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Case Report

Sarcoidosis and Tuberculosis: A Case Report and Literature Review

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Abstract

We present a 52-year-old Iraqi female patient who presented with extensive bilateral pulmonary micronodules on a chest X-ray (CXR) after a recent month-long visit to Turkey. She had a history of sarcoidosis, diagnosed 2 years ago, and was initially treated with a tapering dose of prednisone and maintained on a high dose of inhaled budesonide. High resolution computed tomography of the chest showed the new development of pulmonary nodules in a miliary pattern. Infectious causes were excluded with bronchoalveolar lavage. Non-necrotizing granulomatous inflammation and a lymphocyte count of 29% were obtained from a transbronchial lung biopsy and the differential cell count of the bronchoalveolar lavage, respectively. The patient started a treatment regimen of methotrexate and prednisone. Her repeat CXR at a subsequent follow up session showed resolution of the pulmonary micronodules. The association between sarcoidosis and tuberculosis was discussed. Published cases of miliary pulmonary nodules were examined for association with tuberculosis. To date, there has been no definitive evidence of tuberculosis as a cause for sarcoidosis despite the reported association. This case report emphasizes that sarcoidosis patients with pulmonary miliary patterns may have underlying risk factors for tuberculosis, and calls for more investigations to be performed to further delineate the association.

Introduction

Sarcoidosis is a disease of unknown etiology which results in the formation of granulomas in any organ.[1] Infectious agents including mycobacterium and propionibacterium have been implicated in the pathogenesis of sarcoidosis[2] although this has not been conclusively confirmed. In addition, it is possible that the triggering antigen varies depending on ethnicity, geographic location, and individual background.[2] The exact cause of sarcoidosis continues to be debated and we hope that this case report will shed some light on the association between sarcoidosis and tuberculosis, and will spur more studies to be done to distinguish these closely related diseases.

Keywords: Sarcoidosis; Tuberculosis; Miliary pulmonary nodules.

Abbreviations: CXR, chest X-ray; TB, tuberculosis; MTB, mycobacterium tuberculosis; HRCT, high-resolution computed tomography; BAL, bronchoalveolar lavage; PCR, polymerase chain reaction; TST, tuberculin skin test.

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Case report

We present a 52-year-old female patient who was diagnosed with sarcoidosis 2 years ago when she presented with a month history of persistent cough and chest discomfort. She was a lifelong non-smoker. The patient had a tuberculin skin test (TST), which was negative, 15 years ago prior to moving to Canada from Iraq. There was no history of occupational dust exposure. Initial investigations included a chest X-ray (CXR) that showed bilateral hilar lymphadenopathy (Fig. 1a, c) which was confirmed by high resolution computed tomography (HRCT) of the chest. A bronchoscopy was completed with a bronchoalveolar lavage (BAL) differential cell count revealing 56% of lymphocytes. The CD4:CD8 ratio of the subset of lymphocytes was 6.6 and a polyclonal B cell population was observed. There was no evidence of infection. Endoscopic bronchial ultrasound biopsies of the lymph nodes showed non-necrotizing granulomatous inflammation. With these findings, the patient was diagnosed with sarcoidosis and was treated with a tapering dose of oral corticosteroids starting from 30 mg to 0 mg over a month. The treatment also included a high dose of inhaled budesonide, which resulted in the stability of lung function and complete resolution of her cough.

Twelve-months following treatment initiation, the patient developed a recurrent cough and experienced significant weight

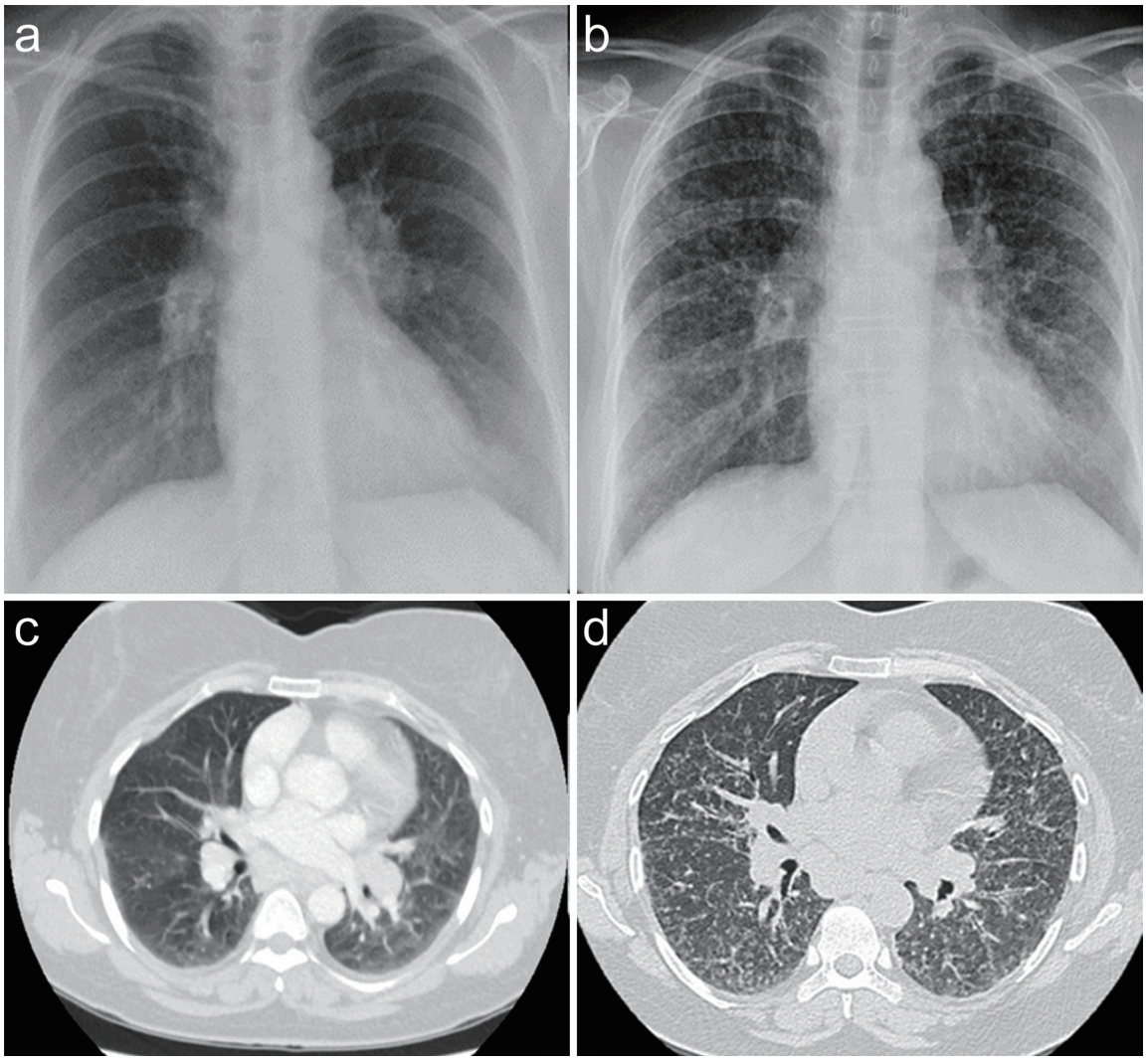

Fig. 1. Initial CXR (a) and HRCT (c) chest showed bilateral lymphadenopathy. CXR (b) and HRCT (d) of the chest performed a year later showed a miliary pattern along with bilateral lymphadenopathy. The micronodules were intense, with thickened peribronchovascular interstitium. Contacting micronodules or lines connecting the pleura to the parenchyma can be recognized, which correspond to the perilymphatic pattern, and were occasionally seen in sarcoidosis. In MTB, the micronodules are intense and random in distribution. Perilymphatic changes were not common on HRCT in MTB. CXR, chest X-ray; HRCT, high-resolution computed tomography; MTB, mycobacterium tuberculosis.

loss of 7kg. She demonstrated no other constitutional symptoms. Of note, she recently returned from a month-long visit to Turkey for a dental procedure prior to the development of her symptoms. A physical examination did not reveal any abnormalities. Peripheral blood tests were normal apart from a slightly elevated c-reactive protein value of 13.9mg/L. A CXR demonstrated extensive bilateral pulmonary micronodules (Fig. 1b, d). HRCT revealed innumerable bilateral pulmonary nodules in a military pattern. A bronchoscopy was repeated with negative microbiologic studies. Transbronchial biopsies were again obtained, and analysis revealed non-necrotizing granulomatous inflammation and a BAL differential cell count showed 29% of lymphocytes. The CD4:CD8 ratio of the subset of lymphocytes was 30.1. A diagnosis of progressive sarcoidosis was made and treatment with prednisone and methotrexate was initiated. A repeat CXR performed four months later showed resolution of the pulmonary micronodules.

Discussion

In 1960, Scadding reported a high proportion of sarcoidosis cases that developed overt tuberculosis in the chronic stage of the disease, and the development of sarcoidosis in a minority of tuberculosis cases.[3] In his series of 230 cases, he added that tuberculous bacilli were found at some stage in 29 or 13% of patients.[3] Since then, numerous studies have expanded our understanding of the controversial relationship between sarcoidosis and tuberculosis. Using PCR techniques, Saboor *et al.*[4] found mycobacterium tuberculosis (MTB) DNA in half of sarcoidosis lung samples and identified non-MTB DNA in an additional 20%. In contrast, Zhou *et al.*[5] found low levels of MTB-specific IS 986 DNA in sarcoidosis and control tissue compared with tuberculosis granulomas.[4,5] From the epidemiological point of view, the overall prevalence of TB in a given study population likely has a significant impact on the rate of discovery of MTB DNA in all comers. Mootha *et al*.[6] reported

Table 1. Published case reports of sarcoidosis with miliary opacities

Author	Year of publication	Age of patient	Gender	Identified risk factors for MTB infection
Sugino *et al.*[12]	2020	37	Female	None identified
Arar *et al.*[13]	2019	55	Male	Indian origin
Taki *et al.*[1]	2015	40	Female	None identified
Bostantzoglou *et al.*[10]	2014	48	Male	Possible prior TB infection
Luetkens *et al.*[14]	2014	37	Male	History of tuberculous spondylodiscitis
Kumar *et al.*[15]	2012	45	Male	None identified
Hatzakis *et al.*[9]	2000	47	Male	History of gastric tuberculosis

a high prevalence of mycobacterial DNA in sarcoidosis samples compared to control in a population in India, a country with an incidence of 199 cases per 100,000.[6,7] In contrast, Hosoda *et al.*[8] reported no epidemiological link between sarcoidosis and tuberculosis in Japan, which has an MTB infection incidence of 14 cases per 100,000. However, this difference may be due to the difference in the methodology used. While Mootha *et al*.[6] used a PCR technique to detect mycobacterial DNA in sarcoidosis patients, Hosoda *et al.*[8] utilized a more clinical-based method using chest X-ray and the tuberculin skin test in a working Japanese population.

Despite the uncertainty about a potential mechanistic relationship, it is well established that tuberculosis and sarcoidosis share a number of similar clinical, radiographic, and histopathologic features.[9] Diffuse miliary (meaning similar to millet seeds) opacities can be observed in both diseases, but are rare findings in sarcoidosis.[1] The most common radiographic presentation of sarcoidosis includes bilateral hilar lymph node enlargement, alone or in combination with mediastinal lymph node enlargement, which most commonly detected on CXR. When parenchymal nodules are observed in sarcoidosis, they typically present as bilateral, symmetric, and are well-defined in a perilymphatic distribution.[10] Tuberculosis commonly presents as unilateral lymphadenopathy, consolidation, and less commonly, cavitation and diffuse miliary pattern. In miliary sarcoidosis or tuberculosis, the micronodules are dispersed randomly throughout the lungs with no topographic predilection. Supporting a possible etiologic connection, Hatzakis *et al.*[9] reported a case of sarcoidosis with a diffuse miliary pattern on HRCT, which manifested one year after the diagnosis of tuberculosis.

Recently, Wang *et al.,*[11] in their retrospective longitudinal cohort study, found that patients with tuberculosis exhibited an 8.08-fold higher risk of developing sarcoidosis than the non-tuberculosis patients over 5 years of observation. In contrast, patients with sarcoidosis exhibited a 1.85-fold higher risk of developing tuberculosis than non-sarcoidosis patients but the risk was only significant within a 1 year follow-up period.[11]

To our knowledge, our patient had never been diagnosed with tuberculosis, and with a negative TST, the likelihood of prior mycobacterial infection was low. Despite our suspicion for possible MTB exposure given her travel to an endemic area, MTB was not seen on her bronchoalveolar lavage. It is interesting to note the development of a pulmonary miliary pattern in this patient after her visit to Turkey as part of the progression of sarcoidosis. This case report is also interesting in that our patient presented with bilateral and mediastinal hilar adenopathy prior to the miliary presentation, contrary to case reports published so far. Therefore, this raises the question of whether the miliary presentation was related to her recent visit to Turkey or merely occurred by chance. It is also possible that she may have been exposed to mycobacteria at some point during her visit, and that her immune response was able to control the infection triggered by MTB. Based on the review of the previously published case reports, there may be an associated risk factor of prior tuberculosis infection in sarcoidosis patients who present with diffuse miliary opacities, as shown in Table 1.[1,9,10,12-15]

This case adds to the current literature of miliary presentations of sarcoidosis, which affects less than 1% of sarcoidosis cases.[10] Most of the cases reported so far, presented in their fifth decade with a male preponderance and initial radiographic findings of miliary opacities.[1] In contrast, in our case, the initial radiographic presentation of bilateral hilar lymphadenopathy evolved to a miliary pattern over time. Out of the eight cases of sarcoidosis with miliary opacities, including our patient, six had either an underlying risk factor for tuberculosis or a prior history of tuberculosis. Therefore, careful evaluation for possible MTB infection is warranted in patients with suspected sarcoidosis presenting with miliary opacities. This case report also reignites the decades long debate of the association between sarcoidosis and tuberculosis and the need to further delineate the potential etiologic connection between these two diseases.

This case report illustrates several important points. First, the association between sarcoidosis and tuberculosis continues to be an enigma despite intensive research investigating the mycobacterial DNA in sarcoidosis patients, and immunological research comparing sarcoidosis and tuberculosis. Perhaps research focusing on immunological cells in combination with genetic susceptibility may provide insight regarding the tendency of the development of sarcoidosis or tuberculosis. Also, rather than looking at a direct causal relationship, a 'two-hit' hypothesis at the causality between sarcoidosis and tuberculosis should be explored before we consider the classification system of sarcoid-tuberculoid proposed by Agrawal *et al.*[16]

Conclusions

Miliary presentation of sarcoidosis is not common. A broad differential diagnosis needs to be considered in the presentation of the miliary pattern of micronodules, which includes tuberculosis, hypersensitivity pneumonitis, and granulomatous polyangiitis. Currently, miliary sarcoidosis is diagnosed after exclusion of other diagnoses and the precipitating factors for the progression of sarcoidosis are still uncertain. In this case report, the question remains whether the patient's recent visit to a high endemic area of tuberculosis played a role in the exacerbation of her sarcoidosis. More extensive research is needed to address this question, and to elucidate the cause of sarcoidosis and differentiate it from tuberculosis.

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Conflict of interest

All authors declare no conflict of interest.

Author contributions

Conceptualization (SGC), collection of data (SGC), draft preparation (SGC), review and editing (SGC, SC), consent (PGC). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

Written informed consent was obtained from the patient for treatment and for publication of this case report and the accompanying images.

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