

Received: 2013.11.10
Accepted: 2014.02.08
Published: 2014.05.16

Mycobacterium tuberculosis as a sarcoid factor? A case report of family sarcoidosis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: **Male, 26**
Final Diagnosis: **Sarcoidosis**
Symptoms: **Disseminated lung parenchymal changes**
Medication: —
Clinical Procedure: —
Specialty: **Pulmonology**

Objective: **Rare disease**





Background: Sarcoidosis is a granulomatous inflammatory disease that is induced by unknown antigen(s) in a genetically susceptible host. Although the direct link between *Mycobacterium tuberculosis* (MTB) infection and sarcoidosis can be excluded on the basis of a current knowledge, the non-infectious mechanisms may explain the causative role of mycobacterial antigens. The co-incidence of tuberculosis (TB) and sarcoidosis, and higher incidence of mycobacterial DNA in biological samples of sarcoid patients, have been reported by many authors.

Case Report: We present a case in which MTB infection in 1 family member triggered a sarcoid reaction in the infected subject and 2 other non-infected family members. We discuss different aspects of diagnosis and differentiation, as well as up-to-date hypotheses on the possible mechanisms leading to sarcoid inflammation in patients exposed to MTB.

Conclusions: This case series documents the possibility of familial spreading of sarcoidosis, and points to MTB as a potential etiological factor.

MeSH Keywords: **Tuberculosis • *Mycobacterium Tuberculosis* • Sarcoidosis**

Full-text PDF: <http://www.amjcaserep.com/download/index/idArt/890014>

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Background

Authors of early reports on sarcoidosis were convinced of the causative role of *Mycobacterium tuberculosis* (MTB) in its pathogenesis, mostly due to clinical and histo-pathological similarities. After more than 100 years, the etiologic factor(s) able to induce the Th1 lymphocytic response and granuloma formation is still unknown. During the last decades many studies on sarcoidosis have been published documenting the presence of MTB DNA in a high proportion of tissues or bronchoalveolar lavage (BAL) fluid samples collected from patients, but negative results have also been reported [1]. Moreover, the convincing case reports revealed the sequential occurrence of tuberculosis and sarcoidosis, sarcoidosis and tuberculosis, and simultaneous coexistence of these 2 clinical entities [2–4]. Nowadays, it is proposed that not the whole bacteria, but its antigens, may induce a sarcoid reaction in a genetically predisposed host, with different possible immunological mechanisms involved [5,6].

We present a case of a family in which MTB could be a factor causing an outbreak of intrathoracic sarcoid lesions in the infected subject and 2 other non-infected household family members.

Case Report

In February 2011 the 26-year-old male patient (“the case”), a never smoking professional soldier, was referred to the Department of Pneumology and Allergy with disseminated lung parenchymal changes. His chest X-ray was performed as part of a routine medical check-up before admission (Figure 1A). A previous X-ray taken 1 year earlier was normal. After his X-ray had been evaluated, he was admitted to the pulmonary unit of a district hospital, where lung CT scans were performed (Figure 1B). Bronchial aspirate examined for the presence of *Mycobacterium tuberculosis* taken at this time, both direct smear (Ziehl-Neelsen stain) and in culture (Löwenstein-Jensen medium) were negative. His tuberculin skin test (TST) was also negative (0 mm). Based on the clinical and radiological picture, stage II sarcoidosis was suspected, and he was referred to the Department of Pneumology and Allergy, Medical University of Lodz for further diagnosis. Although BAL fluid cellular pattern and laboratory results were not typical for sarcoidosis (Table 1), transbronchial lung biopsy (TBLB) revealed non-caseating granulomas (Figure 1C), confirming the initial diagnosis. Due to asymptomatic course, normal lung function and lung diffusing capacity for CO (DLCO) and lack of extrapulmonary locations, the decision of treatment was suspended and the patient was asked to visit the out-patient pulmonary clinic within 3 months. In the meantime, 8 weeks after the collection, BAL fluid culture for *Mycobacterium tuberculosis* appeared positive. He was referred to a regional tuberculosis

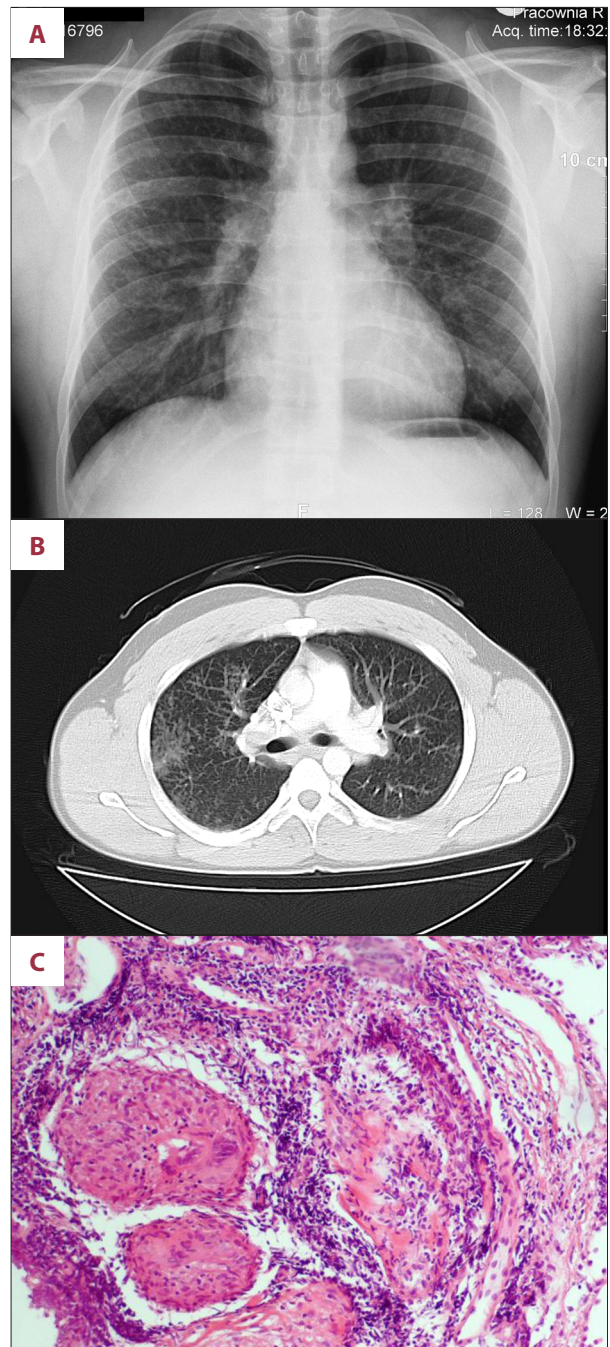


Figure 1. Radiological and histopathological results of the first twin-brother. (A) Chest X-ray showing enlarged hili and disseminated micronodular changes with predominance to middle zones; (B) Selected chest CT scan showing parenchymal micronodular changes; (C). Transbronchial peripheral lung biopsy showing non-caseating granulomas consisting of multinucleated giant cells, epithelioid cells, and surrounding lymphocytes.

clinic and anti-TB treatment composed of isoniazid, rifampicin, pyrazinamide, and ethambutol was started according to directly observed treatment short-course strategy.

Table 1. Selected laboratory test results of the family members.

	Twin-brother 1	Twin-brother 2	Mother
BAL lymphocytes [%]	6	39	31
CD4/CD8	1.76	3.58	5.42
Sarcoid granuloma in TBLB	Yes	No	Yes
SACE [IU/L]	58.2	36	155.2
Serum calcium [mmol/L]	2.49	2.46	2.68
24-hrs urine calcium loss [mmol/24 hrs]	5.04	6.20	15.06
Tuberculin skin test	0	0	0
Quantiferon TB GOLD	Negative	Negative	Negative
<i>Mycobacterium tuberculosis</i> in BAL	+	-	-

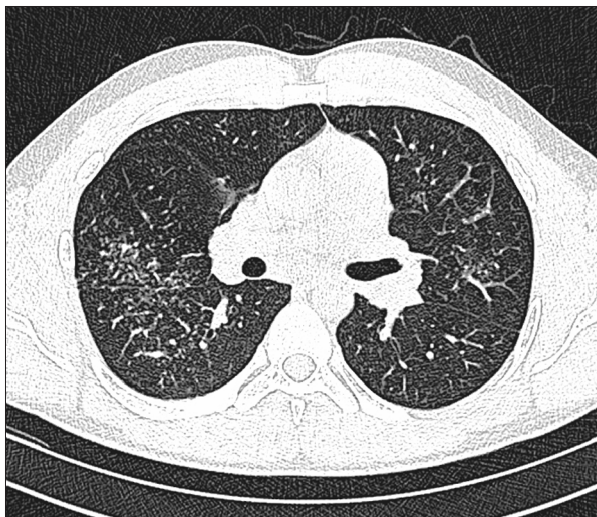


Figure 2. CT-scan of the case's twin brother showing enlarged hilar lymph nodes and disseminated micronodules.

The household members (the case's mother and twin brother) were asked to visit a regional TB out-patient clinic for routine examination of household contacts. Chest X-ray revealed disseminated parenchymal changes with enlarged hili in both family members. The previous X-rays of the twin brother and mother had been performed 3 months and a year ago, respectively, and were both normal. The chest X-ray of the case's older brother, who was living separately, was normal. Therefore, the mother and twin brother were referred to the Department of Pneumology and Allergy for further diagnosis. Chest CT scans confirmed the presence of bilateral hilar enlargement and disseminated nodular changes and thickening of broncho-vascular bundles with predominance of upper and middle zones (Figures 2, and 3A). BAL cellular pattern was typical for sarcoidosis (Table 1) in both. TBLB of the case's twin brother was non-diagnostic (normal lung structure) and he refused further invasive examinations. The mother's TBLB showed non-caseating granulomas (Figure 3B). BACTEC examination of BAL

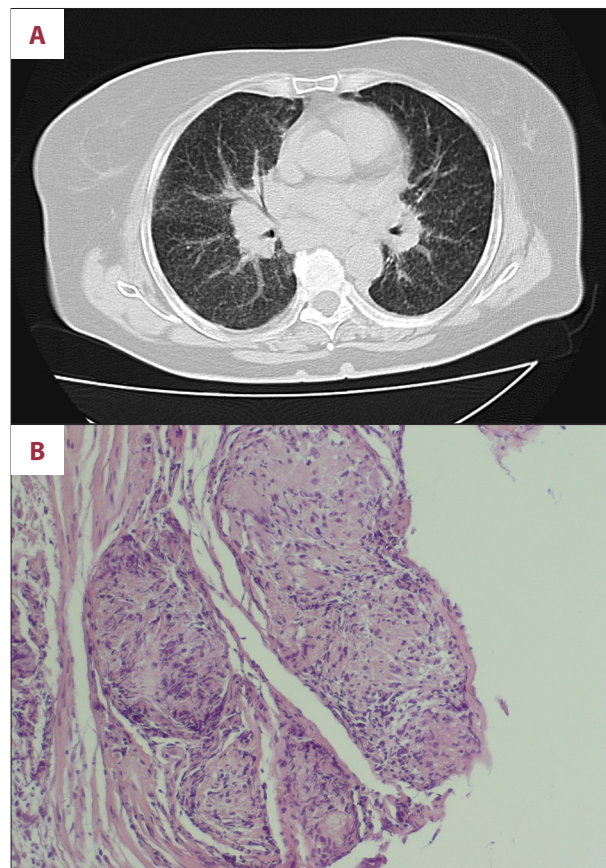


Figure 3. Radiological and histopathological results of the case's mother; (A) CT-scan showing enlarged hilar lymph nodes and disseminated micronodular changes; (B) Transbronchial peripheral lung biopsy showing non-caseating granulomas.

fluid was negative in both the case's mother and twin brother. Due to asymptomatic course, well-preserved lung function, and lack of extrapulmonary symptoms, they were left untreated. Anti-TB treatment was also abandoned.

At a follow-up in November 2011, the chest X-ray of the case was not different from the initial X-ray, but lung HRCT done in March 2012 showed substantial regression of parenchymal changes and sustained slightly enlarged mediastinal lymph nodes (picture not shown). Chest X-ray of the case's twin-brother performed in November showed complete regression of the previously described changes. The mother's chest X-ray performed at this time showed neither progression nor regression. Laboratory markers (SACE, CRP, serum calcium, liver function tests, and peripheral blood count) were within normal limits in all 3 patients. Twenty-four hour urinary calcium loss was increased in the mother but was normal in both twin brothers. Blood for QuantiFERON-TB testing was taken in November 2011 and the results were negative in the whole family. MTB were not found in lung biopsies of any family members (Ziehl-Neelsen stain).

Discussion

We present the case of a patient with concomitant sarcoidosis and tuberculosis, whose mother and twin brother, with similar radiographic changes, were diagnosed with sarcoidosis. The clinical presentation and radiological findings in these 2 diseases may be similar, and the histopathological criteria do not always allow a clear identification of the underlying disease [7,8]. Still, the criterion standard for the diagnosis of TB is identification of MTB in culture. All 3 patients presented small nodular changes on chest CT scans, with enlarged mediastinal lymph nodes. Taking into account the relatively high incidence rate of TB in Poland (about 20 cases per 100 000 population over age 30 years, [9]) and obligatory anti-TB vaccination in newborns, mediastinal/hilar lymphadenopathy as a presentation of primary TB in adult subjects is highly unlikely. Despite discordant results of BAL fluid cytological examination in the case, which showed low lymphocyte count and CD4/CD8 ratio, transbronchial lung biopsy revealed non-caseating granulomas. Elevated SACE concentration and negative TST, although not specific for this disease, also suggested sarcoidosis. Finally, after bacteriological confirmation, concomitant sarcoidosis and tuberculosis were diagnosed in the patient and anti-TB treatment was introduced. The coexistence of sarcoidosis and tuberculosis has been well documented by many authors, but is rare [2,4,10]. We hypothesize that prolonged exposure to mycobacterial proteins might stimulate host immune system to hypersensitivity reactions leading to non-caseating granuloma formation. Numerous epitopes of mycobacterial peptides (e.g., katG, ESAT-6, CFP-10, hsp) have been found to serve as targets of adoptive immune response eliciting Th1 immunophenotype [5,13–15]. Various genetic factors, probably linked with HLA class I and II alleles, can further influence immunological response, leading to sarcoidosis

or TB [16,17]. Strong immune reactions result in protection against progression of infection. This hypothesis seems to have epidemiological confirmation, as TB distribution worldwide is quite opposite to that of sarcoidosis. Consistent with this concept is the simultaneous occurrence of sarcoidosis in all 3 household members.

Familial aggregation of sarcoidosis has been reported by many authors from countries all over the world. The risk of the disease among siblings or parents of a patient with sarcoidosis is increased from 5-fold to 80-fold in monozygotic twins, as compared to the controls [11,12]. Of note is the simultaneous occurrence of lung changes in all 3 patients, pointing to the role of a microbial etiological factor.

It is interesting that the QFT-G-IT result was negative in an infected patient. Although it is well known that sarcoidosis produces tuberculin anergy, there are no data on interferon gamma release assays (IGRAs) results in patients with concomitant sarcoidosis and TB. IGRA tests were developed for diagnosis of LTBI (latent TB infection), and were shown to overcome some important limitations of TST, like cross-reactivity with *Mycobacterium bovis* bacilli Calmette-Guerin (BCG) and most non-tuberculous mycobacteria. However, the negative results of QFT-G-IT, even in immunocompetent patients with active TB, are not unusual. A recent meta-analysis including studies from 35 different countries revealed that the sensitivity of QFT-G-IT for the diagnosis of active TB was about 80% [17]. A prospective study conducted in Cape Town on 395 patients confirmed that negative results of IGRAs did not exclude active disease, both in HIV-positive and HIV-negative patients [18]. Moreover, in contrast to the ELISpot assay, the positive immune response in QFT-G-IT was more dependent upon the level of immunosuppression [19]. On the other hand, different authors reported positive results of QFT-G-IT in patients with sarcoidosis from low and high TB burden countries, irrespective of immunosuppressive treatment [20,21]. However in those studies, sarcoid patients were screened for LTBI because there were no patients with coexistent TB. As TST in cases with sarcoidosis has high specificity but low sensitivity, further investigations are needed to assess the usefulness of IGRAs in patients with sarcoidosis and active TB, but such patients are unique.

Conclusions

This case presentation illustrates on the importance of genetic predisposition (family spreading), as well as the influence of a common environmental factor able to induce a similar clinical and radiological picture in all family members living together. *Mycobacterium tuberculosis* is the suspected etiological factor.

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