Disseminated *Mycobacterium terrae* Infection in a Patient with Advanced Human Immunodeficiency Virus Disease

***Mycobacterium terrae* has been rarely implicated in human disease and never in patients infected with human immunodeficiency virus (HIV). We describe an HIV infected patient with disseminated infection by *M. terrae* with pulmonary and cutaneous clinical manifestations. *M. terrae* was isolated from both sputum and urine, and identified by both conventional tests and high-performance liquid chromatography. Clinical and microbiological characteristics of this case are compared with those reported in the literature.**

The *Mycobacterium terrae* complex *(M. terrae, Mycobacterium nonchromogenicum,* and *Mycobacterium triviale)* includes slow-growing, nonchromogenic mycobacteria (Runyon group III). Up to 18% of isolates of nontuberculous mycobacteria [1, 2] that are recovered from humans are *M. terrae* complex organisms, and these isolates are rarely related to clinical manifestations, thus signifying nonpathogenic colonization. A few cases of human disease that involved joints [3, 4], lungs [5–10], skin [11], gut [12], urinary tract [13], and lymph nodes [14], or appeared as disseminated disease have been described elsewhere [15, 16]. To our knowledge, isolation of *M. terrae* complex has been described only in 1 series of 35 HIV-infected patients (isolation occurred only in 1 case) [1], but clinical manifestations were not mentioned. We describe here an HIV-infected patient with disseminated infection by *M. terrae* that was associated with progressive pulmonary and cutaneous disease. Clinical and microbiological characteristics of this case are compared with those reported in the literature.

Case report. A 29-year-old HIV-infected woman had fever (temperature up to 38.57C) and productive cough. The patient was receiving treatment with didanosine plus stavudine and cotrimoxazole prophylaxis. Physical examination revealed multiple painless, nonitching, papulonodular skin lesions (up to 5 mm) throughout the body, mainly on the face, and slight bilateral enlargement of axillary lymph nodes. Skin tests with multiple recall antigens (Pasteur Merieux, Lyon, France) and with PPDs from *Mycobacterium tuberculosis* (Biocine; Chiron, Siena, Italy) and nontuberculous mycobacteria (Statens Serum Institut, Copenhagen) were all negative. Results of the usual blood chemistry analyses were normal, except for those that revealed leukopenia, lymphocytopenia, and anemia. The CD4+ lymphocyte count was 19/μL.

Microbiological and serological analyses were performed—particularly repeated cultures of blood, sputum, and urine—for viruses, fungi, bacteria, and mycobacteria. Direct examinations of 3 consecutive sputum samples were negative for acid-fast bacilli (AFB), although 2 of 3 urine samples were positive.

This latter finding did not seem pertinent because the patient had no signs of urinary tract involvement. An echocardiogram, a CT scan of the brain, and a chest radiogram were normal. After 2 weeks of continual fever (temperature, 38.57C), the patient had mild dyspnea, pale skin, and a marked increase of

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skin lesions. High-resolution CT showed diffuse pulmonary interstitial involvement with a slender miliary pattern (figure 1) and slight enlargement of both mediastinal and axillary lymph nodes. Analysis of a sputum smear revealed AFB.

Before specific treatment could be initiated, the woman developed severe respiratory failure compatible with adult respiratory distress syndrome and died. Permission to perform an autopsy was not given, but biopsy of the skin lesions showed granulomatous foci evolving into microabscesses and AFB. Culture of the skin biopsy specimen for mycobacteria was not performed.

After 3 weeks, cultures of 2 sputum specimens and 1 urine sample yielded mycobacteria. All other cultures were negative. Mycobacterial isolates grew at 377C and 257C but not at 457C; results of all cultures and biochemical tests were compatible with *M. terrae.* Colonies were rough, and the growth showed no pigment production in the dark or after light exposure. Mycolic acids from culture colonies were analyzed by HPLC (Beckman Coulter, Milan, Italy) [17]. The typical chromatographic pattern for *M. terrae* resulted (figure 2).

PCR analyses of sputum and urine samples and isolates for *M. tuberculosis* complex were performed by use of 2 sets of primers from the IS6110 sequence of *M. tuberculosis* [18]; the results of these analyses were negative. After electrophoresis, the final 123-bp product was hybridized with the specific probe (Diasorin, Saluggia, Italy). Lastly, in vitro susceptibility testing was performed by means of the macrodilution method with use of radiometric broth [19] that was developed for isolates of the *Mycobacterium avium* complex; this method was suitable for our isolate because of similar growth kinetics in liquid medium. The strain was susceptible to rifampin (1 μg/mL), rifabutin (<0.12 μg/mL), ethambutol (<2 μg/mL), streptomycin (<2 μg/mL), ciprofloxacin (<0.5 μg/mL), and clarithromycin (<2 μg/mL).

Discussion and literature review. Organisms of the *M. terrae* complex are usually described as occasionally isolated non-pathogenic colonizers [1, 2]. Therefore, cultures positive for these agents should be carefully interpreted. To date, few cases of human disease caused by *M. terrae* complex have been reported [3, 4, 5–16], and isolation of *M. terrae* complex from HIV-infected patients has been described only in 1 series of 35 patients (isolation occurred only in 1 case, apparently without clinical disease) [1]. Our patient, therefore, represents the first HIV-related case of clinically relevant disseminated infection by *M. terrae.*

According to current criteria of the American Thoracic Society [20], our patient had pulmonary disease by *M. terrae;* in fact, clinical symptoms and/or signs together with abnormalities revealed by high-resolution CT, the absence of any other reasonable cause of disease, the isolation of *M. terrae* from 2 sputum samples, and 1 sputum smear positive for AFB all support this diagnosis. Moreover, a low CD4+ count is considered an important risk factor for pulmonary disease due to nontuberculous mycobacteria. In addition, on the basis of AFB found by histological examination and their resemblance to organisms that cause similar skin lesions ascribed to the same agent, the skin lesions were most likely caused by *M. terrae* [16]. Finally, in the absence of other pathogens, fever with involvement of multiple anatomic sites (lung, skin, and lymph nodes), the isolation of *M. terrae* from 2 distinct sources (sputum and urine samples), and the histological evidence of

AFB in skin lesions strongly suggest disseminated disease by *M. terrae,* although blood cultures were negative.

Table 1. Features of 14 previously reported cases of pulmonary disease and disseminated disease that were related to *Mycobacterium terrae* complex.

Underlying condition [ref]	*Mycobacterium* species identification	Clinical manifestation(s)	Basis for diagnosis	Results of in vitro drug susceptibility testing	Treatment	Outcome
NR [5]	*M. nonchromogenicum*	Fibrocaseous lesion	Sputum cultures	R: Rif, INH, Stm, PAS, Cyse, Km, vm, Cpm; S: Eth, Ethi	Eth, INH, then T, Km, INH	Died of cor pulmonale
NR [5]	*M. nonchromogenicum*	Solitary cavity	Sputum cultures	R: Rif, INH, Stm, PAS, Ethi, Cyse, Km, Evm, Cpm; S: Eth	Rif, INH, Stm	Sputum became negative, cavity resolved
NR [5]	*M. nonchromogenicum*	Solitary cavity with pericavitary infiltration	Sputum cultures	R: Rif, INH, Stm, PAS, Ethi, Cyse, Km, Evm, Cpm; S: Eth	Rif, INH, Stm	Sputum became negative, cavity resolved
PT [5]	*M. nonchromogenicum*	Large cavity with fibrotic process	Sputum cultures	R: Rif, INH, Stm, PAS, Ethi, Cyse, Km, Evm, Cpm; S: Eth	NR	Died of cor pulmonale
PT [5]	*M .nonchromogenicum*	Bullae with fibrosis	Sputum cultures	R: Rif, INH, Stm, PAS, Ethi, Cyse, Km, Evm, Cpm; S: Eth	Rif, Eth, Km, INH	Sputum became negative, cavity remained
PT [5]	*M. nonchromogenicum*	Cavity in sclerotic lesion	Sputum cultures	R: Rif, INH, Stm, PAS, Cyse, Km, Evm, Cpm; S: Eth, Ethi	NR	Died of cor pulmonale
PT [5]	*M. terrae*	Solitary large cavity	Sputum cultures	R: Rif, INH, Stm, PAS, Ethi, Cyse, Km, Evm, Cpm; S: Eth	Rif, Eth, Km	Sputum became negative, cavity remained
None [6]	*M. terrae* complex	Cavities	Sputum and resected cavity cultures, granuloma	R: Rif, INH, Stm, PAS, Km, Cyse, Evm; S: Eth, Ethi	Rif, INH, Eth, Km	Persistently positive cultures until cavity resection
None [7]	*M. terrae* complex	Cavity	Sputum cultures	R: INH, Stm, PAS; S: Rif, Eth	Rif, INH, Eth	Sputum became negative, cavity resolved after 4 w
Glucocorticoid therapy [8]	*M. terrae*	Patchy infiltrates, cavities	Sputum and gastric washing cultures	R: INH, Stm, Eth, PAS; S: Rif, Cyse	Rif, INH, Eth, PZA, Stm, Pfx	Sputum became negative
Alcohol addiction [9]	*M. terrae* complex	Cavity	Sputum cultures	NR	Rif, Eth	Resolution after 18 mo
NR [10]	*M. terrae*	Large mass	Bronchoscopy specimen cultures	R: INH	Rif, Eth, INH, PZA	Spontaneous reduction of mass before therapy
PT [15]	*M. terrae* complex	Disseminated disease (kidney, bone arrow, liver)	Urine, bone marrow, and liver specimen cultures; hepatic granuloma	NR	No therapy	Spontaneous resolution
Cancer, BMT, chemotherapy [16]	*M. terrae* complex	Disseminated disease: pulmonary (miliary infiltrates), skin (papulonodular lesions)	Transbronchial biopsy specimen culture, lung and skin granulomas	R: Rif, INH, PZA, Stm, Cpm, Cpfx, Km, Cyse	Rif, INH, PZA	Recovery after 6 w

NOTE. BMT, bone marrow transplant; Cpfx, ciprofloxacin; Cpm, capreomycin; Cyse, cycloserine; Eth, ethambutol; Ethi, ethionamide; Evm, enviomycin; INH, isoniazid; Km, kanamycin; NR, not reported; PAS, *para*-aminosalicylic acid; Pfx, pefloxacin; PT, prior tuberculosis; PZA, pyrazinamide; ref, reference; R, resistant; Rif, rifampin; S, susceptible; Stm, streptomycin; T, thiacetazone.

Figure 1. High-resolution CT scan of the lungs of a patient with advanced HIV disease and disseminated *Mycobacterium terrae* infection. Scan shows diffuse interstitial involvement with a slender miliary pattern.
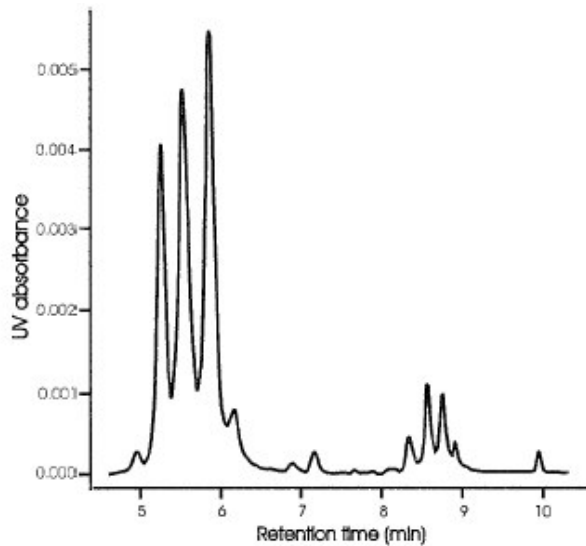
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Figure 2. Representative HPLC pattern for *Mycobacterium terrae* UV, ultraviolet.

The strict application of diagnostic criteria for disease due to nontuberculous mycobacteria in immunocompromised patients is controversial. Some investigators have stated that a single *Mycobacterium kansasii* isolate from the respiratory tract of a HIV-infected patient should be indicative of disease [21]; furthermore, diagnosis of disseminated *Mycobacterium scrofulaceum* disease in a patient with AIDS was based on clinical manifestations and isolation of the organism from 2 different sites (sputum and skin) independent of blood cultures [22].

Our patient's characteristics were compared with those of other patients previously described in the literature (the features of 14 previously reported cases of pulmonary disease and disseminated disease that were related to *M. terrae* complex are listed in table 1). No study included patients with HIV infection. This condition, in addition to predisposing for disease by normally nonpathogenic nontuberculous mycobacteria, might also explain several features that we observed. We diagnosed disseminated infection with involvement of multiple anatomic sites; only 2 cases of disseminated disease have been reported [15, 16], 1 of which occurred in an immunosuppressed patient with cancer who had received a bone marrow transplant and repeated chemotherapy [16]. The remaining reports described localized infections in immunocompetent patients, who most frequently had tenosynovitis [3, 4] and pulmonary lesions [5–10]. The radiological aspect of lung involvement in our patient is also noteworthy, since diffuse interstitial involvement and absence of cavitary lesions were described only in 1 immune-impaired non–HIV-infected patient [16]. These findings resemble those of tuberculosis in advanced HIV disease [23]. The negative results of skin testing with mycobacterial and recall antigens for our patient reflect an anergy condition that is also common in severe immunodeficiency.

As for the clinical course, non–HIV-infected patients with *M. terrae* complex disease often have microbiological clearance after brief treatment [7], no treatment [10, 15], or even the use of drugs associated with in vitro resistance [5, 16]. In contrast, in the absence of specific therapy because of the delayed diagnosis, our patient had a rapidly progressive course with a fatal outcome.

Previously described cross-reactivity between *M. terrae* complex and DNA probes for *M. tuberculosis* [24] was not found in our case, since the DNA sequence from IS6110 was chosen as the PCR target. Moreover, *M. terrae* isolated from our patient appeared susceptible in vitro to most antimycobacterial medications. This finding contradicts the multidrug resistance associated with *M. terrae* complex [5–8, 16] and is probably due to our use of liquid media, which are more reliable than solid media for testing for nontuberculous mycobacteria [25].

In conclusion, increasing pathogenicity has been observed for nontuberculous mycobacteria in recent years, especially those isolates from HIV-infected patients. Our experience strongly suggests that *M. terrae* can cause disseminated and progressive disease in the absence of specific treatment. Broad-range use of rapid and sensitive diagnostic procedures is needed to permit early and specific treatment of unusual mycobacterial diseases.

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