Spectrum of tuberculosis in patients with HIV infection in British Columbia: report of 40 cases

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Objective: To review the clinical features, treatment and outcome of all known cases of tuberculosis in patients with human immunodeficiency virus (HIV) infection in British Columbia between 1984 and 1990.

Design: Retrospective case review.

Setting: Provincial tuberculosis registry and university-affiliated HIV clinic.

Patients: All people with HIV infection in whom active tuberculosis was diagnosed during the study period.

Results: All 40 patients identified were men; their mean age was 38 years. Of the subjects 30 (75%) were homosexual, 6 (15%) were homosexual and used intravenous drugs, 2 (5%) just used intravenous drugs, and 1 (2%) had had heterosexual contact with prostitutes; for the remaining subject the risk factor for HIV infection was not established. In all cases cultures of specimens from 15 body sources yielded *Mycobacterium tuberculosis*. Thirty-five of the patients had acquired immunodeficiency syndrome (AIDS), and five had HIV infection uncomplicated except for tuberculosis. In 28 (70%) of the cases no AIDS-defining disease had previously been diagnosed, and in 23 (58%) extrapulmonary tuberculosis represented the AIDS-defining disease. Symptoms at presentation included weight loss (in 80% of the cases), fever (in 75%), cough (in 70%) and night sweats (in 55%). The mean CD4 lymphocyte count was 0.2×10^9/L (in 15 cases). Tuberculin skin test results were positive in 8 of 16 cases. The most striking radiologic finding was intrathoracic adenopathy. All except one of the 36 patients who received appropriate treatment responded favourably at first. Adverse reactions necessitating changes in treatment occurred in 12 (33%) of the cases. Relapse occurred after completion of therapy in two cases (one at 3 weeks and the other at 9 months after treatment was stopped). Tuberculosis was the cause of death in five cases.

Conclusions: Tuberculosis in people with HIV infection commonly presents as extrapulmonary disease and precedes or coincides with other AIDS-defining opportunistic infections. In most cases tuberculosis is the AIDS-defining disease. Even though radiologic findings are often unusual physicians should suspect tuberculosis. A careful examination for evidence of disease at multiple sites should be done. The duration and choice of therapy must be adequate to avoid relapse.

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Objectif : Examiner les caractéristiques cliniques, le traitement et le résultat de tous les cas connus de tuberculose chez les patients atteints d'une infection au virus de l'immunodéficience humaine (VIH) en Colombie-Britannique entre 1984 et 1990.
Conception : Étude de cas rétrospective.
Cadre : Registre provincial des cas de tuberculose et clinique VIH affiliée à une université.
Patients : Toutes les personnes à infection au VIH chez lesquelles on a diagnostiqué une tuberculose active pendant la période de l'étude.
Résultats : Les 40 patients identifiés étaient des hommes; leur moyenne d'âge était de 38 ans. Parmi ces sujets, 30 (75 %) étaient des homosexuels, 6 (15 %) étaient des homosexuels et utilisaient des drogues par voie intraveineuse, 2 (5 %) utilisaient simplement des drogues par voie intraveineuse et 1 (2 %) avait eu des relations hétérosexuelles avec des prostituées; en ce qui a trait au dernier sujet, le facteur de risque à l'infection au VIH n'a pas été établi. Dans tous les cas, les cultures de spécimens de 15 sources corporelles ont donné comme résultat *Mycobacterium tuberculosis*. Trente-cinq de ces patients souffraient du syndrome d'immunodéficience acquise (SIDA) et cinq étaient atteints d'une infection au VIH sans complication, sauf la tuberculose. Chez 28 (70 %) des cas, aucune maladie révélatrice du SIDA n'avait antérieurement été diagnostiquée et chez 23 (58 %) la tuberculose extrapulmonaire constituait la maladie révélatrice du SIDA. Les symptômes à la présentation englobaient la perte de poids (dans 80 % des cas), la fièvre (75 %), la toux (70 %) et les suées nocturnes (55 %). Le dénombrement lymphocytaire CD4 moyen était de $0,2 \times 10^9$/L (dans 15 cas). Les tests cutanés à la tuberculine ont donné des résultats positifs dans 8 cas sur 16. Constatation radiologique la plus frappante : une adénopathie intrathoracique. Des 36 patients qui ont reçu un traitement approprié, 35 ont d'abord bien réagi. Il y a eu des réactions contraires obligeant à un changement de traitement dans 12 (33 %) des cas. Il y a eu rechute après achèvement de la thérapie dans deux cas (une à 3 semaines et l'autre, 9 mois après l'arrêt du traitement). La cause du décès a été la tuberculose dans 5 cas.
Conclusions : La tuberculose chez les personnes atteintes d'une infection au VIH se présente habituellement sous forme de maladie extrapulmonaire et précède les autres infections opportunistes caractéristiques du SIDA ou coïncide avec elles. Dans la plupart des cas, la tuberculose est la maladie révélatrice du SIDA. Même si les constatations radiologiques sont souvent inhabituelles, les médecins doivent soupçonner la tuberculose. Il faut faire un examen minutieux pour trouver des indices de la maladie à de nombreux endroits. La durée et le choix de la thérapie doivent être adéquats, afin d'éviter la rechute.

The recent increase in the incidence of tuberculosis has been attributed to dual infection with the human immunodeficiency virus (HIV) and the tubercle bacillus.[1-4] This effect is most evident in developing countries, where there is potential for a dramatic increase in the number of cases of tuberculosis.[5] HIV-induced immunosuppression predisposes people to many infections, resistance to which is mediated by cellular immunity.

Tuberculosis is not uncommon in people with HIV infection. It may precede the development of acquired immunodeficiency syndrome (AIDS) and when it involves extrapulmonary sites may indicate the presence of AIDS.[6] The pathogenicity of *Mycobacterium tuberculosis* and its ability to spread to new hosts make this agent one of the most transmissible among the opportunistic organisms associated with HIV infection. The main mechanism for the development of clinically active tuberculosis appears to be the endogenous reactivation of dormant infection.[7] More recent reports from Italy suggest that direct progression to active tuberculosis in HIV-positive people newly infected with the tubercle bacillus may occur.[8]

In Canada 4647 cases of AIDS have been reported since 1982.[9] By the end of 1990, 809 cases had been reported in British Columbia.[9] Although tuberculosis has been documented as occurring in this population, no detailed reports have been published on the Canadian experience; two abstracts have been published on the experience in British Columbia.[10,11] We therefore describe the clinical features of tuberculosis in people with HIV infection in order to (a) assist the early recognition of this combination, (b) understand the temporal relation between the two diseases, (c) appreciate the risk of tuberculosis in the presence of HIV infection and AIDS, and (d) understand the requirements of drug treatment in this setting.

Methods

In British Columbia tuberculosis is a reportable communicable disease. Its control as well as the

distribution of antituberculous drugs is centralized under the direction of the Division of Tuberculosis Control, British Columbia Ministry of Health. Mycobacteriologic investigation in this province is also centralized, under the ministry's Division of Laboratories, which is a level 3 laboratory by US standards.[12] All cases of tuberculosis in British Columbia are recorded in the Registry of the Division of Tuberculosis Control. This registry provided the cases for our study.

Reporting of AIDS is legally required in British Columbia but is anonymous. HIV seropositivity is not reportable, and testing may be requested on an anonymous basis. All positive HIV antibody test results are accompanied by a note explaining the importance of tuberculosis in people with HIV infection.

We evaluated the charts and chest radiographs of all patients with HIV infection and active tuberculosis before and after treatment of tuberculosis between 1984 and 1990. A single observer collected the following data on a standardized form: demographic information, risk factors for HIV infection, symptoms and signs of disease, microbiologic results, CD4 and CD8 counts, CD4–CD8 ratios, results of the purified protein derivative (PPD) skin test when performed, presence of other diseases complicating HIV infection, type and duration of tuberculosis treatment, adverse reactions to treatment and outcome of therapy.

Cases of active tuberculosis were defined according to the *Classification and Reporting of Tuberculosis in Canada*,[13] revised in January 1990.[14] Unless otherwise stated "pulmonary tuberculosis" included pleurisy, alone or in combination with lung disease, for the purpose of categorizing the site of disease. For cases of AIDS we followed the 1987 revision of the US Centers for Disease Control case definition (for surveillance);[6] pleural involvement was considered extrapulmonary.

Statistical analysis

Fisher's exact test and the χ^2 test were used to examine group differences. The Kaplan–Meier life table method was used for the survival analysis. Survival was compared among subjects with pulmonary and extrapulmonary tuberculosis with the use of the log-rank test.

Results

Forty people with HIV infection and tuberculosis were identified; all were men. Their mean age was 38 (extremes 25 and 54) years. In all, 33 were Canadian born (29 white, 3 native Indian and 1 black), 2 (white) had emigrated from Britain, and 5 (2 white, 2 black and 1 oriental) were from countries with a high prevalence of tuberculosis. Thirty were homosexual, six were homosexual and used intravenous drugs, two just used intravenous drugs, and one had had heterosexual contact with prostitutes. In the remaining case the risk factor for HIV infection was not established.

In all but one of the subjects HIV seropositivity was discovered before or at the time the active tuberculosis developed; in the remaining case the course and symptoms suggested that HIV infection was present at the start of the active tuberculosis, but the HIV seropositivity was confirmed only about 1 year after the tuberculosis was detected.

An AIDS-defining disease was diagnosed before (in 11 cases [28%]) or at the same time (in 1 [2%]) as the tuberculosis. *Pneumocystis carinii* pneumonia was the most common opportunistic infection preceding tuberculosis (occurring in six cases). The interval between the diagnosis of AIDS and the diagnosis of tuberculosis varied from 0 to 19 (mean 5.6, standard deviation [SD] 5.7, median 3.5) months.

Tuberculosis was the first major opportunistic infection in 28 subjects (70%); 23 of them had extrapulmonary tuberculosis. In 3 of the 23 subjects other AIDS-defining conditions (esophageal candidiasis in 2 and Kaposi's sarcoma in 1) were diagnosed during the same hospital admission. Five subjects had no AIDS-defining disease diagnosed at the time of presentation.

At presentation 17 subjects were found to have oral candidiasis, 5 herpes simplex, 6 generalized lymphadenopathy, 2 hairy leukoplakia and 13 asymptomatic HIV infection. Oral candidiasis was found in 7 (58%) of the 12 subjects who met the criteria for AIDS and in 10 (36%) of the remaining 28.

Symptoms

All 40 subjects had symptoms at the time the tuberculosis was diagnosed (Table 1). Shortness of breath was observed more often in those with abnormal chest radiographs than in those with normal ones ($p < 0.05$). Five of the six subjects with miliary tuberculosis reported dyspnea. Diarrhea was present in 13 subjects. Acid-fast bacilli were found in stool samples from five of the nine whose diarrhea was investigated. Three of the five samples were cultured: two were positive for *M. tuberculosis*, and one was positive for *M. avium–intracellulare*.

Sites of tuberculosis and bacteriologic results

Cultures of 18 types of specimens (including

those from patients in relapse) from 15 body sources were found to be positive for *M. tuberculosis*. In 28 cases (70%) the respiratory tract, including the pleura but not the regional lymph nodes, was involved. Pulmonary parenchymal involvement alone was found in 10 cases (25%). In two cases there was concomitant pleurisy, and in another case pleurisy was present without obvious parenchymal disease. Lung involvement or tracheobronchial involvement or both were found along with one or more extrapulmonary sites in the remaining 15 cases; in 3 cases sputum cultures or bronchial washings or both yielded positive results for *M. tuberculosis* in the absence of any detectable tracheobronchial or lung lesion.

Pulmonary involvement was proven by means of sputum culture in 24 cases; in 16 sputum was positive on direct smear. In three other cases sputum samples were not investigated, but cultures of bronchial washings gave positive results. *M. avium-intracellulare* was identified concomitantly with *M. tuberculosis* through sputum culture (in one case) and bronchial washing (in one).

The most frequently involved extrapulmonary sites were the mediastinal nodes (in 5 cases — 3 proven by means of culture and 2 by means of acid-fast staining), the abdominal nodes (in 3) and other peripheral nodes (in 13). In 10 cases lymph nodes alone were involved. Altogether tuberculous lymphadenopathy was present in 21 (52%) of the 40 subjects.

The pleura was involved in six cases. A smear of pleural fluid gave a positive result in one of the five subjects with a positive culture result. In one case pleural involvement was diagnosed by means of pleural biopsy alone; smear and culture of the pleural fluid yielded negative findings.

M. tuberculosis was found in smears of stool samples in five cases; culture yielded *M. tuberculosis* in two cases and *M. avium-intracellulare* in one. *M. tuberculosis* was found in blood cultures in 3 of the 20 subjects from whom blood samples were taken for mycobacterial culture. In two other cases *M. avium-intracellulare* was isolated from the blood.

Lymphocyte counts

The total lymphocyte count varied from 0.1 to 4.0 (mean 1.1, SD 0.9, median 0.8) $\times$ 10^9/L. The CD4–CD8 ratio was available in 17 cases at the time tuberculosis was diagnosed; it varied from 0.15 to 1.07 (mean 0.42, SD 0.25, median 0.36). The absolute CD4 lymphocyte count, available for 15 subjects, varied from 0.03 to 0.7 (mean 0.2, SD 0.2, median 0.1) $\times$ 10^9/L.

Five subjects with pulmonary tuberculosis had a CD4 lymphocyte count of 0.1 to 0.7 (mean 0.3, SD 0.2, median 0.3) $\times$ 10^9/L; 10 subjects with extrapulmonary tuberculosis had a count of 0.03 to 0.5 (mean 0.2, SD 0.1, median 0.01) $\times$ 10^9/L. This difference was not significant.

PPD skin test results

Of the 16 subjects who underwent the PPD skin test with 5 tuberculin units at the time tuberculosis was diagnosed 8 had a positive result (diameter of area of induration 10 mm or more). If the cutoff point had been 5 mm another subject would have had a positive result. All of the five subjects with an area of induration 15 mm or more in diameter had pulmonary tuberculosis; three had asymptomatic HIV infection, and in two AIDS had been diagnosed before the tuberculosis. One of the two with AIDS had an absolute CD4 count of 0.4 $\times$ 10^9/L. Six (67%) of the nine patients with pulmonary tuberculosis had a positive skin test result, as compared with two (29%) of the seven with extrapulmonary disease.

Seven subjects had previously had a positive

Table 1: Symptoms in 40 men with human immunodeficiency virus infection in whom tuberculosis was diagnosed between 1984 and 1990 in British Columbia

Symptom	No. (and %) of patients	Duration of symptom, wk
Weight loss	32 (80)	14.7
Fever	30 (75)	4.2
Cough	28 (70)	9.3
Malaise	26 (65)	10.9
Night sweats	22 (55)	7.3
Shortness of breath	19 (48)	4.5
Chills	16 (40)	3.9
Sputum production	14 (35)	9.1
Increase in node size	13 (33)	5.0
Diarrhea	13 (33)	4.0
Chest pain	7 (18)	6.3
Hemoptysis	3 (8)	2.5

skin test result; two had a negative result when the test was repeated at the time of presentation.

History of chemoprophylaxis

Three subjects reported having received chemoprophylaxis with isoniazid. In two the therapy had been for only 1 and 3 months respectively (inadequate for prevention). The remaining person had received the drug for 11 months but in retrospect probably had active disease at the time prophylaxis was started.

Radiologic and laboratory findings

Chest radiographs were available for review for 39 of the 40 subjects. They appeared normal in eight cases; *M. tuberculosis* was isolated from the respiratory tract in three of these cases. There was a striking prominence of mediastinal and hilar lymphadenopathy in 11 cases. Other unusual findings included disease localized exclusively in the lower zones of the lungs (not in the apical segments of the lower lobes) (in five cases) and a diffuse miliary pattern (in six).

Pleural effusion as the sole radiologic sign of disease was seen in two cases (one proven bacteriologically). In five more pleural effusion was present with other abnormalities; in one it occurred on relapse.

Among the patients with an AIDS-defining disease other than tuberculosis that had been identified before or at the time the tuberculosis was diagnosed the proportion with infiltration predominantly in the upper lobes of the lungs was similar to that of patients who were only HIV positive (25% and 18% respectively).

At least one positive liver function test result was found in 22 subjects: abnormalities were found in the lactate dehydrogenase level (in 8 of 27), the aspartate aminotransferase level (in 15 of 33), the gamma glutamyl transferase level (in 7 of 16) and the alkaline phosphatase level (in 13 of 30).

Treatment of tuberculosis

Of the 36 patients who received treatment of tuberculosis 17 (47%) had completed the chemotherapy by the time the data were collected, 10 (28%) were still receiving treatment, 8 (22%) died before treatment could be completed, and 1 (3%) did not complete the treatment. Twenty-eight (78%) had completed at least the intensive phase of treatment (2 months).

Pyrazinamide, isoniazid and rifampin were the first drugs given in 24 cases (67%). Fourteen patients completed the intensive phase of treatment with these three drugs. All 36 patients received isoniazid and rifampin at first, and 18 (50%) were given ethambutol. Five patients received streptomycin at first, but this drug was not well tolerated. Eight subjects received additional regimens containing amikacin, ciprofloxacin, clofazimine, ethionamide or cycloserine before acid-fast bacilli were identified as *M. tuberculosis.*

In all cases, including two relapses, acid-fast bacilli were found to be sensitive to all first-line drugs (streptomycin, isoniazid, rifampin and ethambutol).

Adverse reactions occurred in 15 (42%) of the 36 patients. In 12 (33%) the reactions were severe enough to lead to an alteration in the drug regimen. Side effects were caused by pyrazinamide in eight patients, isoniazid in seven and rifampin in six. The most common side effect was a rash (in 10 cases). Reactions were severe enough to cause permanent withdrawal of pyrazinamide in eight cases, rifampin in four and isoniazid in three. Streptomycin was withdrawn because of local pain (in two cases), vertigo (in two) and renal failure (in one); the patient with renal failure had other risk factors for a nephrotoxic effect. Ethambutol was well tolerated.

A good clinical response was noted in all but 1 of the 36 patients. Follow-up chest radiographs showed improvement in 23 of the 24 patients who had abnormal findings before therapy. Follow-up cultures of sputum from 17 of the 24 patients with pulmonary involvement who had had a positive result and had been treated were negative for *M. tuberculosis.*

Two relapses occurred among the 17 patients who had completed the prescribed course of treatment. One occurred 3 weeks after a 9-month course of isoniazid, pyrazinamide and ethambutol (which was discontinued by the family physician, who judged the course and duration of therapy to be adequate) and the other 9 months after a 12-month course of the same drugs. Both patients had been intolerant of rifampin.

The length of follow-up of the 17 subjects who finished treatment varied from 1.0 to 31.5 (mean 15.9, SD 9.4, median 14.0) months.

Deaths

Twenty subjects had died by the time the data were analysed, eight while receiving treatment. Tuberculosis was the cause of death in five cases. One subject died of disseminated tuberculosis, confirmed at autopsy, after 3 weeks of treatment. Four subjects, all with extrapulmonary tuberculosis, died before treatment could be started or after inadequate treatment; three with smears positive for acid-fast bacilli were assumed to have had *M. avium–intracellulare*

infection, because multiple smears from extrapulmonary sites were positive.

Follow-up

The follow-up period was 0.5 to 33.0 (mean 18.3, SD 12.8, median 18.0) months. In 28 subjects who did not meet the criteria for AIDS at the time of presentation *P. carinii* pneumonia was the most common major opportunistic infection that developed after the diagnosis of tuberculosis. Other complications included Kaposi's sarcoma (in two), *Toxoplasma* encephalitis (in two) and progressive multifocal leukoencephalopathy (in two). The interval between the diagnosis of tuberculosis and the diagnosis of the above-mentioned complications in 13 cases varied from 1 to 31 (mean 7.7, SD 7.8, median 5.0) months.

The median survival was 29 months for the 35 subjects who had received tuberculosis treatment and were available for follow-up, 39.5 months for the 12 treated subjects with pulmonary tuberculosis alone and 25 months for the 23 subjects with extrapulmonary tuberculosis. The difference in survival between subjects with pulmonary disease and those with extrapulmonary disease was significant ($p = 0.03$) (Fig. 1).

Discussion

Our findings confirm that tuberculosis is a significant cause of illness and death among a minority of people with HIV infection in British Columbia.

The 35 cases in which tuberculosis was associated with AIDS or was the AIDS-defining disease represent 4.3% of the 809 cases of AIDS reported to the end of 1990. There is no reliable denominator for HIV infection. Between the beginning of 1983 and the end of 1990, 2647 cases of active tuberculosis were reported in British Columbia. People with AIDS or HIV infection complicated by tuberculosis represent 1.5% of those with active tuberculosis in the province. The unique importance of tuberculosis as an opportunistic infection lies in its ability to infect others, especially those who are immunocompromised, through casual exposure.[8]

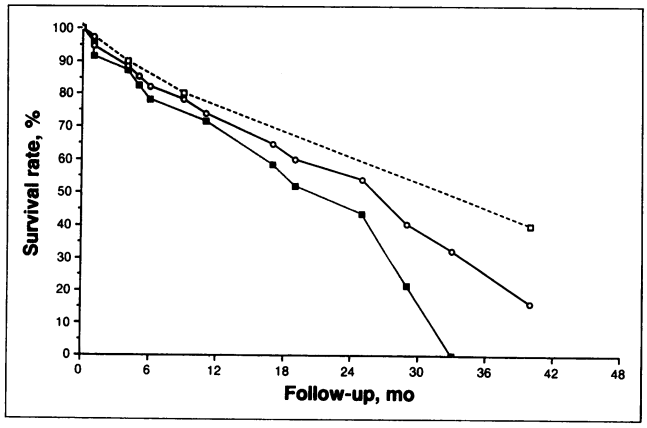

Fig. 1: Survival rates among 35 people with human immunodeficiency virus infection who were treated for active tuberculosis and were available for follow-up. Solid line with black squares represents patients with extrapulmonary tuberculosis, solid line with white circles represents all patients, and broken line with white squares represents those with pulmonary tuberculosis.

Unlike the usual presentation of tuberculosis, patients with concomitant HIV infection often present with extrapulmonary disease or disease involving unusual or disseminated sites.[15-18]

In our study homosexual men were at highest risk for combined tuberculosis and HIV infection. Such people also constitute the largest risk group for HIV infection in British Columbia; this finding differs from most US data, which indicate that intravenous drug users, inner-city black people and immigrants from countries highly endemic for AIDS are at highest risk.[5,16,18-20]

Unusual radiographic patterns were relatively common in our study: frequent enlargement of the intrathoracic lymph nodes, infiltration seen exclusively in the lower zones of the lungs and miliary changes. Others have noted such atypical presentations, but it has been suggested that tuberculosis presenting early in HIV infection may not be associated with such a prevalence of atypical radiologic features.[17,21-24] We found no significant difference in the proportion of subjects with usual upper-lobe involvement between those with AIDS and those without AIDS before the diagnosis of tuberculosis.

Most of the patients in our study presented with pyrexia and respiratory tract symptoms. Sputum culture and bronchial washing confirmed the diagnosis of tuberculosis in all cases of pulmonary involvement; thus, it is important to collect adequate specimens for microbiologic testing. The failure to do so has recently been documented as a significant cause of underdiagnosis of tuberculosis in people with HIV infection and as a factor in avoidable deaths in this population.[25] In our study sputum smears were positive in 66% of the cases with a positive culture result; this finding is similar to those in HIV-negative populations.[1] In fact, a suspicion of pulmonary involvement, even in the absence of radiologic abnormalities, is enough to justify mycobacterial testing, as demonstrated in three of our cases. The high proportion of smear-positive cases underscores the potential for transmission of tuberculosis.

Positive PPD skin test results occurred in 8 of the 16 patients who underwent such testing. Skin

testing is important, particularly in cases of newly diagnosed HIV infection. An area of induration 10 mm or more in diameter was previously considered positive, but in people with HIV infection a cutoff point of 5 mm has recently been suggested. All people who are found to be HIV positive should be offered PPD skin testing and isoniazid chemoprophylaxis, regardless of age, unless there are contraindications. Subjects with a history of a positive skin test result should be offered chemoprophylaxis.[26,27] Selwyn and associates[7] have shown that the annual risk of reactivated tuberculosis is at least 8% among people who also have HIV infection. It is reasonable to expect that chemoprophylaxis will be effective given the success of drug treatment in active disease and the hope that a positive tuberculin reaction will in many cases represent a relatively early stage in the course of HIV infection. The results of a study involving a small number of patients with HIV infection given isoniazid chemoprophylaxis are encouraging,[7] as are the preliminary data from an African study.[28] We have recently reported the cost-effectiveness of isoniazid prophylaxis in low-risk Mantoux-positive patients,[29] and it would be expected that such an intervention would be even more cost-effective in people who also have HIV infection. Others have stressed the failure of inadequate chemoprophylaxis.[30]

Although reactivation of dormant infection is the most likely cause of tuberculosis in our patients a recent nosocomial outbreak of tuberculosis on an AIDS ward in Italy emphasized that disease may be related to recent infection with *M. tuberculosis* and that those who are immunocompromised are at high risk.[8]

Because of the high proportion of patients with extrapulmonary disease in our study, the presence of a normal radiograph and lack of mycobacteriologic proof of disease from sputum samples should not preclude the possibility of tuberculosis. In the appropriate setting all body fluids should be considered for mycobacteriologic testing through smear and culture. When lymph nodes are obtained through biopsy they should also be examined for acid-fast bacilli and cultured before the tissue is dropped in formalin or another preservative. All the patients in our study had positive mycobacteriologic results from 15 different body sources.

Patients whose smears are positive for acid-fast bacilli should be assumed to have tuberculosis and be appropriately treated before the identification of the bacilli. Failure to do so contributed to the death of three patients in our study and increased the risk of transmission of *M. tuberculosis*. Infection with atypical mycobacteria, as occurred in this study, does not preclude simultaneous infection with *M. tuberculosis*.

As in other studies[17,18] the initial response to treatment of tuberculosis in all of our subjects was good. Primary therapy in cases of concomitant HIV infection should be with isoniazid, rifampin and pyrazinamide in the first intensive phase (at least 2 months' duration). The optimum duration of therapy in the continuation phase is undecided as yet, but the severity of tuberculosis in some of our cases appears to justify the prolongation of isoniazid and rifampin therapy beyond the routine additional 4 months to a total of 9 months. In any event, therapy should be continued for at least 6 months beyond the point at which sputum smears and cultures yield negative results. Patients not given isoniazid or rifampin should continue to receive therapy for at least 18 months.[31] In our study relapses occurred in two patients whose length of treatment with drugs other than rifampin was inadequate. Reassessment during drug therapy should be readily undertaken to confirm the absence of other causes. Whatever the duration of therapy in these cases follow-up should be frequent and lifelong.

Because of the risk of adverse reactions in patients with HIV infection it may be difficult to adhere to the optimum duration of therapy. Our study underlines this difficulty. Others have indicated a similarly high prevalence of adverse reactions to antituberculous drugs in people with HIV infection.[18,22] Excessive ethanol intake (reported in 9 subjects) and previous viral hepatitis (reported in 16) may also have been factors in the actual or perceived high prevalence of toxic effects in our patients. A history of hepatic insult may make physicians hesitate to use potentially hepatotoxic drugs; thus, the best treatment would be unnecessarily abandoned in some instances.

In our study the patients with pulmonary tuberculosis had a longer survival and a higher proportion of positive tuberculin skin test results than those with extrapulmonary disease. This reinforces the likelihood that extrapulmonary disease is a marker of more advanced immunodeficiency.

Clearly there is a tendency for tuberculosis to disseminate through the blood to many sites when the immune system reaches a certain level of deficiency. Not all of these sites necessarily advertise themselves clinically. Thus, clinical reports of tuberculous involvement are likely to differ widely depending on the zeal with which the search is conducted. Sputum may not be collected in the absence of a lung lesion and even in the presence of respiratory tract symptoms. Furthermore, the frequency with which samples of stool, blood, bone marrow and duodenal aspirate or biopsy are positive may not be widely appreciated. Before the advent of AIDS these sites rarely yielded mycobacteria.

Conclusion

This is the first detailed report from Canada of a reasonably large series of patients who have tuberculosis associated with HIV infection. The diagnosis should be pursued aggressively with the use of appropriate smears and cultures of all available secretions. The response to therapy is usually good, but careful follow-up during and after therapy is mandatory because of the high risk of adverse drug reactions, opportunistic infections and relapse.

Addendum

Since the manuscript was submitted we have diagnosed seven additional cases of tuberculosis in patients with HIV infection.

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