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Clinical Features, Diagnoses, and Management of Tuberculosis in Immunocompromised Hosts

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For many years tuberculosis has been known to occur with greater frequency among persons with disorders that impair host defenses. In most instances these processes interfere with the immune response to *Mycobacterium tuberculosis,* whereas, in a few, such as silicosis, the probable abnormality is a nonimmune defect in macrophage function. Infection with the human immunodeficiency virus (HIV) causes progressive and ultimately profound depression of both humoral and cell-mediated immunity and, thus, is an extremely potent risk-factor for tuberculosis. Presumably the major effect of HIV infection that predisposes persons to developing tuberculosis is the reduction in circulating T-helper ($CD4^+$) lymphocytes which causes a reduction in cytokine production and a consequent decrease in the functional capabilities of macrophages. However, a number of questions concerning pathogenesis of tuberculosis related to HIV remain.

Available data suggest that the magnitude of the risk for developing tuberculosis among persons infected with both HIV and *M. tuberculosis* is very high, 8% in one prospective study. Because of the epidemic of HIV infection, the progressive downward trend in the incidence of tuberculosis in the United States has reversed and in 1989 there was a 5% increase in the number of cases. Preliminary data for 1990 suggest that there will be an 8 to 10% increase over 1989. Also in the United States approximately 3% of tuberculosis patients have been found to be HIV seropositive.

The clinical features of tuberculosis in patients with HIV infection vary depending on the degree of immunosuppression. With mild immunosuppression early in the course of HIV infection tuberculosis presents in a "typical" way with positive tuberculin skin tests, upper lobe cavitary infiltrates on chest film and positive sputum smears and cultures. As the HIV infection progresses, the mode of presentation of tuberculosis becomes more "atypical" with negative skin tests, multiple sites of involvement, chest films showing diffuse noncavitary infiltrates often accompanied by intrathoracic lymphadenopathy. The key to diagnosis is maintaining a high index of suspicion for tuberculosis, especially in patients with advanced HIV disease and including appropriate laboratory examinations in the evaluations of such persons.

Regardless of the stage of HIV infection the response to treatment for tuberculosis is generally favorable if it is begun promptly. Standard therapy utilizing isoniazid, rifampin, and pyrazinamide with or without ethambutol have been associated with high rates of cure.

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Relapse has been uncommon. There has been, however, at least one outbreak of tuberculosis caused by isoniazid and rifampin resistant organisms in which the response to therapy was very poor. Preventive therapy with isoniazid is probably effective as well but this has not been substantiated.

Issues related to infection control are of special concern given the interaction between HIV infection and tuberculosis. Transmission of *M. tuberculosis* to other HIV-infected patients and to health-care workers has been documented to be associated with the use of aerosol pentamidine prophylaxis for *Pneumocystis carinii* and with diagnostic sputum induction.

Since antiquity tuberculosis has been known to occur in persons whose health is impaired in some fashion. This was clearly articulated by the seventeenth century English physician Richard Morton (quoted by Keers[1]), "For in this so slippery a state of health they are wont upon every little occasion of this nature to fall headlong into a fatal consumption." Morton went on to describe some of the factors that led to, "so slippery a state of health" and to indicate how these factors predisposed to tuberculosis.

In more modern times both naturally occurring immunosuppressive disorders and therapies are known to be associated with an increased likelihood of tuberculosis[2)~7)]. The common feature of these conditions that is thought to be the basis for the predisposition to tuberculosis is a reduction in cell-mediated immunity. Some of these disorders are listed in Table 1. Currently both the most profound and the most frequent immunosuppressing disorder is human immunodeficiency virus (HIV) infection.

The epidemic of infection with HIV has produced an entirely new group of persons who have or will have a progressive reduction in cell-mediated immunity[8)]. Given our understanding of host defenses against tuberculosis and the potential for *M. tuberculosis* to be an opportunistic organism, it should not be surprising that tuberculosis has emerged as an important disease in patients with HIV infection[9)10)]. The importance of tuberculosis as an HIV-associated process relates to several features of the infection. First is its high frequency, especially in populations having a high prevalence of preexisting tuberculous infection. Second, tuberculosis is perhaps the only HIV-associated infection that can be transmitted from person to person, whether or not they are HIV-infected. Third, if diagnosed the disease is easily and effectively treated. Finally, the use of isoniazid preventive therapy is likely to greatly reduce the risk of tuberculosis in persons known to be infected with *M. tuberculosis* and HIV.

Table 1 Conditions with which Tuberculosis May Occur as an Opportunistic Infection

Malnutrition
Hematologic and reticuloendothelial malignancies
Solid tumors
Corticosteroid therapy
Immunosuppressive to cytotoxic drug therapy
Diabetes mellitus
End stage renal disease
Human immunodeficiency virus infection

HOST DEFENSES AGAINST *M. TUBERCULOSIS*

Host defenses against *M. tuberculosis* have both nonimmunologic and immunologic components. These are listed in Table 2. In persons who have not previously been infected with and sensitized by *M. tuberculosis*, only nonspecific nonimmunologic mechanisms are available to defend against infection. Because infection with *M. tuberculosis* nearly always occurs via the airborne route, the initial line of defense consists of the mechanical barriers in the nasal passages and upper airway and the mucociliary clearance system of the lower airways. Larger airborne particles ($>5\mu$m) carrying *M. tuberculosis*

Table 2 Host Defenses Against Tuberculosis

Nonimmunologic
Filtration in upper airway
Impaction in large airways and clearance by mucociliary system
Nonspecific phagocytosis and killing by alveolar macrophages
Immunologic
Enhanced phagocytosis and killing by specifically sensitized macrophages/monocytes
Circulating antibodies (? role)

cannot penetrate to the alveoli because of these protective mechanisms. Particles that are $\leq 5\mu m$ can reach the alveolar level[11]. Within the alveoli the organisms are engulfed by patrolling alveolar macrophages. Because specific sensitivity to *M. tuberculosis* is lacking, the macrophages have a limited ability to kill the organism ; thus, it may proliferate within and subsequently outside of the cell[12]. In normal hosts, phagocytosis initiates a chain of events that eventually leads to a specific immunologic response to *M. tuberculosis*. Generation of the specific response requires not only phagocytosis of the organism, but also presentation of its antigens to antigen–responsive lymphocytes, particularly T cells, although B lymphocytes are involved and produce humoral antibodies to several components of the organism. Sensitized T lymphocytes are then capable of generating lymphokines that activate macrophages, greatly enhancing their killing ability. The time required for this response to become effective is not known but probably parallels the development of cutaneous reactivity to tuberculin, approximately 6 weeks.

During the interval between initial implantation of the organism within the alveolus and the subsequent development of specific cell–mediated immunity, there is a (usually) silent tuberculous bacillemia resulting in seeding of the lungs as well as other organs. Once the cell–mediated response is mature, infection in all areas is nearly always contained and the majority of organisms are killed. However, killing is not uniform and viable organisms persist in sites that were inoculated during the early bacillemic phase. The factors responsible for the continued containment of *M. tuberculosis* are not well understood but likely include maintenance of an intact cell–mediated response.

Soon after infection occurs, prior to cell–mediated immunity becoming effective, is the time of greatest risk for developing tuberculosis. A variety of studies have shown that the risk of disease is 3% to 10% in the first year following infection and declines sharply thereafter[13]. The risk for the remainder of the lifetime of the infected person is thought to be in the range of 5%, leading to an overall likelihood of disease of approximately 10%. As was noted previously, conditions that impair cell–mediated immunity may substantially increase this risk, presumably both at the time of new infection and at any later time.

EFFECTS OF HIV INFECTION ON LUNG DEFENSES

Although there are still many unknowns concerning the effects of HIV infection on lung defenses, it is well established that HIV directly infects blood monocytes and macrophages[14]. The effects on macrophage function are not clearly defined, however, it seems likely that the effectiveness of alveolar macrophages in the initial nonspecific response to *M. tuberculosis* may be limited in persons with HIV infection, at least in the later stages of infection. The antigen presentation function of the macrophage may also be impaired, resulting in a failure to initiate an effective immunologic response.

Because the CD–4 receptor–bearing lymphocyte (T–helper cell) is known to be the major

Table 3 Effects of HIV Infection on Lung Defenses

Monocyte and Macrophage Function

Function	Blood Monocyte	Alveolar Macrophage
Chemotaxis	Decreased or normal	Unknown
Phagocytosis	Normal	Unknown
Intracellular killing	Normal	Normal
Superoxide generation	Normal	Normal
Antibody-dependent cellular cytotoxicity	Decreased normal or increased	Unknown
MHC expression	Decreased or normal	Decreased
Antigen presentation	Decreased	Unknown
IL-1 elaboration		
Resting	Normal or increased	Normal
Stimulated	Decreased or normal	Increased
Tumor necrosis factor elaboration	Decreased or normal	Unknown

Lymphocyte Function

Function	T Cells	B Cells
Mitogen-induced proliferation	Decreased	Decreased
Interferon gamma elaboration	Decreased	—
IL-2 elaboration	Decreased	—
Spontaneous immunoglobulin secretion	—	Increased
Response to new antigen	—	Decreased

Modified from Beck J M, Shellito J : Effects of human immunodeficiency virus on pulmonary host defenses. Semin Respir Infect 4 : 75-84, 1989.

target of HIV, it is logical to assume that the responsiveness of these cells when presented with mycobacterial antigens will be limited, both because of reduced numbers and because of functional impairment[14]. Clonal proliferation in response to antigens and elaboration of soluble factors, such as interferon-gamma and interleukin-2 (IL-2), are demonstrably reduced by HIV infection[15]. Interferon-gamma is necessary for specific activation of macrophages and IL-2 amplifies T cell proliferation. Given the presumed essential nature of these responses in the immunologic reaction to *M. tuberculosis,* it is likely that the effects of HIV on $CD4^+$ lymphocytes is a major factor in predisposing to tuberculosis. Table 3 summarizes the effects of HIV infection in pulmonary defenses.

The foregoing is more easily understood as it relates to the potential for new infection with *M. tuberculosis* to progress quickly to cause disease. It is likely, however, that at least in the United States most new cases of tuberculosis in HIV-infected persons, as in the general population, arise from old, rather than new, infections[16]. Because the factors required for continued containment of old infections are not clear, the effects of HIV infection that cause breaches in these containment barriers can only be speculative but, presumably, are the same as those effects that influence the initial response.

The development of infectious diseases in persons with HIV infection is a result of the interaction of the specific organism with the defenses of the host. It appears that the acquired immunodeficiency syndrome (AIDS) - defining opportunistic infections, such as *Pneumocystis carinii* pneumonia and disseminated *Mycobacterium avium* complex infection occur late in the course of HIV infection, as indicated by patients with these processes having markedly reduced

CD-4 lymphocyte counts[17]. This probably relates to the virulence of the organism, with lower-virulence organisms not being capable of producing disease until host responsiveness is severely impaired. *M. tuberculosis* on the other hand is a much more pathogenic organism. Thus, less, if any, recognizable impairment of host defenses is required for *M. tuberculosis* to cause disease. For this reason, tuberculosis tends to occur relatively early in the course of HIV infection. This is attested to by the finding of Theuer and associates[18] that HIV-seropositive patients with tuberculosis had a median circulating CD-4 lymphocyte count of 354/μL. In this group of 17 patients, tuberculosis was the initial manifestation of HIV infection in all but two patients, one of whom had limited Kaposi's sarcoma and the other oral candidiasis.

RISK OF TUBERCULOSIS IN PERSONS WITH HIV INFECTION

The first report of tuberculosis occurring in patients with AIDS appeared in 1983 and described the illness associated with severe immunosuppression in a group of Haitian patients in South Florida[19]. The 10 of 20 patients (50%) either had tuberculosis at the time the immune compromise was noted or had previously had the disease. Similarly, in a description of AIDS in Haiti, 11 of 46 patients (24%) had tuberculosis, usually preceding the diagnosis of AIDS[20]. A second report of Haitian patients with AIDS living in the United States revealed 27 (60%) with tuberculosis[21]. Subsequently, several reports have described the association between tuberculosis and HIV infection with and without AIDS[18)22)~26)]. Common to all of these reports was the occurrence of tuberculosis in individuals and populations that are known to have relatively high rates of tuberculosis infection : Haitians, intravenous drug users, and minority populations. However, the disease has not been limited to such populations and has involved American-born, white, middle-class men in addition to groups known to have high rates of tuberculous infection.

Matching of tuberculosis and AIDS registries in 43 states has revealed that 3.8% of AIDS cases appeared on tuberculosis case registries[27]. However, this percentage is widely variable in different states and areas. In Florida 10% of AIDS patients have or have had tuberculosis, and in Connecticut and New York 5% have had the disease. A few states have had no reported cases.

The frequency with which tuberculosis develops in persons who are infected with both HIV and *M. tuberculosis* is not well-established but appears to be substantially in excess of what would be expected in a non-HIV infected group. Several early reports suggest that the short-term (2 to 5 years) risk of tuberculosis is very much in excess of the lifetime risk in a normal host[28]. Reports of the prevalence of tuberculin reactivity among Haitians arriving in the United States indicated that approximately 75% to 90% had positive (≥ 10 mm) skin test reactions[29]. Subsequent reports of the frequency of tuberculosis among Haitian patients with AIDS showed that within a 30-month period, 50% had tuberculosis before, at the time of, or after the diagnosis of AIDS[19].

More direct data on the frequency of tuberculosis in HIV-infected patients have been provided by Selwyn and coworkers[30] in a prospective study of tuberculosis among HIV-seropositive and -seronegative intravenous drug users in New York City. Of 49 HIV-seropositive subjects, seven (14%) tuberculin skin test-positive drug users developed tuberculosis. This was the equivalent of 7.9 cases per 100 person years of observation. One person who had been anergic also developed tuberculosis. These observations suggest that seven and perhaps all eight patients who developed tuberculosis had had preexisting tuberculous infection, indicating that endogenous reactivation was the dominant if not the only pathogenetic mechanism for developing tuberculosis. Of additional concern was the observation that 11% and 13% of the seropositive and seronegative subjects, respectively, developed positive tuberculin skin tests during the period of the study. If this is truly indicative of new infections, the rate is very high and suggests that there was a very large number of in

ses within the population to which this group

was exposed.

PREVALENCE OF HIV INFECTION AMONG PATIENTS WITH TUBERCULOSIS

Several prospective studies in public tuberculosis clinics have described the prevalence of HIV infection among patients with tuberculosis. Pitchenik and coworkers[26] reported that 31% of 71 consecutive tuberculosis patients in Miami were HIV-infected. In Seattle, Nolan and associates[31] found 23% of non-Asian adults were HIV-infected. Theuer and colleagues[18] reported that in San Francisco 28% of non-Asian tuberculosis patients between 15 and 55 years of age were HIV-seropositive.

Beginning in 1988 a more systematic nationwide sampling was undertaken by the Centers for Disease Control in 14 urban tuberculosis clinics[32,33]. The median seropositivity rate in the 14 clinics in 4301 persons with or suspected of having tuberculosis was 3%. The rates varied widely among clinics ranging from 0 to 46%. The highest rate was reported from New York City (46%) followed by Newark (34%), Boston (27%), Miami (24%) and Baltimore (13%).

Data from developing countries are scarce but indicate a substantial rate of HIV infection among patients with tuberculosis[34~37]. This finding would be expected given the concommitant high prevalence of both tuberculous infection and infection with HIV in developing countries.

IMPACT OF HIV INFECTION ON THE EPIDEMIOLOGY OF TUBERCULOSIS

The full impact of HIV infection on the epidemiology of tuberculosis has not been defined either in the United States or abroad. Inferential information suggests, however, that the influence may be substantial. Data from the Centers for Disease Control (CDC) indicate that there have been approximately 22,000 "excess" cases of tuberculosis in the United States between 1984 and 1989 (Fig. 1). This was determined by comparing the number of cases actually reported with the estimated cumulative number of cases that would have occurred had the rate of decline in the annual number of cases reported before 1984 continued through 1989. Before 1984 there had been a consistent decrease in the number of newly reported tuberculosis cases, averaging 5% to 6% per year. However, in 1985 there was no decrease from 1984 and in 1986 there was a 2.2%

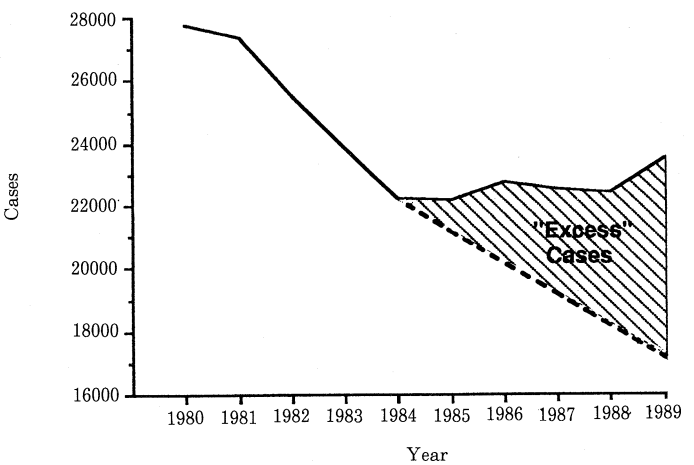

Fig. 1. Newly reported cases of tuberculosis in the United States by year 1980 to 1989. The broken line represents a projection of the number of cases from 1985–1989 if the annual decrease from 1980–1984 had continued. The shaded area represents approximately 22,000 excess cases occurring between 1984 and 1989.

increase. In 1987 there were slightly fewer cases than in 1986. In 1988 there was a slight reduction but in 1989 there was a 4.7% increase compared with 1988. Provisional data for 1990 indicate an approximate 8% increase compared with 1989[39]. Although the excess cases occurring since 1984 are not proven to be attributable to HIV infection, the largest increases have occurred in the areas with the greatest number of AIDS cases and, therefore, the highest prevalence of HIV infection.

CLINICAL FEATURES AND DIAGNOSIS

Clinical Features

Available evidence suggests that the clinical manifestations of tuberculosis occurring in patients with HIV infection vary considerably, depending on the severity of the immunosuppression[18)~25)]. As noted previously, presumably because of the virulence of *M. tuberculosis*, tuberculosis tends to occur earlier in the course of HIV infection. In most series the majority of tuberculosis diagnoses have preceded the identification of an AIDS-defining disease. A substantial number of patients have tuberculosis diagnosed at the time of AIDS diagnosis, and in a smaller number, tuberculosis appears after an AIDS diagnosis. This is in part a semantic distinction in that the surveillance definition of AIDS revised in 1987 now includes extrapulmonary tuberculosis in an HIV-seropositive person[40)].

Seemingly, the earlier tuberculosis develops, the more "usual" is its clinical presentation, whereas the later it occurs, the more atypical are its features (Table 4). This conclusion is somewhat difficult to support from published information, owing largely to the fact that most series in the literature describe the features of tuberculosis in patients who either have or subsequently develop AIDS. Patients identified by cross-matching AIDS and tuberculosis registries clearly are likely to have advanced HIV disease even if their tuberculosis develops before an AIDS-defining diagnosis appears.

In the earliest report describing tuberculosis in Haitian patients with AIDS, only one of ten patients had pulmonary tuberculosis, while one had brain abscesses and the other eight had miliary or disseminated tuberculosis[19)]. There was no immunologic characterization of the patients at the time tuberculosis occurred ; thus, the stage of their HIV disease could not be inferred. Nevertheless, tuberculosis occurred 2 to 15 months prior to an AIDS-defining diagnosis in seven patients and was concurrent with AIDS in the other three patients.

Subsequent reports focusing on patients who have or develop AIDS have expanded on the atypical presentations contained in the first description[21)~25)]. These series have emphasized that the disease is frequently disseminated, has unusual radiographic manifestations, and nonreactive tuberculin skin tests. Lymph node involvement, including intrathoracic adenopathy, was frequently described. In these series as well

Table 4 Clinical Features of Tuberculosis in HIV-Infected Patients

Early in the course of HIV disease
Typical features
Predominantly pulmonary
Upper lobe location
Cavitation
Positive tuberculin tests
Late in the course of HIV disease
Atypical features
Increased proportion of extrapulmonary sites
Diffuse infiltration
Both early and late
Infectious
Good response to therapy

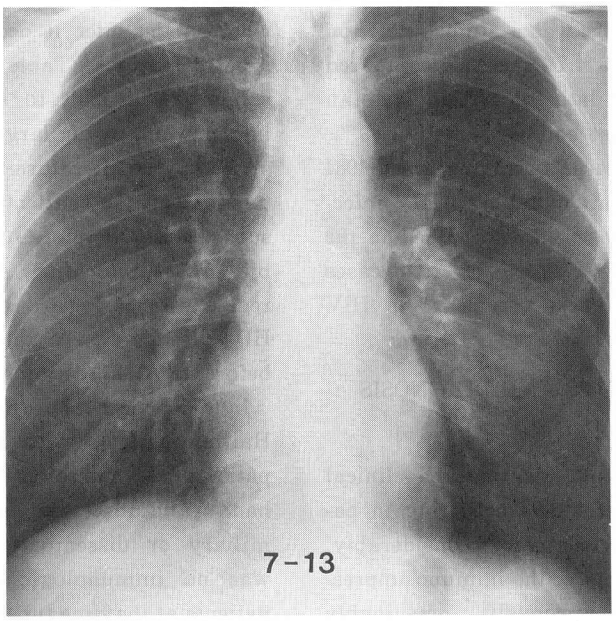

Fig. 2–A. Frontal view chest film showing bilateral hilar and paratracheal adenopathy.

as in individual case reports a variety of unusual manifestations have been noted. These include central nervous system involvement with brain abscesses, tuberculomas and meningitis[23)41)42)], bone, including vertebral disease[23)43)], pericarditis[23)44)], gastric tuberculosis[45)], tuberculous peritonitis[46)], and scrotal tuberculosis[47)]. In addition, *M. tuberculosis* has been cultured from the blood as well as bone marrow[48)~50)].

Despite the increased frequency of unusual forms of tuberculosis in persons with HIV infection, several reports have described a predominance of "standard" pulmonary disease[18)26)30)]. These reports presented series collected prospectively in which either tuberculosis patients had HIV antibody measured[18)26)] or HIV–seropositive subjects were followed for the development of tuberculosis[30)]. Thus, these patients presumably were less immunocompromised.

Chest Radiographic Findings

The atypical findings on chest radiographs of HIV–infected patients who have tuberculosis have received considerable emphasis. In retrospective studies, features that are not regarded as "typical" for pulmonary tuberculosis have been the norm[25)51)]. Lower lung zone or diffuse infiltrations commonly have been observed rather than the usual upper lobe involvement. Cavitation has been unusual and intrathoracic adenopathy, a very unusual finding in nonimmunosuppressed adults with tuberculosis, has been relatively frequent. Figure 2 shows a series of chest films during a 3–week period in the same patient. The initial finding was adenopathy (Fig. 2–A) that progressed to diffuse infiltration (Figs.2–B and –C) before a diagnosis of tuberculosis was established.

In the prospective study by Theuer and colleagues[18)], the radiographic findings in patients with HIV infection were not distinguishable from those in patients who were HIV seronegative. The findings included typical upper lobe infiltration often with cavitation. A greater prevalence of atypical findings than reported by Chaisson and associates was noted in the prospective study by Pitchenik and colleagues[26)]. These findings included a higher frequency of adenopathy, diffuse or lower lobe infiltration, and a lower frequency of cavitation compared with HIV seronegative patients.

Tuberculin Skin Tests

As would be predicted, the tuberculin skin test

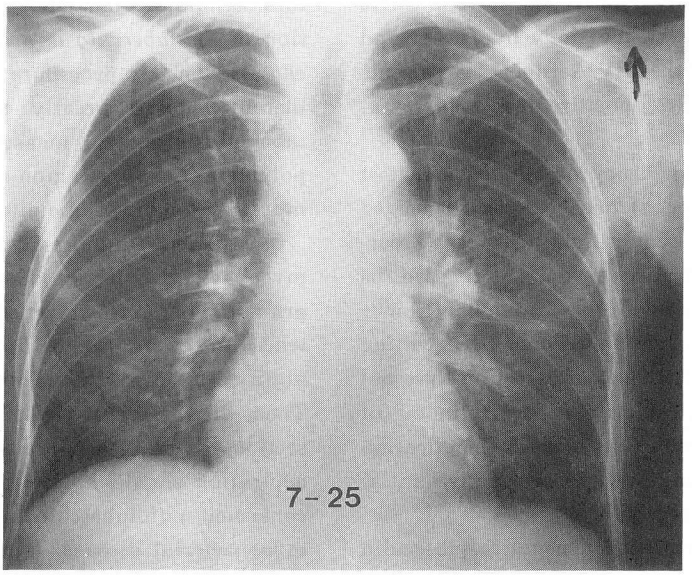

Fig. 2–B. Film of same patient 12 days later showing persistence of the adenopathy and interval development of bilateral interstitial infiltrates.

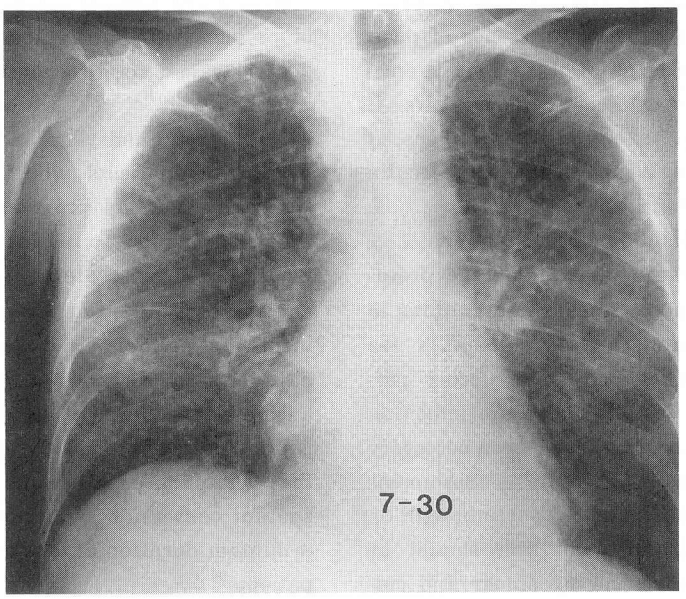

Fig. 2–C. Film of same patient 17 days after the initial film showing extensive bilateral infiltration and persistent adenopathy. At this time the patient was found to have tuberculosis.

commonly shows little or no reaction in persons with advanced HIV infection. However, in earlier stages of the infection, reactivity may be maintained. The ability to respond to tuberculin is an indicator of the status of cell–mediated immunity that in turn is an indicator of the stage of HIV infection. Most studies that describe the prevalence of reactive ($\geq$10 mm) tuberculin tests

indicate that approximately 40% have positive reactions. However, in the study by Theuer and associates[18] 80% of the HIV−seropositive patients with tuberculosis had positive reactions to tuberculin.

Because of the frequency of blunted skin test responses or anergy, it has been recommended that a reaction of ≥5 mm induration to 5 tuberculin units of purified protein derivative be regarded as indicative of tuberculous infection[27]. The implications of using 5 mm as the cutting point for defining tuberculous infection have not been determined. Likewise, the likelihood of boosting the tuberculin response by application of a second skin test soon after a negative initial test has not been examined.

In order to determine if a negative tuberculin test is the result of immunosuppression or is truly negative, control antigens should be applied. These include antigens such as candida and mumps, to which most persons with intact cell−mediated immunity will respond. A negative tuberculin reaction in the presence of positive reactions to one or more of the control antigens can be interpreted as a true negative. If there is no reaction to any of the antigens, it cannot be determined if the negative tuberculin test is a true or false negative.

Bacteriologic and Histologic Examinations

Most reported series indicate that the prevalence of positive sputum smears and cultures in patients with pulmonary tuberculosis is the same in HIV−infected and −noninfected persons[18)25)26]. In some instances, sputum induction or bronchoscopic procedures have been necessary to diagnose pulmonary tuberculosis. Specimens from any site of abnormality in patients with or suspected of having HIV infection should be examined for mycobacteria by smear and culture. Potential high−yield sources include lymph nodes, bone marrow, urine, and blood.

In general, any acid−fast organism identified in any specimen should be regarded as being *M. tuberculosis* until proven otherwise. Such a policy will result in prompt initiation of appropriate therapy and contact evaluations. With standard techniques, speciation of an organism requires 6 to 10 weeks. Use of radiometric culture techniques and DNA probes for identification of *M. tuberculosis* and *M. avium* complex can shorten this procedure to seven to ten days, thereby adding greatly to the efficiency of tuberculosis control measures. The use of the polymerase chain reaction should result in much more rapid and specific diagnoses[52].

In patients with more advanced HIV infection, mycobacterial infection does not produce classic granulomas[23]. However, because tuberculosis tends to occur earlier in HIV infection, the ability to form granulomas may be intact. Thus, the finding of granulomas either in tissue sections or cytologic preparations from needle aspiration should be interpreted as being more consistent with tuberculosis than nontuberculous mycobacterial disease. It must be remembered, however, that other organisms, including *P. carinii,* may cause granulomas.

TREATMENT

With a few notable exceptions, reported series of patients with tuberculosis and HIV infection demonstrate a good response to antituberculosis treatment[18)19)21)~23)25)26)53]. However, in the series reported by Sunderam and coworkers[23] there were three patients who did not respond to treatment and had progressive disease. A case report from the same institution described a recurrence of tuberculosis at an extrapulmonary site (scrotal) after apparently successful treatment for pulmonary disease[47]. These reports have led to expressions of concern regarding the adequacy of current standard 6−month therapy[54], and subsequently to recommendations that 9 months or 6 months beyond the time of sputum conversion, whichever is longer, be the minimum duration of treatment in HIV−infected patients[10].

Because in the reported series the regimens used were not uniform in duration or composition, advantages of longer versus shorter durations of treatment cannot be determined. Nearly all patients were treated with regimens that contained isoniazid and rifampin. Some patients also were given various combinations of pyrazinamide, ethambutol, and streptomycin together with isoniazid and rifampin. Current recom

mendations indicate that in adult patients with HIV infection, treatment for tuberculosis should include 300 mg/d isoniazid, 60 mg/d rifampin (450 mg/d for persons weighing less than 50 kg), and 20 to 30 mg/kg/d pyrazinamide during the first 2 months of therapy ; isoniazid and rifampin should be continued for at least another 7 months, making the total duration of therapy at least 9 months[10]. For patients judged to be potentially noncompliant, therapy should be given under direct observation. This can be facilitated by twice weekly drug administration after an initial phase of daily teatment.

For patients with pulmonary tuberculosis, response to therapy should be determined by bacteriologic examination of sputum as well as by clinical and radiographic examination. For patients with less accessible sites of disease, only clinical and radiographic evaluations can be used to determine the response. It should be kept in mind that worsening clinical and radiographic findings may be caused by other HIV-related diseases.

It appears that the rate of adverse reactions to antituberculosis drugs is greater in persons with HIV infection[53]. For this reason patients with HIV infection should be followed closely with appropriate laboratory and clinical monitoring. There has been no systematic evaluation of possible interactions of antituberculosis drugs with antiretroviral agents. The potential for increased toxicity should, however, be kept in mind. The antifungal agents ketoconazole and fluconazole both have interactions with isoniazid and rifampin resulting in reduction in serum concentration of the antifungal agents[55][56]. In addition ketoconazole interferes with the absorption of rifampin[55].

In view of the generally good response reported by all investigators, there appears to be no reason to prolong treatment beyond the recommended period unless bacteriologic conversion was delayed, or treatment was interrupted because of noncompliance or adverse reactions. Patients who cannot take isoniazid and rifampin together should be treated for a minimum of 18 months, usually with isoniazid or rifampin and ethambutol. This also applies to patients whose disease is caused by organisms that are resistant to isoniazid or rifampin.

Because of the modifications of standard treatment regimens for patients with HIV infection, HIV antibody testing is desirable and should be offered to all patients with new diagnoses of tuberculosis.

PREVENTION

Preventive therapy with isoniazid has been proven to be widely effective in preventing tuberculosis among various groups of persons with tuberculous infection[57]. Although the effectiveness of isoniazid preventive therapy in persons infected with both HIV and *M. tuberculosis* has not been documented, there is no reason to assume that it would not work. For this reason, tuberculin testing should be performed as a routine part of management for patients with HIV infection. Patients with reactions of ≥ 5 mm to 5 tuberculin units of purified protein derivative should be considered as having tuberculous infection and be offered preventive therapy. Although the usual preventive therapy recommendations for persons with normal chest films state that 6 months is sufficient, treatment for 12 months is recommended in the presence of HIV infection[10][57]. There are no data in any group treated with isoniazid preventive therapy that suggest treatment for more than 12 months confers additional protection.

Attempts at immunization against tuberculosis with Bacille Calmette-Guérin (BCG) should not be undertaken in patients with AIDS because of the possibility of developing disseminated BCG disease. The use of BCG in HIV-infected persons without AIDS, although not shown to be associated with a high rate of adverse reactions, is probably risky, and, at least in areas of low prevalence of tuberculosis such as the United States, should not be done.

INFECTION CONTROL

As noted in the introdution, tuberculosis is the only common HIV-associated infection that can be transmitted from person to person, including persons who are not HIV-infected. For this

reason, it is extremely important that tuberculosis be taken into account in applying infection control measures in persons with HIV infection. In patients who are being evaluated because of respiratory symptoms and/or findings, respiratory precautions should be applied until tuberculosis is excluded. Sputum induction and bronchoscopy should be performed in areas with adequate ventilation with the exhausted air not being recirculated to other parts of the building. Similar considerations should apply to areas in which aerosol pentamidine is administered. Transmission of tuberculous infection has occurred in a poorly ventilated clinic where aerosol pentamidine prophylaxis for *P. carinii* pneumonia was being administered to two patients whose sputum contained *M. tuberculosis*[58]. Nosocomial transmission of *M. tuberculosis* has also been described in several other reports, including one large outbreak in which the organisms were resistant to at least isoniazid and rifampin[59)60)]. The latter outbreak was associated with a very poor response to therapy and a high case-fatality rate.

In general, once a patient is being given effective therapy for tuberculosis, he or she is regarded as being noninfectious. However, because of the potentially severe consequences of new tuberculous infections in immunocompromised patients, it is probably prudent to be more cautions in persons with tuberculosis who will be in contact with HIV-infected persons. In most patients being treated effectively, because of the decrease in the number of bacilli present in sputum and a decrease in the frequency of coughing, infectivity is reduced by more than 99 % within 2 weeks of beginning treatment[61]. Even with a reduction of this magnitude, sputum smears may still show acid-fast bacilli. To be even more confident that infectiousness is extremely low, precautions may continue to be applied until sputum smears are negative. In most instances, however, 2 weeks is sufficient.

Infection control for HIV is also of major concern. Medical personnel working with tuberculosis patients should use appropriate infection control measures to prevent HIV transmission. In general, universal blood and body substance precautions should be applied. Special care should be taken in blood drawing and administration of tuberculin skin tests and intramuscular injections. This last consideration is of particular relevance to developing countries where facilities for sterilization are inadequate but where streptomycin is used commonly.

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