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Originals

Severe tuberculosis in patients with human immunodeficiency virus infection

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Abstract. Tuberculosis has now been well documented as a complication of infection with human immunodeficiency virus (HIV), but no studies concern patients requiring admission to the ICU. We report 12 cases of severe disseminated tuberculosis in patients who were seropositive for HIV. Eight patients had diffuse pulmonary involvement responsible for acute respiratory failure, 7 of whom required mechanical ventilation. Four developed septic shock, and in 3 blood cultures were positive for *M. tuberculosis*. Four patients had central nervous system involvement, with coma requiring mechanical ventilation 3 times. Rapid diagnosis was permitted in 10 patients by acid-fast smears of pulmonary specimens (8 patients) and/or tissue biopsies (4 patients). Seven patients died despite intensive therapy; autopsy was performed in 4 patients, showing disseminated tuberculosis. On the basis of this report, tuberculosis in HIV infection may present as an overwhelming systemic disease and thus requires an aggressive diagnostic and therapeutic approach.

Key words: HIV – Aids – Tuberculosis – Intensive care

Recent reports suggest that tuberculosis is common in the setting of infection with human immunodeficiency virus (HIV), especially among demographic groups with a high background prevalence of tuberculous infection [1–8]. Moreover, the recent increase of tuberculosis cases in the United States in 1986 is thought to be due to the occurrence of tuberculosis among HIV-infected persons [9].

Although prospective data suggest that "standard" tuberculosis is common in HIV-infected patients [10], extrapulmonary sites are frequently involved, especially when tuberculosis occurs later in the course of immunodeficiency [1–8, 11]. Thus the revised Centers for Disease Control surveillance case definition for AIDS included HIV-positive patients with extrapulmonary tuberculosis [12]. This study describes the clinical course, diagnostic procedures and the outcome of 12 patients with HIV infection and tuberculosis who required intensive care.

Patients and methods

The records of all patients with HIV infection and verified tuberculosis who were admitted to the intensive care unit of Claude Bernard Hospital from April 1983 through June 1988 were reviewed retrospectively. The patients were counted as having verified tuberculosis only if they had positive cultures for *M. tuberculosis*. The reviewed data included demographic information, risk factors for HIV infection, prior diagnosis of AIDS, CD4+ lymphocyte counts, radiographic patterns, microbiological and histological findings. The severity of acute illness on admission was assessed with the simplified acute physiology score [13]. When mechanical ventilation was required because of respiratory failure, initial PaO_2/FiO_2 ratio and maximum PEEP level were recorded. When shock developed, the results of hemodynamic monitoring with pulmonary artery (Swan Ganz) catheters were collected. The data are expressed as mean±SEM.

Results

During the study period, 61 patients with HIV infection and tuberculosis have been followed in the Infectious Diseases Department of Bichat-Claude Bernard Hospital; 12 of them required intensive care. In the same period, 20 patients with non-HIV-related tuberculosis were treated in the ICU. The age of the 12 ICU patients with HIV infection and tuberculosis was 37.6±4.2 years; 7 of them were male. The risk factor for HIV infection was intravenous drug abuse in 5 patients, male homosexuality in 4, history of blood transfusion in 1 and undetermined in 2. The CD4+ lymphocyte count was available at the time of hospital admission in 4 patients, and was 256±101 cells per cubic millimeter. One patient was treated with zidovudine at the time of diagnosis of tuberculosis. A previous diagnosis of AIDS had been made in 3 patients (1–2 months before) while in 9, tuberculosis was the first opportunistic infection. The simplified acute physiology score on admission was 14.2±1.3. Mechanical ventilation was required in 10 patients, because of acute respiratory failure (7 patients) or coma (3 patients). The initial PaO_2/FiO_2 ratio and maximum PEEP level in the 7 patients with respiratory failure were 144±22 and 9.4±2.1 cm H_2O, respectively. Four of them had evidence of shock and underwent hemodynamic studies, yielding the following results: mean arterial pressure

Table 1. Sites of tuberculosis and microbiological data

Site	No. of patients	AFB[a] on smears	Positive culture
Lung	10	8	10
Lymph node[b]	4	2	4
Liver[b]	4	1	4
Cerebrospinal fluid	4	0	4
Bone marrow	3	1	1
Blood	3	0	3
Urine	2	1	2
Skin[b]	2	0	1
Ascites	1	0	1
Pleural fluid	1	0	1

[a] AFB indicates acid-fast bacilli
[b] Biopsy specimen

52 ± 3 mm Hg, mean pulmonary capillary wedge pressure 8.5 ± 1.9 mmHg, cardiac index 5.1 ± 0.4 l/min·m^2 and systemic vascular resistance index 747 ± 72 dyne·s/cm^5·m^2. Inotropic support (dopamine and/or dobutamine) was required in all 4 patients. One or more blood cultures were positive for *M. tuberculosis* in 3 of these patients.

Table 1 shows the sites of tuberculosis involved and the microbiological data in all 12 patients. Positive acid-fast smears of sputum, tracheal aspirate and bronchoalveolar fluid allowed rapid diagnosis in 8 of 10 patients with culture-proven pulmonary tuberculosis. A chest radiograph showed a diffuse interstitial (6 patients) or alveolar (2 patients) pattern; 2 had a normal radiograph. All patients had at least 1 extrapulmonary site affected. Central nervous system involvement included meningitis in 4 patients, with computed tomographic scan showing hypodense areas (3 patients), arachnoiditis (2 patients) or hydrocephalus (1 patient). Bone marrow specimens were aspirates (1 patient) or biopsies (2 patients). Skin involvement consisted of diffuse cutaneous papules in 2 patients.

Eleven tissue biopsies were obtained from 8 patients; histologic data are summarized in Table 2. Despite a positive culture, 3 specimens (1 skin biopsy and 2 liver biopsies) failed to show any granulomata. Interestingly, 3 of the 4 patients with central nervous system tuberculosis had evidence of disseminated infection: despite negative smears of spinal fluid, a rapid diagnosis was permitted by positive smears of urine (1 patient) or tissue biopsies (2 patients: liver or lymph node). Although this often aggressive approach permitted rapid diagnosis of tuberculosis in the ICU setting, the delay between hospital admission and diagnosis was 19 ± 4 days for the overall 12 patients.

A concomitant opportunistic infection was diagnosed in 2 patients: cytomegalovirus pneumonia and esophageal candidiasis. Moreover, one patient with circulatory failure and mycobacteremia had evidence of superimposed *Ps. aeruginosa* sepsis.

All but 1 patient were treated with a standard 3- or 4-drug regimen. Steroids were added in 7 patients, because of severe hypoxemia (5 patients) or coma (2 patients). Seven died despite intensive therapy; 3 had severe respiratory failure with shock, while 3 with central nervous system tuberculosis died in coma; the remaining patient died of *Candida albicans* sepsis after a protracted course. The 6 nonsurvivors that received antituberculous therapy died 31 ± 13 days after specific treatment was instituted. Autopsy was performed in 4 patients, and disclosed clinically unsuspected sites of infection, including abdominal lymph nodes, pancreas, adrenal glands and kidneys in 2 patients, pleura and bone in 1 patient; in 1 patient, evidence of cytomegalovirus infection was found in stomach and adrenal glands.

Discussion

Tuberculosis now appears as part of the HIV-associated spectrum of opportunistic infections. In all our patients it developed early in the disease: it was the first opportunistic infection in 9, and in 3 tuberculosis and AIDS were diagnosed within 2 months. Other studies have yielded similar findings [1–8]. This is not surprising since *M. tuberculosis* is a more virulent organism than other opportunistic pathogens (for example *M. avium intracellulare* complex), and may be more likely to cause disease at an earlier stage of immunodeficiency.

There are many reports of severe tuberculosis requiring admission to the ICU [14–18], but not in the setting of HIV infection. Eight of our patients developed acute respiratory failure, 7 of whom required mechanical ventilation. They had evidence of acute, moderate to severe parenchymal lung injury, and thus could be included in the expanded definition of the adult respiratory distress syndrome [19]. This infrequent complication of miliary tuberculosis has been reported in patients with other underlying diseases [14–18].

Four patients developed shock and underwent hemodynamic studies, disclosing normal or high cardiac index, low systemic vascular resistance index and normal mean pulmonary capillary wedge pressure. *M. tuberculosis* bacteremia was detected by the isolator lysis-centrifugation system [20] in 3 of these patients. There have been few recent reports regarding this phenomenon, in or out of the setting of HIV infection [3, 4, 20–25]. In addition, 2 of our patients with positive blood cultures had diffuse cutaneous papules (with one skin biopsy specimen growing *M. tuberculosis*), another sign of septicemic disseminated disease. Mycobacteremia with skin localization is very unusual, and has only been reported twice in HIV infection [3, 4]. Except for one patient with concomitant Gram-negative sepsis, *M. tuberculosis* was the only bacterial pathogen isolated, and therefore was reasonably responsible for septic shock.

Table 2. Tissue biopsy results

Site	Type of granuloma		
	None	Non-caseating	Caseating
Lymph node	0	1	3
Liver	2	1	1
Bone marrow	0	0	2
Skin	1	0	0

In the HIV-infected population, central nervous system tuberculosis is not uncommon and patients may present with single or multiple brain mass lesions [26]. Three of our patients had space-occupying lesions in addition to meningitis; none required a brain biopsy, since other less invasive procedures allowed a rapid diagnosis.

In HIV-infected individuals, the diagnosis of tuberculosis on the basis of clinical or radiographic data may be difficult; thus a high index of suspicion for tuberculosis and an aggressive diagnostic approach are required, especially if life-threatening organ failure is present. In this study, pulmonary specimens (bronchial secretions and/or bronchoalveolar lavage) were valuable since positive acid-fast smears permitted a rapid diagnosis in most patients. Previous studies have yielded similar findings [3, 5, 6]. However, all tissue and fluid specimens should be smeared and cultured for mycobacteria, including urine, blood, lymph node, bone marrow and liver, regardless of histologic findings.

Although in some patients with HIV infection and tuberculosis granuloma formation may be absent or rare, it still is more prominent than in *M. avium intracellulare* disease [2]. In this study, we found a high yield of granulomas in biopsy specimens or at autopsy. This supports the previously stated premise that tuberculosis occurs early, when a more adequate inflammatory response can be mounted.

Seven of 12 patients in this study died. In 2 patients, the fatal outcome was undeniably related to tuberculosis, with no other opportunistic infection at autopsy. One patient had evidence of cytomegalovirus infection at autopsy, in addition to disseminated tuberculosis. In 2 patients, nosocomial bacterial or fungal sepsis were diagnosed at the time of demise. In the 2 remaining patients, other undiagnosed opportunistic infections may have contributed to the fatal outcome.

In summary, we have described the clinical features of 12 intensive care unit patients with HIV infection and severe infection due to *M. tuberculosis*. Physicians caring for patients with or at risk for HIV infection should be aware of the possibility of disseminated tuberculosis with septic shock. This warrants an aggressive and, if necessary, invasive diagnostic approach; moreover, therapy aimed at *M. tuberculosis* should be instituted early, pending final identification of the organism.

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