Case Report: Cutaneous Extensively Drug-Resistant Tuberculosis


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Abstract. A 48-year-old immunocompetent man without known exposure to tuberculosis had a > 10-year history of recurrent skin lesions. Cutaneous tuberculosis without any current or past history of pulmonary tuberculosis was diagnosed. Culture of biopsy specimens showed the organism to be resistant to multiple first-line and second-line agents. The patient had a broad, vigorous CD4-specific immune response against multiple tuberculosis antigens. This case is the first report of cutaneous extensively drug-resistant tuberculosis.

A 48-year-old man was referred to the infectious disease clinic at King Edward VIII Hospital (University of KwaZulu-Natal, South Africa) for assessment of skin lesions believed to be caused by erythema induratum (Bazen’s disease). Approximately one year earlier, the patient developed 3–4 nodules on his shins and thighs. The lesions began as subcutaneous nodules that evolved into ulcerative lesions with surrounding erythema and induration over 4–6 months. The lesions were confined to the lower limbs.

The patient had similar lesions 12 years earlier, and a biopsy specimen showed granulomatous panniculitis that was interpreted as erythema induratum. Apart from the skin lesions, the patient was asymptomatic. At that time, investigations for a site of tuberculosis infection, which consisted of a chest radiograph and induced sputum samples, did not show any signs of visceral infection. Despite these findings, the patient was given a full course of antituberculosis treatment as per national tuberculosis treatment guidelines of South Africa1 and showed complete resolution of the lesions. Although the therapy used was not directly observed therapy (DOT), the patient reported compliance.

The lower limb skin lesions appeared a second time two years after he completed his initial antituberculocidal treatment and were accompanied by a painless right testicular swelling, but without associated constitutional symptoms. A clinical diagnosis of erythema induratum was made without a skin biopsy. He was again treated with antituberculosis treatment using the re-treatment regimen as per national tuberculosis treatment guidelines of South Africa.1 The skin lesions and testicular mass resolved while he received non-DOT treatment, which was similar to his prior experience.

The patient remained healthy for nine years but then developed similar lesions for a third time. A dermatologist diagnosed erythema induratum by skin biopsy. A tuberculin skin test was performed and the result was strongly positive. Results of a chest radiograph were normal. He was treated for active tuberculosis with rifampicin, isoniazid, ethambutol, and pyrazinamide. Over the ensuing nine months despite good compliance with treatment, the lesions remained unchanged. He was subsequently referred to the infectious disease clinic at King Edward VIII Hospital.

When seen at the clinic, he had several lesions on his thighs and lower legs (Figure 1). The closed-skin lesions were not painful, but the ulcerated lesions were minimally painful to firm palpation. Apart from the skin lesions, the patient remained well with no symptoms suggestive of any visceral tuberculosis infection.

Aside from his presenting symptoms and the history of erythema induratum, he had no medical or surgical history of note. He had no disease predisposing him to extrapulmonary tuberculosis, i.e., he was negative for human immunodeficiency virus (HIV), did not have diabetes, and had not taken any immunosuppressive medication. His family history was non-contributory, and none of the persons he contacted had similar skin lesions. He had not had any known contact with tuberculosis, had received a bacille Calmette-Guérin vaccination as a child, had no history of pulmonary tuberculosis infection, and did not use alcohol or recreational drugs. He worked as a hairdresser and had never traveled outside South Africa.

Aside from the lesions seen in Figure 1, results of his physical examination were unremarkable. He had no abnormal lymph node enlargement, hepatosplenomegaly, or genitourinary abnormalities. Results of a complete blood count, electrolyte tests, and liver function tests were normal. He had a slightly elevated erythrocyte sedimentation rate (19 mm/hour). Results of an abdominal and testicular ultrasound examination and a chest radiograph were normal.

Analysis of biopsy specimens from his lesions showed chronic inflammation, marked hyperkeratosis and parakeratosis, acanthosis with surface exudates, and transmural inflammation of the arterioles and venules by lymphocytes without any evidence of caseation. The specimen was negative for acid-fast bacilli. Biopsy results were interpreted to be consistent with erythema induratum. Biopsy specimens also showed positive growth for Mycobacterium tuberculosis. Drug sensitivity testing showed resistance to multiple first-line and second-line anti-tuberculosis chemotherapeutic agents (rifampin, isoniazid, ethambutol, streptomycin, kanamycin, and ciprofloxacin).

Because of the repeated episodes and the unusual manifestation of his disease, we assessed his immunologic responses to tuberculous antigens. Lymphocytes were isolated from the patient’s blood for the analysis of tuberculosis-specific cellular immune responses.2 CD4 T cell responses against two M. tuberculosis proteins, CFP10 and ESAT6, were detected (Figure 2).

On the basis of skin culture and drug susceptibility test results, a diagnosis of extensively drug-resistant tuberculosis of the skin (cutaneous XDR-TB) was made.3 Informed dis-
cussion with the patient about his diagnosis, prognosis,\textsuperscript{4} and toxicity associated with use of second-line agents led to a decision to defer treatment. The strategy used was to closely monitor skin lesions and be vigilant for development of symptoms or signs of visceral disease at regular follow-up visits. Any indication of disease progression would prompt a decision to begin treatment.

More than one-third of the world’s population is infected

**Figure 1.** Cutaneous lesions on the lower leg and thigh of the patient with extensively drug-resistant tuberculosis. A. Early lesions observed three months before development of advanced lesions. B. Advanced lesion surrounded by normal skin. C. Skin eruptions in close proximity to each other with marked surrounding erythema. An area of uninvolved skin is shown at the upper left for comparison. This figure appears in color at www.ajtmh.org.

**Figure 2.** Flow cytometric analysis of multi-specific, polyfunctional Mycobacterium tuberculosis--specific CD4+ T cell responses (intracellular cytokine production by CD4+ T cells) in peripheral blood of the patient with cutaneous extensively drug-resistant tuberculosis. An intracellular cytokine staining assay was performed using freshly isolated peripheral blood mononuclear cells stimulated overnight with pools of overlapping 18-mer peptides corresponding to the CFP10 and ESAT6 proteins of *M. tuberculosis*. The percentages in the upper right quadrants indicate the percentage of CD4+ cytokine-positive cells. IFN-γ = interferon-γ; TNF-α = tumor necrosis factor-α; IL-2 = interleukin-2.
with tuberculosis and most of those infected live in developing countries. The most common manifestation of active tuberculosis is pulmonary disease. Extra-pulmonary manifestations occur in some patients with lymphadenitis. Cutaneous tuberculosis is rare in developing countries where the high burden of HIV/acquired immunodeficiency syndrome drives the tuberculosis epidemic and accounts for less than 0.5% of the total extrapulmonary tuberculosis cases seen.

Skin manifestations of tuberculosis can be divided into two categories: cutaneous tuberculosis and tuberculids. The first category includes M. tuberculosis infection of the skin and the second category includes a cutaneous immunologic response to an extracutaneous tuberculous infection. Our patient was initially diagnosed with erythema induratum (Bazén’s disease), a type of tuberculid. Other tuberculids include papulonecrotic tuberculid, lichen scrofulosorum, and a recently defined tuberculid known as nodular tuberculid. Bacilli are not generally identified by acid-fast bacilli stains or cultures of skin lesions of tuberculids. However, the polymerase chain reaction has been used to identify mycobacterial DNA in such lesions. This finding suggests that tuberculids may not be distinct from cutaneous infections. Our patient was reclassified as having cutaneous tuberculosis once mycobacteria were cultured from the skin biopsy specimen.

Cases of cutaneous multidrug-resistant tuberculosis (MDR-TB), which is defined as resistance to both isoniazid and rifampicin, have been reported. In March 2006, the U.S. Centers for Disease Control and Prevention published the results of a multiyear study, which reported several cases of tuberculosis that were resistant to isoniazid and rifampin, as well as multiple second-line drugs; there were no cutaneous or other extrapulmonary manifestations described in the report. A World Health Organization Global Task Force recently formalized the definition of XDR-TB as mycobacterial tuberculosis infections caused by organisms resistant to both isoniazid and rifampicin, as well as fluoroquinolone, and at least one second-line injectable agent (capreomycin, amikacin, or kanamycin). Resistance to the latter two classes of drugs were chosen as defining characteristics because these drugs are considered critical to the success of a salvage second-line regimen against MDR-TB.

Although our patient was given a similar diagnosis by different clinicians each time he was examined, he was treated each time only with first-line antibiotics; only his third treatment regimen was DOT. The question that remains is how the patient acquired his cutaneous XDR-TB.

It is unlikely that he acquired XDR-TB 12 years ago because this is a relatively new disease, and his initial infection was completely cleared with first-line tuberculosis therapy. Another unlikely possibility is that he acquired XDR-TB prior to his referral to us. This is unlikely because he had no known contact with any persons with XDR-TB, he was immunocompetent, and his lesions were always in similar locations. We believe that he was likely non-compliant with one or more of his treatment regimens, which resulted in development of resistance to isoniazid and rifampicin and MDR-TB.

Aminoglycoside resistance could have been associated with his initial infection because a study more than 30 years ago reported resistance to streptomycin in 4% of de novo tuberculosis infections in Tanzania. However, if this drug resistance was present in his initial infection, it would not have affected treatment with first-line drugs. It is not known how M. tuberculosis isolated from this patient became resistant to fluoroquinolones. Ginsburg and others reported fluoroquinolone-resistant tuberculosis in patients who had received fluoroquinolone treatment of a duration as short as one day (median = 4 days, range = 1–66 days). Thus, we postulate that fluoroquinolone resistance may have been associated with fluoroquinolone use for an unrelated infection, which caused development of subsequent resistance during either active or dormant erythema induratum, although the patient did not report use of this drug.

Our patient had no clinical evidence of an immunocompromised state. His CD4 cells showed a robust and polyfunctional response and produced interferon-γ, interleukin-2, and tumor necrosis factor-α after exposure to multiple proteins of M. tuberculosis. Intracellular cytokine-fluorescent staining of CD8 T cells after exposure to tuberculosis-specific antigens showed no responsive cells. This finding may imply that the patient did not have tuberculosis-specific CD8 T cell responses or that such cells were sequestered at the site of infection.

To the best of our knowledge, this is the first report of a cutaneous manifestation of XDR-TB in an immunocompetent host. Management of non-life-threatening manifestations of XDR-TB, especially in immunocompetent hosts, needs to be addressed in light of the tolerability, toxicity, duration of treatment, and expected outcomes of treating such infections. This case report underscores the need to accelerate research for the early diagnosis and treatment of XDR-TB and remain cognizant that any new technology must be available to developing countries in which the disease is most prevalent. Failure to effectively deal with XDR-TB could result in a rapid and unfortunate increase in new cases.

Received April 2, 2007. Accepted for publication June 18, 2007.

Financial support: Douglas P. Olson was supported by a Benjamin H. Kean Traveling Fellowship in Tropical Medicine from the American Society of Tropical Medicine and Hygiene.

Disclosure: None of the authors has any conflicts of interest.

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