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Sarcoidosis during treatment of pulmonary tuberculosis: a rare case report and review of the literature

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Abstract

The coexistence of pulmonary tuberculosis and pulmonary sarcoidosis is rare. Further, the morphological features of pulmonary tuberculosis with comorbid pulmonary sarcoidosis are similar to those of tuberculosis alone. There are obvious clinical, histological, and radiological similarities between sarcoidosis and tuberculosis, which makes differential diagnosis very challenging, particularly in countries with a high burden of tuberculosis. Here, a rare case of computed tomography (CT) findings of sarcoidosis that developed during tuberculosis treatment is reported. The 46-year-old male patient had no significant symptoms and was undergoing treatment for *Mycobacterium tuberculosis* infection. Chest CT revealed enlargement of multiple lymph nodes, without cystic or necrotic changes, in the mediastinum and both hili, and post-infectious changes consistent with the sequelae of tuberculosis infection in the left upper lobe. Chest radiographic evidence was accompanied by compatible clinical features and noncaseating granulomas on biopsy. As the patient was clinically stable, corticosteroid treatment was not initiated. To date, the patient remains without specific symptoms and outpatient follow-ups continue. Although rare, sarcoidosis may occur during treatment of pulmonary tuberculosis, and requires attention for diagnosis and treatment. The present case draws a radiological picture of how tuberculosis evolved to sarcoidosis.

Keywords

Tuberculosis, sarcoidosis, aetiology, computed tomography, chest radiography, comorbidity

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Introduction

Tuberculosis is one of the leading causes of death due to infectious diseases, and is a global health threat. Most tuberculosis infections comprise pulmonary tuberculosis, characterized by granuloma with caseous necrosis, and the mortality rate among patients with pulmonary tuberculosis is 7–35%.[1] Sarcoidosis is a systemic inflammatory disorder of unknown aetiology characterized by the presence of non-caseating epithelioid cell granulomas.[2] The overall mortality rate of sarcoidosis is 1–5%.[3] Pulmonary tuberculosis and pulmonary sarcoidosis rarely occur together. Although the cause of sarcoidosis remains unknown, a particular trigger is believed to induce an immune response in a genetically susceptible individual.[4] As the lungs are the most commonly affected organ in sarcoidosis, the search for an aetiologic agent has focused on airborne antigens, including infectious or non-infectious bacteria.[5,6] The clinical, histological, and radiological similarities between sarcoidosis and tuberculosis that make differential diagnosis very challenging, particularly in countries with a high burden of tuberculosis, including South Korea, have stimulated the search for an association between mycobacterium and sarcoidosis. Recent advances in immunologic and molecular techniques have helped to elucidate the strong association between mycobacterial infection and sarcoidosis.[4]

Few case reports on the coexistence of pulmonary tuberculosis and pulmonary sarcoidosis have been published. Herein, the case of a 46-year-old male patient with computed tomography (CT) findings of sarcoidosis that developed during the treatment of pulmonary tuberculosis, and correlate with pathologic findings, is reported. The case report was approved by the Chungbuk National University Hospital Institutional Review Board (CBNUH 2020-09-021), and was produced in compliance with the EQUATOR Network CARE guidelines.[7] All patient details were de-identified and written informed consent was obtained from the patient for treatment and publication of this case report and accompanying images.

Case report

A 46-year-old male patient with no previous medical history was admitted to the emergency department of Chungbuk National University Hospital, two years prior to the time of writing, following a four-week history of cough with yellowish sputum. There were no complaints of fever and dyspnoea and no history of smoking. All laboratory findings were within normal limits. No physical abnormalities were observed.

Extensive biochemical and radiologic evaluations were conducted to uncover the origin of prolonged cough with yellowish sputum. Chest X-ray on admission showed reticulonodular opacities in the left upper lung zone (Figure 1a). High-resolution computed tomography (CT) revealed peribronchial infiltration, cavity, and centrilobular nodules in the left upper lobe (Figure 1b) with multiple small lymph nodes in the mediastinum and both hili (Figure 1c). Sputum acid-fast bacilli (AFB) smear examination and microbial culture were performed to rule out tuberculosis infection, and the sputum AFB smear was positive. The patient tested negative for HIV and no signs of immunosuppressive disorders were found. He was immediately admitted to Chungbuk National University Hospital for the treatment of radiologically-confirmed and AFB smear-positive tuberculosis.

Treatment was started with a standard anti-tuberculosis drug regimen composed of 300 mg isoniazid, 600 mg rifampin, 1500 mg pyrazinamide, and 1200 mg ethambutol, orally, once daily for 2 months. Pyrazinamide was then excluded from the regimen, and triple therapy was continued

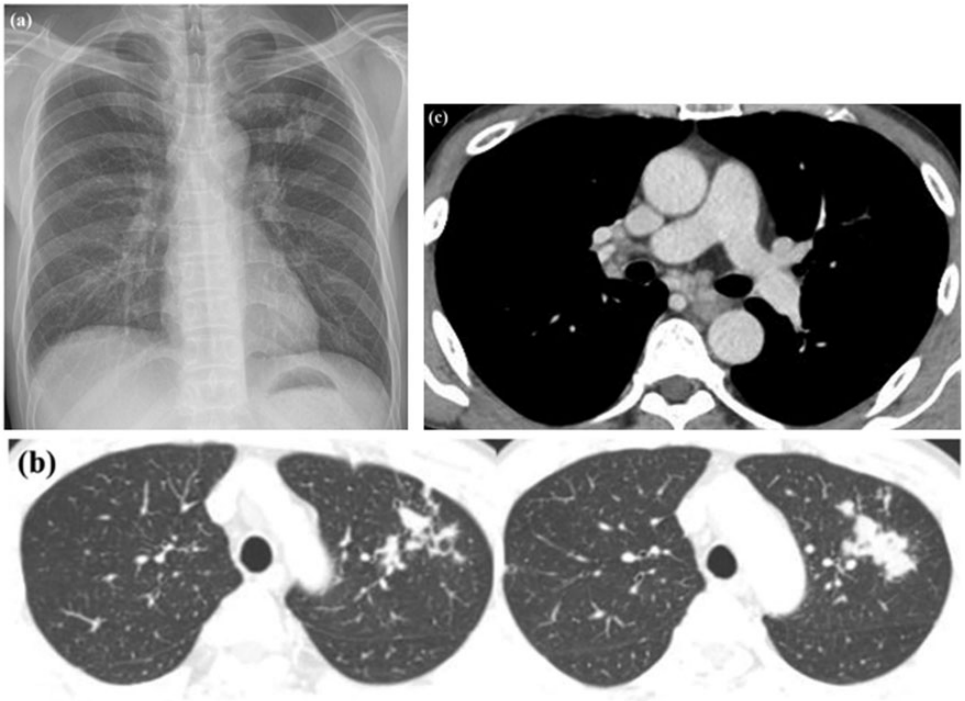

Figure 1. Representative images showing: (a) initial chest radiograph displaying reticulonodular opacities in the left upper lung zone; (b) high-resolution computed tomography (CT) image of the chest revealing peribronchial infiltration, cavity, and centrilobular nodules in the left upper lobe; and (c) high-resolution CT image displaying multiple small lymph nodes in the mediastinum and both hili.

for 4 months. The patient was in good clinical condition and laboratory investigations including liver enzymes (aspartate aminotransferase, 20 IU/l; alanine aminotransferase, 33 IU/l; and alkaline phosphatase, 68 IU/l) and renal function indices (blood urea nitrogen, 13 mg/dl; and creatinine, 0.9 mg/dl) were normal during the total treatment period. No physical abnormalities were observed. During the treatment period, the sputum AFB culture results that were requested three weeks previously confirmed positive results for *Mycobacterium tuberculosis*.

Following 2 weeks in hospital, when sputum samples were acid-fast bacilli-negative for three consecutive days, the patient was discharged from the ward and asked to visit the out-patient pulmonary clinic at Chungbuk National University Hospital during anti-tuberculosis therapy.

About 6 months after starting treatment for *Mycobacterium tuberculosis* infection, the patient's follow-up chest radiograph showed fibrotic changes in the left upper lung zone consistent with the sequelae of tuberculosis infection. However, a new finding of bilateral hilar enlargement was also revealed (Figure 2a). High-resolution CT showed enlargement of multiple lymph nodes in the mediastinum and both hili, without cystic or necrotic changes (Figure 2b), and post-infectious changes consistent with the sequelae of tuberculosis infection in the left upper lobe (Figure 2c). The patient had no symptoms, such as cough, fever, weight loss, and night sweating.

Initially, the reactivation of tuberculosis could not be excluded. Bronchoscopy with lavage and video-assisted thoracoscopic surgery (VATS) along with mediastinal lymph node biopsy were performed. No acid-resistant bacilli were found in the fluid lavage. Fungal cultures and KOH test on fluid mount were negative. Sputum AFB staining and culture were negative. Biopsy of mediastinal lymph nodes revealed the presence of noncaseating granulomas (Figure 3). AFB stain, periodic acid-Schiff (PAS) stain, and Grocott's methenamine-silver (GMS) stain were performed on biopsy tissue, and all were negative. Laboratory investigations showed normal parameters, including calcium. Serum

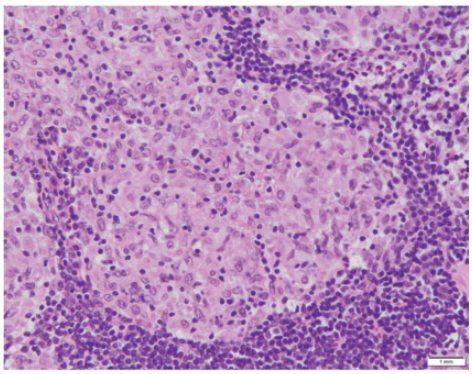

Figure 3. Representative histological examination image showing haematoxylin and eosin-stained mediastinal lymph node tissue section with non-caseating granuloma consistent with sarcoidosis (original magnification, × 400).

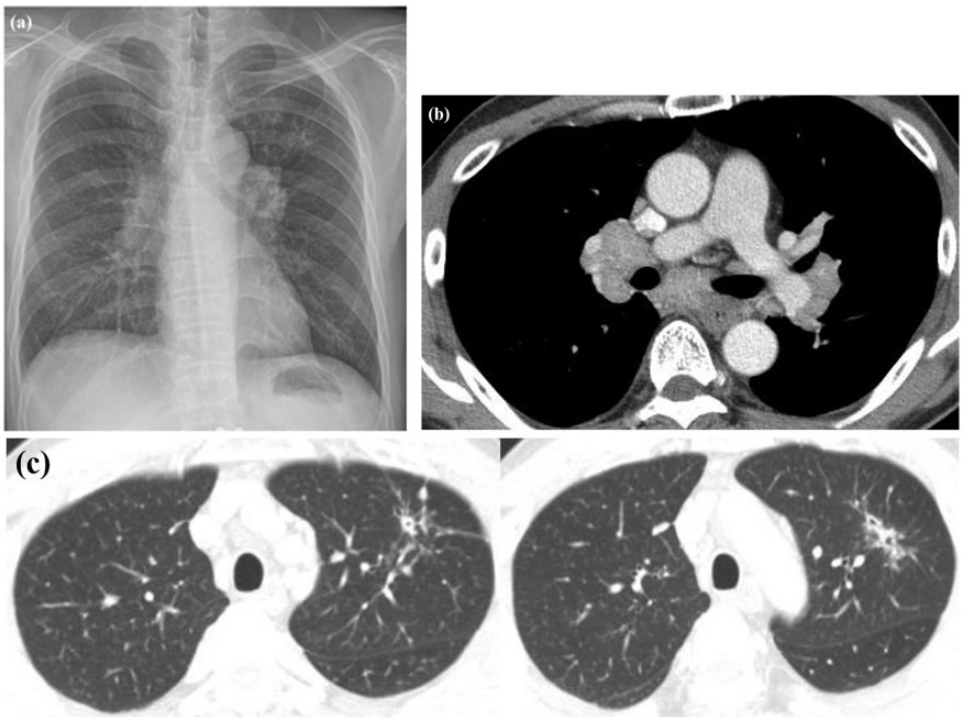

Figure 2. Representative images showing: (a) chest radiograph displaying bilateral hilar enlargement; (b) high-resolution computed tomography (CT) image of the chest revealing enlargement of multiple lymph nodes in the mediastinum and both hili; and (c) high-resolution CT image of the chest demonstrating post-inflammatory changes in the left upper lobe.

angiotensin converting enzyme was elevated to 73.6 U/l (normal range, 18–55 U/l). Additional tests revealed no other organ involvement.

The patient was diagnosed with sarcoidosis manifesting as intrathoracic lymph node enlargement. Furthermore, chest radiographic evidence was accompanied by compatible clinical features and noncaseating granulomas on biopsy. There was no evidence of other causes of granuloma. As the patient's clinical condition was stable, corticosteroid treatment was not initiated. Follow-up of clinical and radiological progress was planned. At the time of reporting, the patient was being monitored at the outpatient clinic and displayed no specific symptoms.

Discussion

The coexistence of tuberculosis and sarcoidosis has sometimes been referred to as tuberculous sarcoidosis, and shows three main patterns: patients who have tuberculosis subsequently develop sarcoidosis; patients develop concomitant sarcoidosis and tuberculosis; and patients with chronic sarcoidosis develop tuberculosis due to treatment-related immunity suppression.[8] The morphologic features of pulmonary tuberculosis with coexisting pulmonary sarcoidosis are similar to that of pulmonary tuberculosis without pulmonary sarcoidosis. Coexistence of pulmonary tuberculosis and pulmonary sarcoidosis is rare, and the pathogenesis of coexisting tuberculosis and sarcoidosis remains unknown, although several hypotheses have been reported. Sarcoidosis development is complex, and genetic susceptibility and environmental factors may play important roles in the pathogenesis of the disease.[9–12] Authors of early reports on sarcoidosis were convinced of the causative role of *M. tuberculosis* in its pathogenesis, mostly due to radiological, clinical, and histopathological similarities with tuberculosis infection, and *M. tuberculosis* as a putative cause of sarcoidosis has been extensively studied. With the use of polymerase-chain-reaction techniques, mycobacterial and propionibacterial DNA and RNA have been recovered from sarcoidal tissue. Serum samples from patients with sarcoidosis have been reported to often contain antibodies to mycobacterial antigens, including recombinant *M. tuberculosis* katG, *M. tuberculosis* heat-shock protein 70 and *M. tuberculosis* mycolyl transferase antigen 85A.[4] A meta-analysis of 31 studies showed that 26.4% of biopsies from patients with sarcoidosis were positive for mycobacterial DNA or RNA, and there were 9–19-fold increased odds over nonsarcoidosis control tissues.[13] Moreover, case reports revealed the sequential occurrence of tuberculosis and sarcoidosis, sarcoidosis and tuberculosis, and the simultaneous coexistence of these two clinical entities.[14–16] These studies may indicate that the presence of mycobacterial antigens is enough to elicit an immune reaction in a susceptible host.

Tuberculosis shares remarkable clinical, radiological, and histological similarities with sarcoidosis, and therefore, it is difficult to distinguish between the two conditions.[17–19] Nevertheless, it is paramount to differentiate the two conditions, as tuberculosis, if misdiagnosed and treated as sarcoidosis, can have disastrous consequences. The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs having noncaseating epithelioid-cell granulomas without organisms or particles.[3]

The patient in the present case had enlargement of multiple lymph nodes in the mediastinum and both hili. Peripheral enhancement (rim enhancement) with central low attenuation of the lymph node is the classical CT finding of a tuberculous mediastinal lymph node.[20] However, the present patient had homogenous enhancement and absence

of the classical CT finding that necessitated further differentiation using bronchoscopy and VATS mediastinal lymph node biopsy. In addition, the incidence rate of tuberculous mediastinal lymphadenopathy in reactivation tuberculosis is low, about 4–5%.[20]

Reactivation of pulmonary tuberculosis was ruled out on the basis that appropriate anti-tuberculosis drugs had been administered and negative findings were observed with AFB staining and culture. Sarcoidosis was diagnosed on the basis of chest radiologic findings, clinical features, noncaseating granulomas on biopsy, and no evidence of other causes of granuloma. Initial high-resolution CT showed multiple small lymph nodes in the mediastinum and both hili. Homogenous enhancement in some lymph nodes could not rule out concomitant sarcoidosis and TB on admission.

The presented case is of clinical interest because sarcoidosis occurring during the treatment of pulmonary tuberculosis is very rare. Because bilateral mediastinal and hilar lymphadenopathy occurred during anti-tuberculosis treatment, differential diagnosis of reactivation of pulmonary tuberculosis had to be ruled out. This rare case of sarcoidosis in a patient during the treatment for pulmonary tuberculosis provides an interesting clue to the ongoing debate on the aetiopathogenesis of sarcoidosis.

In conclusion, the case described here draws a radiological picture of how tuberculosis evolved to sarcoidosis. Only a few case studies have been reported in patients who develop sarcoidosis after culture-positive tuberculosis, and the incidence of sarcoidosis is higher in countries with a high burden of tuberculosis, including South Korea.[21] *M. tuberculosis* plays a role as a cause of sarcoidosis in a proportion of patients. The present case report highlights the association between mycobacterial infection and sarcoidosis.

Author contributions

Manuscript development, writing, data acquisition (HSC); study concept and design, editing, review, supervision (JYY); review (SJK). All authors have read and agreed to the published version of the manuscript.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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