CASE REPORT

Multisystemic tuberculosis with skin involvement in a patient with compromised cellular immunity suggestive of primary immunodeficiency

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INTRODUCTION

Tuberculosis (TB) is a public health care problem. In 2020, the World Health Organization reported that 17.2% of the 5.8 million TB cases were extrapulmonary. Cutaneous TB constitutes less than 2% of extrapulmonary manifestations. Scrofuloderma is a common form of cutaneous TB and results from direct extension of an underlying tuberculous lesion, either a lymph node, a bone, or the epididymis. We present a case of scrofuloderma with systemic involvement and atypical histologic findings, associated with a genetic mutation suggestive of primary immunodeficiency (PID).

CASE PRESENTATION

A 25-year-old man presented with a 3-year history of firm, nonpainful nodules in the bilateral inguinal region; the lesions increased in size until becoming erythematous, whereas some resolved spontaneously. The nodules progressively extended to the thighs, some becoming fluctuant and draining caseous material before ulcerating. He also presented with abdominal pain, liquid stools, hyporexia, and progressive edema. His family medical history was not relevant. Physical examination showed nonpainful, fluctuant, and suppurative nodules in the bilateral inguinal region and the proximal anterior aspect of the thighs. Some nodules had a central ulcer (Fig 1). There were nontender cervical adenopathies, the largest measuring 3 × 5 cm. The abdomen was distended and painful on palpation, with decreased bowel sounds. Chest examination revealed a good passage of the vesicular murmur in both lung fields, without rales. Retinography was remarkable for the presence of choroidal tubercles (Fig 2). Serological test results for syphilis, human T-lymphotropic virus types I and II, hepatitis B,
hepatitis C, and HIV were negative. The tuberculin skin test was rated 0. A QuantiFERON-TB test and 2 sputum smears were negative.

Soft tissue ultrasound and computed tomography scans demonstrated mediastinal, inguinal, and retroperitoneal lymphadenopathy as well as pulmonary micronodules, cervical and pelvic abscesses, and bowel wall thickening (Fig 3).

Skin biopsies of the nodule in the left inguinal region showed a lymphohistiocytic inflammatory infiltrate with extensive caseous necrosis (Fig 4, A and B). The Ziehl–Neelsen staining revealed a large number of acid-fast bacilli (2+); these bacilli also stained with the periodic acid–Schiff (PAS) staining (1+) (Fig 4, C), albeit with lower intensity than with Ziehl–Neelsen. Furthermore, a smear from the purulent discharge of a fluctuant nodule on the left thigh showed 3+ bacilli by Ziehl–Neelsen (Fig. 4, D).

GeneXpert MTB/RIF (Mycobacterium tuberculosis complex/resistance to rifampicin) and MGIT (liquid culture Mycobacterium Growth Indicator Tube) skin biopsy cultures were positive for Mycobacterium tuberculosis sensitive to rifampicin, streptomycin, isoniazid, and ethambutol. The GenoType Mycobacterium assay and solid medium culture for nontuberculous mycobacteria were negative.

The patient started specific intravenous antitubercular therapy (meropenem, amikacin, ciprofloxacin, and ampicillin/sulbactam), because of gastrointestinal involvement for 1 week before the therapy was switched to first-line oral antituberculosis drugs, plus levofloxacin and clarithromycin, for 6 weeks.
Auramine-rhodamine staining and MGIT culture of the fluctuating nodule secretion from the left inguinal region were performed at the 7-week follow-up, revealing 3+/1 bacilli on direct smear and isolation of *M. tuberculosis*, respectively. The patient's absolute lymphocyte count was consistently low before and during treatment. Flow cytometry showed a reduced CD4 lymphocyte count in a peripheral blood sample. His immunoglobulin count was normal. Sequence analysis and deletion/duplication tests of 407 genes studied in the Invitae Primary Immunodeficiency Panel identified 7 gene variants of uncertain significance, including the *PRKDC* gene.

**DISCUSSION**

We present a case of multibacillary cutaneous TB presenting as scrofuloderma. Although previous literature documented the cervical region as the most frequent location, our patient exhibited lesions in the bilateral inguinal region, which is an unusual location.4

The large number of acid-fast bacilli in skin biopsies and secretion smears, which were also positive for PAS staining, led us to suspect coinfection with nontuberculous mycobacteria, such as *Mycobacterium avium intracellulare*. The positivity of the PAS staining found in some mycobacterial infections under special circumstances, such as severe immunosuppression, is a rare phenomenon, not well known by pathologists. Such positivity was described several years ago in lepromatous leprosy, *Mycobacterium avium intracellulare*, and occasionally in TB. In that context, when there is an abundance of bacilli, some *M. tuberculosis* microorganisms may retain polysaccharides in their wall that can be stained with PAS.5,6 Additional tests, such as cultures and molecular, were negative for nontuberculous mycobacteria infection, ruling out coinfection.

Based on the results, we demonstrated that our patient, in addition to cutaneous involvement, exhibited lymph node TB, miliary TB, and probably enteroperitoneal TB. Therefore, we considered the lymphohematogenous route as the main mechanism of dissemination.
Given the diagnosis of multisystemic TB, poor response to therapy, negative reaction to the tuberculin skin test, negative QuantiFERON-TB test, and reduced CD4 lymphocyte count, an underlying defect in cellular immunity was suspected, and genetic studies for PID were therefore conducted.

Although patients with PID are susceptible to multiple infections and manifestations of autoimmunity, some have been found to have a specific risk of mycobacterial infections. Cutaneous manifestations are common in PIDs, affecting between 40% and 70% of these patients. Usually, Mendelian susceptibility to mycobacterial diseases is described in pediatric patients, who are superinfected by nontuberculous mycobacteria, Listeria species, and disseminated bacille Calmette-Guerin infection. Although, 1 cohort reported *M tuberculosis* infection in a 41-year-old patient with a mutation of interferon-gamma receptor 1; in our patient, we did not detect mutations in the interferon-gamma and interleukin 12 axis suggestive of Mendelian susceptibility to mycobacterial diseases.

Our patient exhibited a mutation in the *PRKDC* gene that codes for the catalytic subunit of a protein kinase. This mutation has been associated with dermal granulomas, autoantibodies, and progressive deficiency of T and B cells; the degree of severity and clinical phenotype are multifactorial. In this case, this genetic finding is suspected to have contributed to the disseminated infection by *M tuberculosis*.

Evaluation of PID may be warranted in patients with uncommon presentations of TB and/or poor response to treatment. Other studies, such as exome sequencing, may be necessary to identify new gene mutations that cause specific predispositions to mycobacterial infections.

**Conflicts of interest**
None disclosed.

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