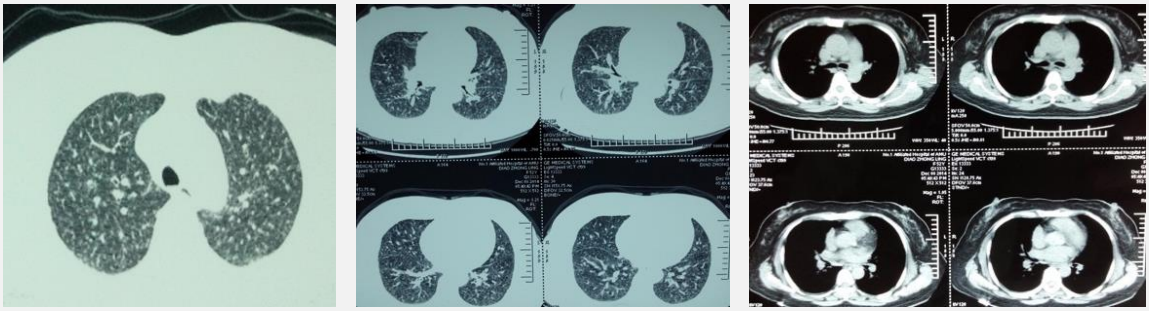

Figure 3. Repeated chest CT scan after 1 month of steroid treatment showed significant improvement and miliary nodules diffusely distributed in both lungs, multiple enlarged lymph nodes in mediastinum, bilateral enlarged hilar lymph nodes, and a small amount of right pleural effusion were all resolved gradually.

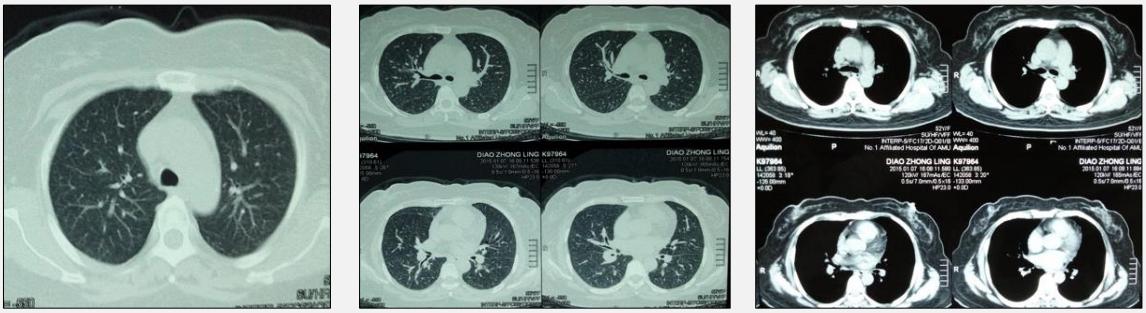

Figure 4. Repeated chest CT scan after 3 months of steroid treatment showed that there was no obvious special abnormality in both lungs, that is, diffuse miliary nodules in both lungs disappeared, and enlarged lymph nodes in mediastinum and hilum of lung decreased significantly.

CONCLUSION

Clinical manifestations of sarcoidosis are unspecific and diverse. Diagnosis can be difficult and depends on the pathological finding of non-caseating granulomas, clinical and radiological manifestation, and evidence of no alternative diseases, none of which is specific enough to be thought diagnostic for sarcoidosis. Systemic treatment was not necessary for many patients, in whom natural remission can be found. But for patients with progressive imaging or pulmonary function accompanied by significant clinical symptoms or extrapulmonary lesions, systemic treatment is of benefit.

Statements

Informed consent statement:

Consent was obtained from the patient for publication of this report and any accompanying images.

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Author Contributions:
Xuebo Yan, Shu Fang, Tong Wang, Huimei Wu, Zifeng Jiang, Lei Fang, Xiaoyun Fan, Yanbei Zhang, and Jiong Wang collected clinical data; Xuebo Yan and Shu Fang designed and wrote the paper and contributed equally to this work.

Declaration of Interest:
The authors declare no conflict of interest for this report.

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