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CASE REPORT

Disseminated nontuberculous infections with *Mycobacterium genavense* during sarcoidosis

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ABSTRACT: Sarcoidosis is a chronic disease characterised by the development and accumulation of granulomas in multiple organs. We report two observations of disseminated *Mycobacterium genavense* infection in patients with proven sarcoidosis. High fever and abdominal pain appeared at 8 and 18 months following the initiation of immunosuppressive therapy. Abdominal computed tomography scans of the patients showed diffuse mesenteric lymphadenitis and splenomegaly. The diagnosis was obtained on bone marrow specimens for both patients with numerous acid-fast bacteria at direct examination and positive specific mycobacterial identification by nucleic acid amplification test. Despite prompt antimycobacterial therapy, occurrence of complications (peritonitis post-splenectomy surgery and lung carcinoma) resulted in a fatal outcome for both patients. These cases highlight that opportunistic infections like *M. genavense* or other nontuberculous mycobacterial infections should be considered for long-standing immunocompromised patients with sarcoidosis.

KEYWORDS: Cell-mediated immune defect, *Mycobacterium genavense*, sarcoidosis

Patient 1, a 72-yr-old male, was diagnosed with sarcoidosis on the basis of fatigue, weight loss (15 kg in 6 months), high angiotensin-converting enzyme level (133 IU) and acute renal failure (creatininaemia at 400 μmol·mL^{-1}) associated with histological evidence of chronic noncaseating granulomatous interstitial nephropathy. A culture of renal parenchyma was negative. No mediastinal or lung involvement was detected by chest computed tomography (CT) and spirometry was normal. Underlying common variable immunodeficiency was excluded. Upon initiation of oral steroid therapy (prednisone at 0.5 mg·kg^{-1}·day^{-1}), the patient experienced an improvement of general condition and renal status (creatininaemia at 189 μmol·mL^{-1}). 8 months after the initiation of therapy, fatigue and weight loss reappeared, along with new symptoms of dyspnoea and cough. The chest radiograph was unchanged; however, cardiac ultrasonography detected mild cardiomyopathy with normal electrophysiological studies. Despite the doubling of steroid therapy, his general condition worsened with a fever of 39°C and intense abdominal pain. Biologically, renal function was impaired (creatininaemia at 324 μmol·mL^{-1}) and pancytopenia appeared. The abdominal CT scan showed enlarged, diffuse abdominal lymph nodes and heteronodular splenomegaly estimated at risk for splenic rupture (fig. 1). A large serological panel was negative (HIV-1 and -2, cytomegalovirus, Epstein–Barr virus, *Campylobacter jejuni*, *Yersinia enterolytica*, *Brucella* spp., and *Coxiella burnetii*) and autoantibody testing was negative. The CD4+ T-lymphocyte count was 75 mm^{-3}. A bone marrow examination showed numerous acid-fast bacteria inside epithelioid cells, with one acid-fast bacteria-containing granuloma. Conventional antituberculosis therapy was initiated shortly after. No mycobacterial growth was obtained in enriched liquid media. However, PCR was positive in identifying nontuberculous *Mycobacterium genavense*. Upon identification, the treatment was switched to an oral combination of rifabutin (450 mg·day^{-1}), ciprofloxacin (1,500 mg·day^{-1}), and clarithromycin (1,000 mg·day^{-1}). The patient died shortly after of stercoral peritonitis complicating preventive splenectomy surgery.

Patient 2, a 58-yr-old male, was diagnosed with sarcoidosis on the basis of fatigue, weight loss

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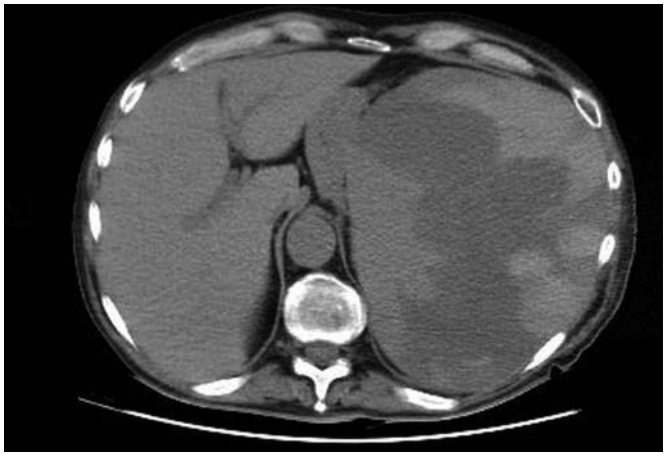

FIGURE 1. Computed tomography abdominal scan of patient 1 showing heteronodular splenomegaly during disseminated *Mycobacterium genavense* infection.

(8 kg in 6 months), anicteric cholestasis (elevated alkaline phosphatase levels) and renal failure (creatininaemia at 364 $\mu mol \cdot mL^{-1}$). Histological evidence of chronic noncaseating granulomatous infiltration was collected from kidney, liver and bone marrow biopsies. Mycobacterial testing (direct microscopic examination, culture and PCR) performed on these specimens were negative. Bilateral hilar adenopathy without parenchymal infiltration was detected by chest CT imaging with normal spirometry. Upon initiation of prednisone and methotrexate, his general condition and organ functions improved (normalisation of alkaline phosphatase level, creatininaemia at 205 $\mu mol \cdot mL^{-1}$). However, after 18 months of treatment, the patient developed a fever of 39°C, weight loss and pancytopenia. The CT scan showed a lung excavated mass in the right lower lobe, and diffuse mesenteric lymphadenitis associated with splenomegaly. The serological panel and the autoantibody testing were negative. The CD4+ T-lymphocyte count was 150 mm^{-3}. A bone marrow examination was performed, and showed numerous acid-fast bacteria inside epithelioid cells and acid-fast bacteria-containing granuloma. PCR rapidly identified *M. genavense*, whereas mycobacterial growth in enriched liquid media was negative both in bone marrow and lung specimens. The histological result of lung biopsies revealed an invasive cell-epidermoid carcinoma at stage IIB (T2N1M0). Surgery was not an option because of the patient's general condition. Antimycobacterial treatment was initiated with an oral combination of rifabutin, ciprofloxacin and clarithromycin. Rapid progression of lung carcinoma caused the patient's death within 5 months, despite the prompt initiation of chemotherapy.

DISCUSSION

Sarcoidosis is an enigmatic multisystemic disease characterised by epithelioid and giant cells containing granulomas involving the lung, lymph nodes and other organs. The hypothesis that sarcoidosis may be triggered by the presentation of poorly degradable mycobacterial antigens is still debated [1]. The occurrence of active tuberculosis in the course of sarcoidosis has been previously reported, but opportunistic infections with nontuberculous mycobacteria (NTM) are considered uncommon [2].

NTM are responsible for insidious and severe disseminated infections in immunocompromised patients [3]. Much remains to be understood about the pathogenesis of NTM infections in human beings as most of these organisms appear to lie at the edge of pathogenicity. A combination of a large infecting dose, long-standing colonisation, and immune status decline may trigger invasive disease. Their clinical presentation can be misdiagnosed as a recurrence of the underlying disease. A decline in the prevalence of tuberculosis in Western countries over the past several years has been accompanied by an increase in the rate of NTM diseases. Rather than an increase in prevalence, it is most likely due to a wider range of long-standing immunocompromised patients in various clinical settings and to the introduction of more accurate methods for NTM identification (replication in liquid media and molecular biology-based methods of detection). Indeed, NTM diseases, unlike tuberculosis, are not reportable to public health authorities; therefore, best estimates are often based on the progress in laboratory isolation of NTM, which has led to the recognition of several new species associated with human disease.

The slow-growing *M. genavense* has emerged as an important NTM among AIDS patients, causing up to 15% of all NTM infections [3–5]. These are the first reports of *M. genavense* infection during sarcoidosis. Disseminated *M. genavense* infection is an alternative diagnosis to *Mycobacterium avium* complex infection, since both infections display similar clinical presentation with a particular emphasis on abdominal pain associated with mesenteric lymphadenitis and splenomegaly [3–8]. This ubiquitous environmental microorganism has previously been isolated from tap water and pets (birds and dogs) [3]. In humans, colonisation of the gastrointestinal tract may represent the main portal of entry. Bone marrow, lymph nodes and intestinal mucosa, as well as liver, stool and blood, are the main sites from which *M. genavense* can be successfully isolated [3–8]. The two cases emphasise the need for further investigation into any concurrent infectious process as a differential diagnosis of a current sarcoidosis recurrence. Fever, intra-abdominal adenopathy and splenomegaly are highly evocative of sarcoidosis recurrence. However, high-level fever, inflammatory syndrome and the absence of intrathoracic lymph nodes are not common features in this setting [6]. Moreover, both patients had reached a point of major immune impairment due to: 1) prolonged steroid and immunosuppressive therapies; 2) a low CD4+ T-lymphocyte count, which is frequently seen in the context of NTM infection and is unlikely to reflect an otherwise quiescent sarcoidosis [3]; and 3) coexistent lung carcinoma, which certainly contributed to immune impairment in patient 2. However, the possibility that *M. genavense* infection was present from the onset of symptoms cannot be completely ruled out. This hypothesis seems more plausible for patient 1. Indeed, typical sarcoidosis thoracic involvement was lacking and only biopsy renal cultures were initially performed. For patient 2, initial mediastinal involvement along with liver and renal impairment was more consistent with sarcoidosis. Furthermore, PCR was initially performed on bone marrow, liver and kidney biopsy specimens.

Four sporadic cases of *M. genavense* infection have been described in patients with non-HIV-related cell-mediated

immune defects: in renal and heart transplant recipients [6], in a case of chronic lymphocytic leukaemia [7], and in a case of an unclassified immunological disorder [8]. The long duration of defective immune status before the onset of symptoms (from 7 months to 14 yrs), the high mortality rate (75%) and the difficulty obtaining a diagnosis by culture methods were the main characteristics of these cases. Indeed, *M. genavense* grows poorly and inconsistently on solid or enriched liquid media, requiring an average of 7 weeks for the reported cases to be detected. This can prevent accurate diagnosis and appropriate medical management. It must be emphasised that, in our cases, the collection of bone marrow specimens and the use of PCR-based detection were decisive in establishing the diagnosis.

Treatment of *M. genavense* infection is often challenging given the limited data available. It is a difficult to treat infection and the best therapeutic combination is not known. Important key points from a literature-based review include: 1) using at least three antimycobacterial drugs, including clarithromycin [3]; 2) reducing or interrupting, when possible, the immunosuppressive drug(s) and/or cause(s); and 3) minimum inhibitory concentration determination of at least clarithromycin should be systematically performed in case of positive culture [9]. *In vitro* susceptibility testings indicate an inhibitory effect of macrolides and rifamycins, and a partial inhibitory effect of aminoglycosides, quinolones and clofazimine, whereas isoniazid and ethambutol appear to have negligible activity [9]. *In vivo*, clarithromycin and rifabutin were more effective than amikacin and ciprofloxacin [10]. A successful clinical outcome has been reported with the additional use of clofazimine and/or moxifloxacin in the combination [6]. The recommended duration of treatment is at least 12–18 months.

In conclusion, these two observations of disseminated *M. genavense* infection during sarcoidosis highlight that NTM opportunistic infections are not restricted to HIV-infected patients. It should be taken into consideration for each patient undergoing significant clinical worsening of their chronic systemic disease while currently treated with long-term immunosuppressive therapies.

STATEMENT OF INTEREST

None declared.

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