Sarcoidosis or Tuberculosis: Should Corticosteroids be Used?

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Abstract

Introduction: Sarcoidosis shows high similarity with tuberculosis in clinical manifestations, imaging features. It is rarely reported whether sarcoidosis patients with suspected latent tuberculosis can be treated safely with immunosuppressive therapy.

Case presentation: We reported a 54-year-old man presenting with enlarged lymph nodes for decades accompanied by renal impairment and refractory hypercalcemia. The patient was diagnosed with sarcoidosis and suspected latent tuberculosis (as suggested by positive tuberculin test and tuberculosis interferon-gamma release assays), who received prednisone under follow-up. The patient showed significant amelioration in hypercalcemia and shrinkage of lymph nodes, without evidence of developing active tuberculosis.

Conclusions: For sarcoidosis patients with suspected latent tuberculosis, immunosuppressive agents can be utilized safely based on close monitoring. Further efforts are required to reveal whether sarcoidosis and tuberculosis can trigger similar immune responses and what the clinical implications are.

Categories: Allergy/Immunology, Infectious Disease, Therapeutics

Keywords: tuberculosis, sarcoidosis, interferon-gamma release assays, immune responses, corticosteroids

Introduction

Sarcoidosis is a multisystem disease with unknown aetiology. More than 90% of sarcoidosis patients have lesions in the lungs that mainly present as pulmonary nodules and enlarged hilar and mediastinal lymph nodes[1]. Approximately 30~50% of patients have extrapulmonary manifestations[2], mainly occurring in the skin, peripheral lymph nodes, eyes, liver and any other organs. The incidence of sarcoidosis varies by race, sex, and age, a higher prevalence for women than for men in all ethnic groups, the incidence rate in black patients is double to triple that in white patients[3]. The aetiology and pathogenesis of sarcoidosis are still not explicitly identified. Although some studies have shown that genetic susceptibility, immune state, environmental exposure and other factors might jointly promote the occurrence of sarcoidosis[4], the exact pathogenic factors and pathogenic gene loci of the disease have not been found. Numerous studies have focused on the potential microbial aetiology of sarcoidosis, most of which are Mycobacteria and Propionibacterium[5]. Although tuberculosis caused by Mycobacterium tuberculosis has a high degree of similarity to sarcoidosis in clinical manifestations, imaging features and histopathological characteristics, in which epithelioid granuloma is the typical pathological change, the therapeutic strategies of the two diseases are quite different. Hence, differentiation between them is important for clinicians.

Here, we report a patient with sarcoidosis combined with suspected latent tuberculosis and discuss connections, differentiation approaches, and treatment strategies for the two diseases.

Case Presentation

A 54-year-old male patient was admitted due to enlarged cervical lymph node for 31 years, renal dysfunction and hypercalcemia for 2 years. Thirty-one years ago, an enlarged lymph node in the left neck was found in the patient at its maximum egg size, which was lessened by perfication with unknown drugs but exerted a recurrent feature. Fourteen years ago, he underwent cervical lymph node biopsy, and "a benign node" was detected as recalled. Six years ago, pulmonary nodules and mediastinal nodules were also diagnosed. The patient has gradually lost approximately 16 kg of weight over the last decade. Two years ago, the patient was found hypercalcemia as well as elevation in serum creatinine (149 µmol/L) and was followed-up by nephrologists. He denied a history of tuberculosis or contact with tuberculosis patients.

The patient was 174 centimetres tall and 58 kilograms with a BMI of 19.16 kg/m2. Upon admission, the patient showed normal vital signs and no fever. A subcutaneous mass, approximately 10 cm in diameter, was palpable on the left side of the neck, soft in texture, well circumscribed, moderately mobile, and nontender.
The suprasternal trachea deviated to right.

Lab tests were as follows: haemoglobin 101 g/L, serum creatinine 261 µmol/L, serum calcium 3.01 mmol/L, serum phosphorus 2.25 mmol/L, PTH 1.49 pmol/L, 24-hour urine calcium level normal, 25-VitD 29.8 nmol/L, adenosine deaminase (ADA) 30.65 IU/L, interleukin-2 receptor (IL-2R) 3914.0 U/ml, angiotensin converting enzyme (ACE) 65 U/L, and β2-microglobulin 22.6 mg/L. Anti-nuclear antibody, anti-double-strand DNA antibody, anticyclic citrullinated peptide antibody, anti-glomerular basement membrane antibody were all negative. Urinalysis, tumor markers, C-reactive protein and ferritin showed no abnormalities. Although the tuberculin test (PPD test) was positive and tuberculosis interferon-gamma release assays (TB-IGRA) test was 4941.39 pg/ml, the results from repeated sputum smear/culture and quantitative polymerase chain reaction (qPCR) for Mycobacterium tuberculosis were all negative. A chest CT scan revealed multiple enlarged lymph nodes in the mediastinum and left cervical root, nodules in the posterior basal segment of the lower lobe of the left lung (Figure 1 A-C, the pictures are marked with the word "before").

FIGURE 1: Enlarged lymph nodes and pulmonary nodules in the left cervical root and mediastinum on chest CT scan (left column pictures marked with the word “before”); changes in the left cervical root, mediastinal lymph nodes and pulmonary nodules in chest CT images after 18 weeks of prednisone acetate treatment (right column pictures marked with the word “after”).

Ultrasound examination of the cervical lymph nodes indicated that the left cervical lymph nodes were enlarged, some of which were structurally abnormal. Bilateral renal calculi were also observed by urinary ultrasound.

After admission, the patient was hydrated and salmon calcitonin was administered to decrease calcium level. Although serum calcium decreased transiently, it rebounded soon after salmon calcitonin withdrawal. The serum creatinine climbed to 292 µmol/L from 239 µmol/L at admission.

Cervical lymph node biopsy was performed, which showed granulomatous inflammation without definite necrosis, IgG4-positive cells were less than 5/HPF, and acid-fast, periodic acid-schiff stain, and hexamine silver were negative. In addition, tuberculosis DNA fragments were not detected by qPCR. PET-CT revealed abnormal elevation in glucose metabolism in the cervical and thoracic lymph nodes as well as in the posterior basal segment of the lower lobe of the left lung (Figure 2).
FIGURE 2: PET-CT scan showed increased pathological FDG uptake involving lymph nodes in the cervical and thoracic, as well as in the posterior basal segment of the lower lobe of the left lung.

According to the 2020 guidelines for the clinical diagnosis and monitoring of sarcoidosis proposed by the American Thoracic Society[6], the diagnosis of sarcoidosis is based on i) clinical manifestations, ii) finding of no necrotizing granulomatous inflammation in one or more tissue samples, and iii) the exclusion of other causes of granulomatous diseases. The patients suffered enlarged cervical and thoracic lymph nodes for decades showing non-necrotizing granulomatous inflammation with high glucose metabolism, accompanied by increased serum calcium, ADA, IL-2R, ACE and β2-microglobulin level. Although being positive in PPD test and TB-IGRA, no evidence of active tuberculosis infection was found.

The patient was clinically diagnosed sarcoidosis and given oral prednisone acetate tablets 20 mg once daily. The serum calcium stabilized at normal range and creatinine gradually decreased to a minimum of 190 µmol/L (Figure 3).

FIGURE 3: Trend in serum creatinine and Ca2+ levels for the patient over time.


Symptoms of numbness and weakness of the limbs also ameliorated. The patient was successfully discharged with regular follow-up. A chest CT after 4 months illustrated that the cervical and mediastinal lymph nodes and pulmonary nodules were significantly diminished (Figure 1 A-C, the pictures are marked with the word "after"). Prednisone acetate tablets were tapered down to 5 mg once daily for maintenance treatment.

Discussion

In this case, we reported a male patient with renal impairment and refractory hypercalcemia, accompanied by cervical lymphadenopathy and thoracic nodules for years. Two lymph node biopsies showed no evidence of tuberculosis or tumor, but the levels of ACE, ADA, and IL-2R were elevated. According to the 2020 American Thoracic Society guidelines for sarcoidosis[6], the patient was diagnosed with sarcoidosis. We gave the patient prednisone acetate tablets 20 mg once daily as per guideline[2] and hypercalcemia was ameliorated. Chest CT scan showed significant shrinkage of pulmonary/mediastinal/cervical lesions, thus
further justifying our diagnosis of sarcoidosis.

The patient was positive in PPD test and TB-IGRA, but negative in sputum smear/sputum culture or neck mass qPCR for M. tuberculosis DNA fragment. The specificity of the PPD test in the diagnosis of tuberculosis is unsatisfactory, which may be due to the fact that the PPD test is greatly affected by BCG vaccination, the immune status of the patient, and subjective interpretation of results. TB-IGRA can exclude the interference of BCG vaccination, so it is viewed as a test with higher sensitivity and specificity than the PPD test. The positive PPD test and TB-IGRA result in this patient reminded us of the possibility of latent tuberculosis, which warranted close monitoring especially in the setting of immunosuppressive therapy with corticosteroids.

Sarcoidosis and tuberculosis showed high similarity in clinical manifestations, imaging features and pathological characteristics, with pulmonary nodules and lymph node enlargement clinically, elevated glucose metabolism in PET-CT and granulomatous inflammation pathologically. The potential connection between these two diseases have been extensively studied. Some studies have suggested that granuloma formation in sarcoidosis is the result of excessive immune reactions to unknown antigens[7,8], therefore, further exploration is required to reveal whether strongly positive PPD test and TB-IGRA are the result of sarcoidosis overreaction and whether their intensity is paralleled to sarcoidosis activity. Previous studies also showed that T cells in sarcoidosis respond to various mycobacterial proteins[9-12], and monocytes in the blood of patients with sarcoidosis increase the production of interferon-γ upon stimulation with tuberculosis antigens, including ESAT6 and KatG[11]. An Indian study showed that QuantiFERON, as the tuberculosis gold standard test, was also positive in some patients with sarcoidosis[13]. Tuberculosis and sarcoidosis cannot be differentiated based on TB-IGRA positivity alone[14].

It is also generally believed that sarcoidosis is caused by the inflammatory reaction to environmental antigens in individuals with genetic susceptibility. Mycobacterium tuberculosis antigen is one of the causes of sarcoidosis[15], in addition to Propionibacterium acnei, fungi and pesticides. Different studies have observed similar pathogen components of Mycobacterium tuberculosis in sarcoidosis tissues[7,8,16]. The gene expression signature of sarcoidosis also exhibited a highly similar pattern in Mycobacterium tuberculosis infection, with shared proinflammatory and signalling pathways[17]. Furthermore, peripheral blood from patients with sarcoidosis and tuberculosis infection displayed widely overlapping transcriptional signatures[17,18]. Based on the above findings, some have proposed an interesting hypothesis that sarcoidosis and tuberculosis are two ends of the same disease spectrum[19], which has not yet been further confirmed.

Conclusions

Here we reported a rare case of sarcoidosis with extraordinarily high level of TB-IGRA, patients with sarcoidosis can easily be misdiagnosed with tuberculosis, leading to delayed or inappropriate treatment. This case demonstrated that when sarcoidosis is complicated by suspected latent tuberculosis, immunosuppressive agents can be utilized safely based on close monitoring. Sarcoidosis and tuberculosis have similar clinical manifestations are interrelated regarding pathogenesis, the potential relationship between TB-IGRA and sarcoidosis and tuberculosis is originally elucidated in this case. Further efforts are required to reveal whether sarcoidosis and tuberculosis can trigger similar immune responses (such as PPD test or IGRA) and what the clinical implications are.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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