NOTES

Disseminated Miliary Tuberculosis of the Skin in Patients with AIDS: Report of Four Cases

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We present clinical, bacteriologic, and pathological findings for four patients with AIDS and cutaneous miliary tuberculosis. All patients had generalized tuberculosis with hematogenous dissemination to multiple organs including the skin. Microscopic examination of the skin lesions revealed ill-formed or no granulomata, extensive necrosis, and numerous acid-fast bacilli. Mycobacterium tuberculosis was detected in the skin lesions by cultures for three patients and by polymerase chain reaction for one. Three of the isolates were resistant to at least isoniazid and rifampin, and one was susceptible to these drugs. The outcome was rapidly fatal for the three patients with multidrug-resistant tuberculosis. This report draws attention to the reappearance of a once-rare manifestation of disseminated tuberculosis which, in the setting of advanced human immunodeficiency virus disease, may offer the first indication of infection with multidrug-resistant M. tuberculosis and a poor prognosis.

Early in the course of HIV infection, the clinical spectrum of tuberculosis is comparable to that for healthy hosts. Later, however, dissemination of Mycobacterium tuberculosis to extrapulmonary sites is more common, and atypical clinical patterns may occur. Disseminated miliary tuberculosis of the skin, or tuberculosis cutis miliaris acuta generalisata, is an uncommon form of tuberculosis characterized by a papulopustular eruption, hematogenous dissemination of tubercle bacilli to multiple organs including the skin, and often, a fatal outcome [1, 2]. This clinical entity, which occurred mainly in infants in the prechemotherapy era [3–5], has reemerged among HIV-infected patients in recent years [6–15]. We present the clinical features, bacteriologic characteristics, and the outcomes for four patients with disseminated miliary tuberculosis of the skin and HIV-1 infection.

Case Reports

Case 1. A 33-year-old homosexual man with AIDS was admitted to the hospital because of a 2-week history of fever, productive cough, and night sweats. His medical history was significant for Pneumocystis carinii pneumonia and cutaneous Kaposi’s sarcoma. Physical examination on admission revealed a temperature of 38.6°C, oral candidiasis, bilateral cervical lymphadenopathy, splenomegaly, and violaceous papular lesions over the right shoulder (Kaposi’s sarcoma). Findings on a chest roentgenogram were normal. Sputum examination demonstrated acid-fast bacilli. Therapy with isoniazid, rifampin, pyrazinamide, and ethambutol was started. Two weeks after the initiation of treatment, the patient developed a diffuse pustular eruption with lesions measuring 2–3 mm in diameter over his arms, trunk, and lower extremities (figure 1A). Examination of a punch-biopsy specimen of skin revealed a dermal microabscess composed of numerous neutrophils and many acid-fast bacilli (figure 1B). The patient was discharged home to continue receiving antituberculous therapy.

One month later, he was readmitted with fever, vomiting, and headache. The skin lesions had resolved but had been replaced with tiny brownish scars. Meningeal signs were present. Examination of the CSF demonstrated a predominantly lymphocytic pleocytosis with 1,389 cells/mm³; a total protein of 274 g/L; and a glucose level of 0.84 mmol/L. Cultures of sputum, blood, bone marrow, stool, a lymph node specimen, the skin specimen obtained during his initial presentation, and CSF obtained during his final hospitalization all yielded M. tuberculosis that was resistant to isoniazid, rifampin, and ethionamide. He became comatose and died 3 days after admission. At autopsy, he was found to have bilateral tuberculous pneumonia with miliary dissemination to the meninges, adrenal glands, kidneys, spleen, liver, lymph nodes, and prostate.

Case 2. A 31-year-old homosexual man who was known to be seropositive for HIV-1 was admitted to the hospital because of a 2-week history of fever, rash, productive cough, night sweats, and weight loss. Physical examination revealed fever (temperature, 39°C), bilateral cervical lymphadenopathy, and bibasilar rales. An acneiform eruption was sparsely distributed...
over his trunk and extremities (figure 2). A chest roentgenogram showed alveolar infiltrates in the right middle and right lower lobes, as well as diffuse, bilateral reticulonodular infiltrates. The absolute CD4⁺ T cell count was 99/mm³. A sputum examination revealed acid-fast bacilli. Examination of a punch-biopsy skin specimen demonstrated suppurrative necrosis in the dermis with many acid-fast bacilli. Treatment with isoniazid, rifampin, pyrazinamide, and ethambutol was started. Six days after his admission to the hospital, the patient developed respiratory distress and died. No autopsy was performed. Cultures of sputum, blood, and the skin biopsy specimen all yielded *M. tuberculosis* that was resistant to isoniazid, rifampin, ethambutol, and ethionamide.

**Case 3.** A 33-year-old homosexual man with HIV-1 infection was admitted to the hospital because of a 3-week history of fever, night sweats, productive cough, and shortness of breath. Results of the patient’s physical examination were unremarkable except for the presence of violaceous papular lesions over his trunk (Kaposi’s sarcoma). A chest roentgenogram revealed diffuse alveolar infiltrates in both lung fields. The absolute CD4⁺ T cell count was 41/mm³. Examination of the sputum revealed many acid-fast bacilli. Treatment with isoniazid, rifampin, pyrazinamide, and ethambutol was initiated. After 2 weeks, the symptoms persisted; therefore, streptomycin and ciprofloxacin were added to the regimen for possible multidrug-resistant tuberculosis.

Five weeks after the initiation of antituberculous therapy, the patient developed papulopustular lesions, 2–3 mm in diameter, that were scattered over his trunk and extremities. Examination of a skin biopsy specimen showed necrosis with numerous neutrophils and abundant acid-fast bacilli. The skin biopsy specimen was not sent for culture. However, examination of a paraffin block of the specimen with use of PCR revealed *M. tuberculosis* DNA [16]. Cultures of sputum, stool, and a bone marrow aspirate yielded *M. tuberculosis* that was resistant to isoniazid, rifampin, ethambutol, and ethionamide. Within 10 days, the papular skin lesions resolved. Four days later, the patient developed respiratory distress and died. No autopsy was performed.

**Case 4.** A 37-year-old HIV-infected woman was admitted to the hospital because of a spontaneous fracture of the right femur. On physical examination she was found to have a temperature of 38.8°C and generalized lymphadenopathy; coarse rales were heard on auscultation of the left lung base. The right thigh was tender and edematous. A chest roentgenogram showed consolidation in the left lower lobe, and a roentgenogram of the right femur revealed a fracture in the upper one-third of the bone. The absolute CD4⁺ T cell count was 9/mm³. Examination of a sputum smear showed numerous leukocytes and acid-fast bacilli. A bone biopsy was performed in the area of the fracture.

Two days after the initiation of treatment with isoniazid, rifampin, and pyrazinamide, the patient developed an acniform papular rash over her face, trunk, and arms; the rash resolved within 2 weeks, with a residual brownish discoloration. Examination of a skin biopsy specimen revealed deep-dermis microabscesses containing neutrophils, cellular debris, and acid-fast bacilli. *M. tuberculosis*, susceptible to all conventional antituberculous medications, was isolated from sputum, the right femur, and the skin biopsy specimen. The patient was poorly compliant with medical treatment and was readmitted to the hospital with cavitary pulmonary tuberculosis 6 months after discharge. Antituberculous therapy was initiated and she was discharged to her home 1 week after admission. The patient was subsequently lost to follow up.

**Discussion**

Tuberculosis cutis miliaris acuta generalisata rarely occurs in adults. From the turn of the century until 1991, only 25 cases were reported in patients >15 years of age [1, 2]. However, in the last 7 years this unusual presentation of tuberculosis has been reported in 15 HIV-infected patients, including the four patients described herein (table 1).

Two factors are mainly responsible for the resurgence of this rare form of tuberculosis in adults: severe immune dysfunction caused by HIV infection and infection due to *M. tuberculosis* that is resistant to standard antituberculous drugs. These factors...
The skin is an uncommon site of involvement with *M. tuberculosis*, the cutaneous manifestations of tuberculosis are highly variable [17]. The main determinant of the type of skin lesions that might develop appears to be the host’s immune response. Analogous to the leprosy model, a moderate-to-vigorous immune response to tubercle bacilli results in skin lesions known as lupus vulgaris, which are characterized by granulomas and a low bacillary load. In contrast, an unsuccessful immune response results in cutaneous miliary tuberculosis characterized by extensive necrosis, absence of granuloma formation, and a high bacillary load. The latter microscopic findings were seen in the skin biopsy specimens from our patients and reflected profound cell-mediated immunosuppression.

Biopsy of the skin lesions associated with cutaneous miliary tuberculosis provides the earliest and simplest method of making a diagnosis. In fact, microscopic examination of the lesions revealed the presence of numerous acid-fast bacilli for all of our patients; cultures yielded tubercle bacilli for three; and *M. tuberculosis* DNA was amplified by PCR for one. Therefore, it is important to perform skin biopsies for all HIV-infected patients with papulopustular eruptions and routinely send the specimens for microscopic examination and mycobacterial cultures. Detection of *M. tuberculosis* DNA by PCR emphasizes the importance of PCR for the rapid diagnosis of tuberculosis in such cases and underlines the utility of this method in situations where a diagnosis is made retrospectively or cultures are not performed.

The eruptions in our patients had major significance as clues to the presence of disseminated tuberculosis. At the time of the appearance of the cutaneous lesions, all of the patients had generalized tuberculosis; *M. tuberculosis* was isolated from blood, bone marrow, and other extrapulmonary sites in addition to the skin. Moreover, dissemination of *M. tuberculosis* to the skin, despite the administration of antituberculous treatment, may provide an indication of infection with multidrug-resistant tuberculosis.

The fatal outcome for three of our four patients supports the previous observation of a high mortality among patients with cutaneous miliary tuberculosis. In two recent reviews of this entity, the outcome was universally fatal for patients who did not receive appropriate antituberculous treatment, whereas those who received isoniazid-based combination therapy generally did well [2, 13]. Similarly, the three patients who were infected with multidrug-resistant *M. tuberculosis* died 1–5 weeks after the rash first appeared, whereas the fourth patient who was infected with susceptible *M. tuberculosis* infection and received appropriate antituberculous treatment survived at least 6 months after the diagnosis.
Table 1. Data on cases of tuberculosis cutis miliaris acuta generalisata in HIV-infected patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)/sex</th>
<th>CD4+ T cell count (/mm$^3$)</th>
<th>Skin biopsy specimen</th>
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<td>[6]</td>
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<td>9</td>
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</table>

NOTE. AFB = acid-fast bacilli; NA = data not available; ND = not done; PR = present report.

* Tuberculosis was caused by multidrug-resistant tubercle bacilli.

$^2$ Mycobacterium tuberculosis DNA was amplified by PCR.

Since the transmission of tuberculosis is accelerated in the setting of HIV infection and the spread of multidrug-resistant tubercle bacilli is continuing among HIV-infected patients [18], more cases of disseminated miliary tuberculosis of the skin are likely to be encountered by health care providers. It is crucial for physicians caring for HIV-infected patients to be aware of this entity and maintain a high level of suspicion, so that this potentially fatal and contagious illness is recognized early and specific therapy and strict isolation measures can be instituted promptly.

References