

Radiology of pulmonary tuberculosis and human immunodeficiency virus infection in Gulu, Uganda

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ABSTRACT: Pulmonary tuberculosis is a major complication of human immunodeficiency virus (HIV) infection. The radiographic manifestations of pulmonary tuberculosis in HIV-infected patients are not typical of those seen in immunologically normal individuals. We sought to determine whether these manifestations provide clues to the pathogenesis of tuberculosis in HIV-infected persons.

The radiographic manifestations of pulmonary tuberculosis were reviewed and classified in 82 HIV-positive and 53 HIV-negative tuberculous patients in Gulu, Uganda.

Pulmonary presentations of tuberculosis were more acute in HIV-positive patients, and often included hilar or mediastinal adenopathy and pleural effusions, findings typical of primary tuberculosis in immunologically normal individuals. Many patients also had chronic forms of tuberculosis, either alone or in combination with acute disease.

The findings of this study support the hypothesis that reactivation of latent infections and progression of pre-existent chronic disease produce a substantial portion of the tuberculosis burden of HIV-positive persons in Uganda. Tuberculosis control efforts should extend beyond efforts at decreasing transmission of new infections.

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The past decade has witnessed an unprecedented resurgence of tuberculosis both in developed and developing countries [1–4]. Among factors contributing to the increased incidence of tuberculosis, epidemic human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) are of major importance [1–3]. Since control of tuberculosis in an individual depends on an intact cellular immunity, it is not surprising that HIV infection is a risk factor for tuberculosis progressing from dormant infection to clinical disease [5–7].

The World Health Organization estimates that 8.8 million new cases of tuberculosis now occur annually worldwide, and that 8.4% of these are HIV-associated [4]. The situation is presently at its worst in sub-Saharan Africa, where the previously high incidence of tuberculosis has been rising since the mid-1980s. Previously, the incidence of tuberculosis was stable or slowly declining [2, 8]. In this population, tuberculosis is now the most common opportunistic infection of HIV-seropositive patients [9, 10].

Patients with both infections may not present with the usual radiological features of tuberculosis. Typical presentations of tuberculosis can be seen, but studies in North America, Europe and Africa report a change in the disease pattern [11–23]. The radiographic pattern frequently seen includes hilar or mediastinal adenopathy, noncavitary infiltrates located in upper or lower

lung zones, and pleural effusions. Miliary patterns occur, and cavitary lesions are rare. The chest radiograph may be normal despite a positive sputum smear for acid-fast bacilli.

The sub-Saharan country of Uganda has a population of approximately 17 million; 1 million are thought to be HIV-infected. In Kampala, the capital of Uganda, 66% of newly diagnosed tuberculosis patients are HIV-seropositive [15]. Epidemiological projections predict that, in the face of HIV prevalences typical of those in Uganda, the annual incidence of HIV-related tuberculosis may rise to 1,000–1,800 per 100,000 population [24, 25]. This enormous increase in tuberculosis due to HIV will strain the fragile health care system in the country, and make the diagnosis and management of tuberculosis difficult. Faced with mounting HIV-associated tuberculosis case rates in sub-Saharan Africa and elsewhere, it is important that physicians have a clear understanding of the effect of HIV infection on the presentation of tuberculosis.

This study compares and contrasts the radiographic features of pulmonary tuberculosis in patients with and without HIV infection in Gulu, northern Uganda. The results provide additional insight into the pathogenesis of tuberculosis in HIV-seropositive persons in Uganda, and they suggest that tuberculosis control programmes must have a broader goal than simply the interruption of new transmission of infection.

Materials and methods

We conducted a cross-sectional study between November 1992 and January 1993 in Gulu and Lacor General Hospitals in Gulu District, Uganda. Consecutive in- and out-patients, 15–60 yrs of age, undergoing treatment for or diagnosed as a new case of tuberculosis and having an abnormal chest radiograph, were asked to participate. Patients on antituberculosis treatment for more than 4 weeks were not included. Informed consent was obtained from each subject before participation. Ethical approval was granted by the AIDS Scientific Subcommittee in Uganda.

Data collection

Information on demography, history of tuberculosis, and signs and symptoms of tuberculosis was collected by interview, review of medical records, and clinical examination. HIV serological status was assessed by three recombinant enzyme-linked immunoassay (ELISA) methods: HIVCHEK 1+2 Kit (Ortho Diagnostic Systems, Rahway, NJ, USA), Retro-Tek (Cellular Products Inc., NY, USA), and Recombigen (Cambridge Biotech Corp., Worcester, MA, USA). Testing positive by all methods was considered as diagnostic of HIV infection. Specimens with discordant results were tested using Novopath HIV-1 Immunoblot (Bio Rad Novopath Kit; Bio Rad Inc., Oxnard, CA, USA); a positive result was considered diagnostic of HIV infection.

The diagnosis of tuberculosis was based either on a positive Ziehl-Neelsen acid-fast stain of a first morning sputum specimen (at least three specimens were evaluated for all patients; potentially confounding non-tuberculous mycobacterial infections are not seen in Uganda [26]), or the combination of both a clinical presentation considered typical of tuberculosis by the attending physician and a chest radiograph considered compatible with tuberculosis by the hospital radiologist.

A posteroanterior chest radiograph was taken of every subject. Two Ugandan radiologists, blinded to the HIV status of the patients, interpreted the radiographs independently. Disagreements in interpretation were resolved by a chest physician and a radiologist at Case Western Reserve University, also blinded to the HIV status of the subject. The radiograph readers were asked to identify the following abnormalities: parenchymal infiltrates; cavitation; hilar/mediastinal adenopathy; pleural effusion; fibrosis; and loss of volume.

Chest radiographs were classified according to whether acute, chronic, or mixed lesions predominated on the radiographs. Acute lesions included: hilar and/or mediastinal adenopathy; pleural effusions; pneumonic infiltrates; and miliary disease. Chronic lesions included: cavitation; loss of volume; fibrosis; and calcification. The mixed category had acute lesions superimposed on chronic ones.

Statistical analysis

Patients were stratified into HIV-seropositive and HIV-seronegative groups, and differences in the radiographic features between the groups were compared. Statistical

significance was determined by Chi-squared tests and Fisher's exact tests. A p-value equal to or less than 0.05 was considered significant. All tests were two-tailed.

Results

One hundred and eighty patients were asked to participate in the study; 176 agreed giving a positive response rate of 98%. Of these, 153 patients had complete clinical and laboratory data or met eligibility criteria. Of the 153 patients, 92 were HIV-seropositive (60%) and 61 (40%) HIV-seronegative. These groups did not differ by age (mean ages 32 and 33 yrs, respectively), marital status, or employment status. The HIV-seropositive group was 46% male and the HIV-seronegative group 66% male ($p=0.024$). Of the 153 patients, normal chest radiographs were seen in 10 HIV-seropositive and 8 HIV-seronegative patients (differences not statistically significant) with positive sputum smears, and were not included in the analysis. Therefore, 135 patients were available for radiographic analysis in this report, of whom 82 were HIV-seropositive (61%) and 53 (39%) HIV-seronegative.

Table 1 summarizes the classification of abnormal chest radiographs into acute, chronic and mixed forms, by HIV status. The frequency of individual features of acute and chronic tuberculosis are also presented. Acute manifestations were 2.5 times more frequent in HIV-infected than uninfected patients. Each of the individual features of acute pulmonary tuberculosis was more frequently seen in those with HIV infection, but only hilar and/or mediastinal adenopathy and pneumonic infiltrate differences were statistically significant. Conversely, chronic tuberculosis was 2.6 times more frequent in HIV-seronegative than HIV-seropositive patients, and except for calcification, individual features of chronic tuberculosis were significantly more frequent in HIV-seronegative subjects. With the exception of pleural effusion,

Table 1. – Radiographic findings of 135 patients with pulmonary tuberculosis and abnormal chest radiographs by HIV serostatus

| | HIV-positive (n=82) | HIV-negative (n=53) |
|---|------------------------|------------------------|
| Overall pattern | | |
| Acute | 47 (57) | 12 (23)* |
| Chronic | 20 (24) | 34 (64)* |
| Mixed | 15 (18) | 7 (13) |
| Individual radiographic findings | | |
| Acute | | |
| Hilar and/or mediastinal Adenopathy | 21 (26) | 3 (6)* |
| Pleural effusions | 19 (23) | 6 (11) |
| Pneumonic infiltrate | 38 (46) | 14 (26)* |
| Miliary disease | 6 (7) | 0 (0) |
| Chronic | | |
| Cavitation | 15 (18) | 30 (57)* |
| Volume loss | 21 (26) | 29 (55)* |
| Fibrosis | 28 (34) | 30 (57)* |
| Calcification | 7 (8) | 9 (17) |

Values are presented as absolute number, and percentage in parenthesis. HIV: human immunodeficiency virus. *: differences between HIV-positive and HIV-negative groups are statistically significant at $p<0.05$ (Fisher's exact test).

miliary disease and calcification, all differences were statistically significant. One hundred and twenty six radiographs had lung field lesions; of these, predominantly lower lung field pulmonary disease was seen in eight (10%) HIV-seropositive and one (2%) HIV-seronegative patients ($p=0.086$).

Discussion

A high frequency of acute radiographic manifestations of pulmonary tuberculosis were observed in HIV-seropositive patients, with the disease often assuming patterns usually associated with primary tuberculosis. These manifestations included hilar and mediastinal adenopathy, pleural effusion, and pneumonic infiltrates. Miliary disease was seen in six HIV-seropositive patients but no HIV-seronegative patients. In contrast, cavitation, volume loss and fibrosis, findings characteristic of chronic tuberculosis, were seen more frequently in HIV-seronegative patients (table 1). In general, the present findings agree with other reports from the United States [11–13, 17, 18, 23], Europe [14], and Africa [15, 16, 19–22].

Previous discussions of the radiographic presentations of tuberculosis in HIV-infected patients have tended to focus on their atypical nature and their similarity to those of primary tuberculosis. Atypical radiographic presentations of tuberculosis in HIV-infected persons have been interpreted to reflect second exogenous infections presenting in forms typical of primary infections. A recent editorial by DALEY [27] emphasizes this point. The findings of the present study support this view.

It is important to note that nearly half of the HIV-seropositive pulmonary tuberculosis patients in our high HIV and high tuberculosis prevalence population presented with chest radiographs typical of chronic or reactivation tuberculosis. Whilst other African studies do not present data in a form that permits direct comparison with the present findings, it is notable that cavitory lesions, which we observed in 15 of the 82 (18%) of HIV-seropositive patients, were found in 19 out of 48 (40%) of such patients in Rwanda [16], 44 of out 99 (44%) [19] and 17 out of 80 (21%) [20] in Tanzania, and 40 out of 202 (20%) in Zimbabwe [21]. Thus, in Africa, a substantial part of the burden of HIV-related tuberculosis is probably due to reactivation of latent infection and progression of chronic disease, perhaps as a result of immunodeficiency.

In Uganda, as is true of much of Africa, tuberculosis control efforts focus on the effective treatment of smear-positive patients. Active case-finding is not undertaken, nor is chemoprophylaxis of infected but nondiseased individuals. Whilst this approach may decrease the transmission of infection, it is not likely to prevent reactivation and progression of pre-existing tuberculosis in relation to HIV infection. Effective reduction of the tuberculosis burden in HIV-endemic Africa may require not only intensification of existing tuberculosis control efforts but extension of programmes into activities not now included.

In conclusion, the radiographic manifestations of pulmonary tuberculosis in human immunodeficiency virus

seropositive individuals in Gulu, Uganda are frequently more acute and more likely to mimic primary tuberculosis than those seen in human immunodeficiency virus seronegative individuals. However, a substantial portion of the tuberculosis burden arises from endogenous reactivation of latent infection or progression of pre-existing chronic disease.

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References

1. Murray JF. Cursed duet: HIV infection and tuberculosis. *Respiration* 1990; 57: 210–220.
2. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. *Bull WHO* 1992; 70: 149–159.
3. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. *Tuber Lung Dis* 1992; 73: 311–321.
4. Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990–2000. *Bull WHO* 1994; 72: 213–220.
5. Selwyn PA, Hartel D, Lewis VA, *et al.* A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *New Engl J Med* 1989; 320: 545–550.
6. Braun MM, Badi N, Ryder RW, *et al.* A retrospective cohort-study of the risk of tuberculosis among women of childbearing age with HIV infection in Zaire. *Am Rev Respir Dis* 1991; 143: 501–504.
7. Allen S, Batungwanayo J, Kerlinkowske K, *et al.* Two year incidence of tuberculosis in cohorts of HIV-infected and uninfected urban Rwandan women. *Am Rev Respir Dis* 1992; 146: 1439–1444.
8. Bleiker MA, Styblo K. The annual tuberculosis infection rate and its trend in developing countries. *Bull IUAT* 1978; 53: 295–298.
9. Goodgame RW. AIDS in Uganda: clinical and social features. *N Engl J Med* 1990; 323: 383–389.
10. Fleming AF. Opportunistic infections in AIDS in developed and developing countries. *Trans Roy Soc Trop Med Hyg* 1990; 84 (Suppl. 1): 1–6.
11. Sunderam G, McDonald RJ, Maniatis T, Oleske J, Kapila R, Reichman LB. Tuberculosis as a manifestation of the acquired immunodeficiency syndrome (AIDS). *J Am Med Assoc* 1986; 256: 362–366.
12. Pitchenik AE, Rubinson HA. The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. *Am Rev Respir Dis* 1985; 131: 393–396.
13. Chaisson RE, Schechter GF, Theuer CP, Rutherford GW, Echenberg DF, Hopewell PC. Tuberculosis in patients with the acquired immunodeficiency syndrome: clinical features, response to therapy, and survival. *Am Rev Respir Dis* 1987; 136: 570–574.
14. Laguna Cuesta F, Chimeno Herrero CP, Garcia Aguado C, Martinez Fernandez R, Gonzalez Lahoz J, Ortega Calderon A. Tuberculosis e infección por HIV: estudio de 50 casos. *Rev Clin Esp* 1989; 184: 230–233.
15. Eriki PP, Okwera A, Aisu T, Morrissey AB, Ellner JJ, Daniel TM. The influence of human immunodeficiency

- virus (HIV) on tuberculosis in Kampala, Uganda. *Am Rev Respir Dis* 1991; 143: 185–187.
16. Batungwanayo J, Taelman H, Dhote R, Bogaerts J, Allen S, van de Perre P. Pulmonary tuberculosis in Kigali, Rwanda: impact of human immunodeficiency virus infection on clinical and radiographic presentation. *Am Rev Respir Dis* 1992; 146: 53–56.
 17. Davis SD, Yankelevitz DF, Williams T, Henschke CI. Pulmonary tuberculosis in immunocompromised hosts: epidemiological, clinical, and radiological assessment. *Sem Roentgenol* 1993; 28: 119–130.
 18. Greenberg SD, Frager D, Suster B, Walker S, Stavropoulos C, Rothpearl A. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology* 1994; 193: 115–119.
 19. Richter C, Pallangyo KJ, Ndosi BN, Chum HJ, Swai ABM, Shao J. Chest radiography and β_2 -microglobulin levels in HIV-seronegative and HIV-seropositive African patients with pulmonary tuberculosis. *Trop Geogr Med* 1994; 46: 283–287.
 20. Mlika-Cabanne N, Brauner M, Mugusi F, et al. Radiographic abnormalities in tuberculosis and risk of coexisting human immunodeficiency virus infection: results from Dar-es-Salaam, Tanzania, and scoring system. *Am J Respir Crit Care Med* 1995; 152: 786–793.
 21. Pozniak AL, MacLeod GA, Ndlovu D, Ross E, Mahari M, Weinberg J. Clinical and chest radiographic features of tuberculosis associated with human immunodeficiency virus in Zimbabwe. *Am J Respir Crit Care Med* 1995; 152: 1558–1561.
 22. Keiper MD, Beumont M, Elshami A, Langlotz CP, Miller WT Jr. CD4+ T-lymphocyte count and the radiographic presentation of pulmonary tuberculosis: a study of the relationship between these factors in patients with human immunodeficiency virus infection. *Chest* 1995; 107: 74–80.
 23. Post FA, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tuber Lung Dis* 1995; 76: 518–521.
 24. Styblo K. The global aspects of tuberculosis and HIV infection. *Bull IUATLD* 1990; 65: 28–32.
 25. Schulzer M, Fitzgerald JM, Enarson DA, Grzybowski S. An estimate of the future size of the tuberculosis problem in sub-Saharan Africa resulting from HIV infection. *Tuber Lung Dis* 1992; 73: 52–58.
 26. Morrissey AB, Aisu TO, Falkinham JO III, Eriki PP, Ellner JJ, Daniel TM. Absence of *Mycobacterium avium* complex disease in patients with AIDS in Uganda. *J Acquir Immune Defic Syndr* 1992; 5: 477–478.
 27. Daley CL. The typically "atypical" radiographic presentation of tuberculosis in advanced HIV disease. *Tuber Lung Dis* 1995; 76: 475–476.