INT J TUBERC LUNG DIS 5(8):746–753

Evaluation of suspected tuberculous pleurisy: clinical and diagnostic findings in HIV-1-positive and HIV-negative adults in Uganda

H. Luzze,*† A. M. Elliott,‡§ M. L. Joloba,† M. Odida,¶ J. Oweka-Onyee,‡ J. Nakiyingi,‡ M. Quigley,§ C. Hirsch,†# R. D. Mugerwa,†** A. Okwera,*† J. L. Johnson†#

* National Tuberculosis Treatment Centre, and † Uganda-Case Western Reserve University Research Collaboration, Mulago Hospital, Kampala, Uganda; ‡ Medical Research Council Programme on AIDS, Uganda Virus Research Institute, Entebbe, Uganda; § London School of Hygiene & Tropical Medicine, London, UK; ¶ Department of Pathology, Makerere University, Kampala, Uganda; # Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA; ** Department of Medicine, Makerere University, Kampala, Uganda

SUMMARY

SETTING: National Tuberculosis Treatment Centre, Mulago Hospital, Kampala, Uganda.

OBJECTIVES: To compare clinical and radiographic presentation, and diagnostic methods, in adults with tuberculous pleurisy who are negative and positive for the human immunodeficiency virus (HIV).

DESIGN: Adults with suspected pleural tuberculosis were screened by clinical examination, thoracocentesis and closed pleural biopsy. Biopsy material was cultured on Middlebrook 7H-10 solid medium and in BACTEC 12B radiometric vials. Pleural fluid was cultured using Löwenstein-Jensen slants, BACTEC and Kirchner liquid medium.

RESULTS: Of 156 individuals enrolled, 142 had tuberculosis, of whom 80% were HIV-positive. Among those with tuberculosis, HIV-positive patients had a more severe and longer illness. The size of effusions was similar in HIV-positive and HIV-negative patients. A higher proportion of HIV-positive patients had parenchymal infiltrates but this difference was not statistically significant. Pleural fluid lymphocytosis was present in all HIV-negative and 97% of the HIV-positive patients. HIV-positive patients had lower pleural fluid lymphocyte counts. Pleural fluid cultures were more often positive in HIV-positive patients. BACTEC and Kirchner liquid media gave higher yields than solid media.

CONCLUSION: HIV-positive patients with tuberculous pleurisy had a more severe illness than HIV-negative patients. Mycobacterial cultures from HIV-positive patients were more often positive, suggesting more mycobacterial extension from the lungs into the pleural space. Liquid culture media were superior to solid media with regard to diagnostic yield and time until diagnosis.

KEY WORDS: pleural tuberculosis; HIV; Uganda; diagnosis

THE CLINICAL and radiological presentation of tuberculosis has changed greatly since the human immunodeficiency virus (HIV) pandemic. Extra-pulmonary disease and smear-negative pulmonary tuberculosis have become more frequent, making the diagnosis of tuberculosis more difficult.[1,2] In particular, tuberculous pleurisy has been shown to be especially strongly associated with HIV in studies from Africa[3,4] and more recently the United States.[5] The diagnosis of pleural tuberculosis is usually made by the demonstration of the organism in pleural fluid or pleural biopsy specimens. In HIV-negative individuals the number of organisms present in the pleural fluid is generally low and the pathogenesis is thought to be an immunologically mediated hypersensitivity response to mycobacterial antigens. Typically, *Mycobacterium tuberculosis* has been cultured from pleural biopsy in 55% to 80% and pleural fluid in less than 30% of HIV-negative patients with tuberculous pleurisy. Liquid media and guinea-pig inoculation have been shown to produce higher yields than conventional Löwenstein-Jensen slants.[6]

In this study, we compared the clinical and radiological presentation of pleural tuberculosis and the diagnostic yield in HIV-negative and HIV-positive adults. We found that HIV-positive patients had a more prolonged and severe illness prior to diagnosis than HIV-negative patients. The histological results were similar for the two groups, while the mycobacterial cultures of pleural fluid and biopsy gave a higher yield in HIV-positive subjects. These findings have implications for the diagnosis of tuberculous pleurisy and for our understanding of the pathogenesis of the disease.

Correspondence to: Henry Luzze, MBChB, National Tuberculosis Treatment Centre, Mulago Hospital, P.O. Box 663, Kampala, Uganda. Fax: (+256) 41 533 531. e-mail: tbru@imul.com

Article submitted 1 August 2000. Final version accepted 10 April 2001.

METHODS

Study population

Adults aged 18 years and over with suspected tuberculous pleurisy were screened for enrolment in the study at the National Tuberculosis Treatment Centre, Mulago Hospital, Kampala, Uganda. Patients without a history of prior tuberculosis or tuberculosis treatment, with pleural effusions occupying at least one third of the hemithorax on chest X-ray and who were willing to participate in the study were enrolled. All participants gave written informed consent for HIV testing and study participation and received pre- and post-HIV-test counselling. A standardised medical history and physical examination were performed on each subject. General condition was measured using the Karnofsky performance scale, on which a score of 50% indicates that a patient is unable to care for him or herself and requires the equivalent of in-patient hospital care; 80% indicates that an individual can perform normal activities with effort but has some signs or symptoms of disease.[7] The study protocol was reviewed and approved by the Uganda National AIDS Research Subcommittee and the ethics committees of the Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine.

Haematology and virology

Venous blood was drawn for complete blood count and CD4 count. HIV-1 testing was performed using a rapid test (Determine HIV-1-2, Abbott Laboratories, Tokyo, Japan) and confirmed by ELISA (Vironostika HIV-1 Microelisa system, Organon Teknika Corporation, Durham, NC, USA). Blood and pleural fluid samples were collected into EDTA-anticoagulated Vacutainer™ tubes for HIV viral load determination. The samples were centrifuged at 1700 g for 10 minutes and the supernatant collected and stored at −80°C until analysis. Samples from 40 consecutive HIV-positive participants were analysed using Amplicor HIV-1 Monitor test (Roche Diagnostic Systems, Branchburg, NJ).

Bacteriology and histopathology

Thoracocentesis was performed under aseptic conditions. Closed pleural biopsy was then performed under local lignocaine anaesthesia, using the Abrams needle. Multiple pieces of pleural tissue were obtained.[8,9]

Pleural tissue was fixed in 10% buffered formalin, stained with haematoxylin and eosin and examined for histopathological changes typical of tuberculosis. The remaining biopsies were aseptically ground in a disposable tissue grinder and homogenised with 2.5 mls of sterile normal saline. BACTEC 12B radiometric culture vials containing Middlebrook 7H-12 broth (Becton Dickinson and Company, Sparks, MD) supplemented with polymyxin B, amphotericin B, nalidixic acid, trimethoprim and azlocillin (PANTA), were inoculated with 0.5 ml of homogenised tissue.[9] Middlebrook 7H 10 agar plates, supplemented with oleic acid albumin-dextrose-catalase, were inoculated with 60 μl of the homogenised tissue.

Pleural fluid was examined for cell count and for differential using Leishman stain. At the bedside, 5 ml of pleural fluid were inoculated into each of two BACTEC 13A vials (Middlebrook 7H-13 broth) supplemented with PANTA for culture. Pleural fluid was collected into 50 ml sterile polypropylene tubes and transported to the laboratory. One 50 ml tube was centrifuged at 1400 g for 15 minutes and part of the sediment used to prepare Gram and Ziehl-Neelsen (ZN) stains. The remaining sediment was inoculated on Löwenstein-Jensen (LJ) (0.5 ml), MacConkey media, 5% sheep's blood agar, and Kirchner liquid medium (0.5 ml). For some of the patients a second sample of 50 ml was centrifuged, and 60 μl of the sediment was inoculated onto solid Middlebrook 7H-10 medium. BACTEC vials were incubated at 37°C and examined daily for positive growth index (⩾20). Vials that were negative after 14 days incubation were examined again at days 18 and 21 and weekly thereafter for up to 6 weeks. Middlebrook 7H-10 plates were incubated at 37°C in 5–10% CO_2 and examined weekly for 4 weeks. Kirchner and LJ media were incubated at 37°C in air. Kirchner cultures were examined weekly for 4 weeks and then subcultured onto LJ slants. All LJ slants were examined weekly for 8 weeks. Positive cultures from samples cultured directly on solid media, or subcultured onto solid media, were confirmed to be *M. tuberculosis* by staining for acid-fast bacilli by the ZN method and by colony morphology. BACTEC isolates were confirmed by ZN staining, subculture on blood agar plates to detect non-fastidious contaminants, and the BACTEC para-nitro-α-acetyl-amino β-hydroxy-propiophenone (NAP) susceptibility method.[10] Three of 312 (1.0%) of the BACTEC 13B cultures directly inoculated in the clinic showed bacterial contamination. One of 146 (0.7 %) LJ slopes showed contamination.

Patients with productive cough were asked to give at least two samples of sputum for ZN staining and culture on LJ slants.

Definition of tuberculosis

The diagnosis of tuberculosis was categorised as follows: 1) confirmed tuberculosis: any culture was positive for *M. tuberculosis*, or pleural biopsy histology was characteristic of tuberculosis; 2) probable tuberculosis: the laboratory investigations were negative but there was a good clinical response to tuberculosis treatment (at least two of three criteria: weight gain of 2 kg or more, improvement in symptoms, radiological improvement); 3) not tuberculosis: a definite diagnosis other than tuberculosis was made; and 4) uncertain: the presenting clinical fea-

tures suggested tuberculosis but no confirmation could be obtained.

Statistical methods

Data were analysed using Epi-Info 6 (Centers for Disease Control and Prevention, Atlanta, GA) and STATA 5 (Stata Corporation, College Station, TX). Comparisons were made using the χ^2 test for proportions and the *t*-test for means. Medians were compared using the Wilcoxon sign rank test for matched pairs and the Wilcoxon rank sum test for independent samples. A level of significance of $P < 0.05$ was used to reject the null hypothesis in all analyses. All analyses were two-tailed.

RESULTS

Between August 1998 and December 1999, 156 patients were enrolled; 42 were HIV-negative and 114 were HIV-positive. Among the HIV-negative patients, 27 had confirmed tuberculosis, six had probable tuberculosis and nine were found to have other conditions (five malignancy and one cardiac failure; for three the diagnosis remained uncertain). HIV-negative patients with malignancy had a higher mean age than those with other diagnoses (46 years and 32 years, respectively, $P = 0.02$). Among the HIV-positive patients 105 had confirmed tuberculosis, four had probable tuberculosis and five were found to have other conditions (one *Salmonella*, one *Corynebacterium* in a patient who had undergone a pleural biopsy procedure elsewhere, and one empyema with no growth; for two the diagnosis remained uncertain). One hundred and forty-two patients had a final diagnosis of tuberculosis and were included in the further analysis: 33 (23%) were HIV-negative and 109 (77%) were HIV-positive. The associations between HIV status and histological and microbiological findings were unchanged when the analysis was restricted to individuals with confirmed tuberculosis.

Clinical findings

Demographic and clinical findings were compared for the 142 HIV-negative and HIV-positive patients with a final diagnosis of tuberculosis. There were no significant demographic differences between the groups: the mean age was respectively 33 and 34 years in the HIV-negative and HIV-positive groups; 42% of the HIV-negative patients and 45% of the HIV-positive patients were female. The median peripheral blood CD4 lymphocyte count among the HIV-positive patients was 122 μL^{-1} (range 1–766 μL^{-1}) and the median plasma HIV viral load in a subset of 38 patients was 244 214 copies/ml^{-1}. The median HIV viral load was significantly higher in pleural fluid than in plasma ($P < 0.001$) (Table 1).

The proportion of HIV-negative and HIV-positive patients with pleuritic chest pain was similar; however, fever, cough, dyspnoea and weight loss were more frequent in the HIV-positive group (Table 1). HIV-positive patients also showed signs of more severe illness with higher temperature, lower body mass index, lower Karnofsky score and lower haemoglobin. Symptoms and signs suggestive of HIV co-infection, such as diarrhoea, herpes zoster scars and thrush, were present only in HIV-positive subjects. Symptoms were generally of longer duration in HIV-positive subjects, although differences in the mean duration of individual symptoms were not statistically significant. When the cardinal symptoms of pleural tuberculosis (cough, chest pain, dyspnoea and fever) were combined, 18% of the HIV-negative patients had symptoms for less than 2 weeks compared to 3% of HIV-positive patients ($P = 0.002$). Thirty-nine per cent of the HIV-negative patients had symptoms for less than one month compared to 19% of HIV-positive patients ($P = 0.02$). The pleural fluid white blood cell (WBC) count was significantly reduced in HIV-positive subjects. This was due to reduction in the absolute mononuclear cell count, while granulocyte counts were similar. All of the HIV-negative and 97% of the HIV-positive patients had a lymphocytic pleocytosis (>50% lymphocytes) in the pleural fluid. HIV-infected patients with peripheral blood CD4 lymphocyte counts <200 μL^{-1} had significantly lower body mass index, haemoglobin, total peripheral blood and pleural fluid WBC counts, higher plasma HIV-1 viral load, and a higher frequency of prior herpes zoster and oral thrush than patients with CD4 counts of ⩾200 μL^{-1} (data not shown).

The size of pleural effusions was comparable between HIV-negative and HIV-positive patients (Table 2). HIV-positive patients had a somewhat higher frequency of parenchymal lung infiltrates, but this was not statistically significant even when both upper and lower lobes were combined (23% vs. 10%, $P = 0.10$). HIV-infected patients with CD4 counts <200 μL^{-1} had smaller pleural effusions than HIV-infected individuals with higher CD4 counts (data not shown).

Bacteriological and histopathological results

Twenty-nine (88%) of the 33 HIV-negative patients and 86 (79%) of the 109 HIV-positive patients underwent closed pleural biopsy ($P = 0.4$). Histological examination showed pleural tissue was present in 19 of the biopsies from HIV-negative patients and in 70 of the biopsies from HIV-positive patients. The proportion of HIV-positive and HIV-negative patients with histological findings consistent with tuberculous pleurisy was comparable (Table 3). Fifty-six of the 58 biopsies which showed features consistent with tuberculosis were reviewed for the nature of granulomas. The granulomas were classified as 'poorly

Table 1 Effect of HIV on symptoms, signs and laboratory findings in pleural tuberculosis

	HIV− (n = 33)	HIV+ (n = 109)	P value
Symptoms			
Fever			
% affected	36	59	0.02
Mean duration * (months)	1.3	1.8	0.41
Cough			
% affected	73	88	0.03
Mean duration (months)	1.5	2.0	0.31
Chest pain			
% affected	88	86	0.81
Mean duration (months)	1.2	1.7	0.20
Dyspnoea			
% affected	70	80	0.22
Mean duration (months)	1.0	1.3	0.42
Weight loss			
% affected	79	91	0.06
Mean duration (months)	1.3	2.0	0.12
Diarrhoea			
% affected	0	9	0.07
Mean duration (months)	—	0.8	
Signs			
Body temperature (°C) (mean)	35.9	37.7	0.007
Body mass index (kg/m^2) (mean)	21.1	19.6	0.001
Karnofsky score			
60–70	9%	34%	0.005
⩾80	91%	66%	
Lymphadenopathy			
Localised	6%	15%	0.19
Generalised	0	1%	0.58
Maculopapular rash	0	4%	0.26
Herpes zoster (active or scars)	0	11%	0.05
Oral thrush†	0	8%	0.08
Haematological and virological findings			
Haemoglobin, g/dl (mean ± SE)	12.4 ± 2.3	10.8 ± 2.2	<0.001
Total WBC count × 10^9/l (mean ± SE)	6.5 ± 0.3	5.3 ± 0.2	0.006
CD4 T cells/μl (median, interquartile range)‡	571 (427–670)	122 (59–248)	<0.001
Viral load (copies ml^{-1}; median; interquartile range) (data for 38 patients§)			
Plasma	ND	244 214 (76 152–407 317)	
Pleural fluid	ND	1 313 000 (315 550–3 608 425)	
Pleural cell counts × 10^6/l (median) (data for 30 HIV− and 98 HIV+ patients)			
Total white cells	1210	800	0.01
Granulocytes	116	80	0.15
Mononuclear cells	1110	681	0.01

Note: χ^2 test for proportions, t-test for means, Wilcoxon rank test for medians.
* Mean duration excluded individuals without symptoms.
† Two missing values.
‡ Three missing values.
§ Viral load was examined in 40 consecutive HIV-positive cases. Two were excluded because the final diagnosis was not tuberculosis.
HIV = human immunodeficiency virus; SE = standard error; WBC = white blood cell; ND = not done.

formed' or 'well formed with giant cells'. Twelve of 43 HIV-positive patients (28%) had well formed granulomas compared with 8 of the 13 (62%) HIV-negative patients (P = 0.03). Among the HIV-positive patients, there was no significant association between CD4 counts and the appearance of granulomas.

Pleural fluid cultures were performed for all patients. Cultures of both biopsy tissue and pleural fluid were more often positive in the HIV-positive group than in the HIV-negative group. Among HIV-positive patients, the diagnostic yield of pleural fluid and biopsy cultures was similar for those with CD4 counts above or below 200 μL^{-1} (data not shown). Among those with a positive BACTEC culture, the mean time to positive was similar for HIV-negative and HIV-positive patients for both biopsy and pleural fluid culture (Table 4).

For both HIV-negative and HIV-positive groups, culture of the biopsy tissue using BACTEC was the most sensitive diagnostic test. Culture of the biopsy tissue using BACTEC liquid medium was significantly more sensitive than Middlebrook 7H-10 agar-based medium (P = 0.03 for HIV-negative and P = 0.002 for HIV-positive subjects). Culture of pleural

Table 2 Effect of HIV infection on radiological findings in pleural tuberculosis*

	HIV− (n = 31)	HIV+ (n = 107)	P value
Right lung affected	45%	47%	0.88
Left lung affected	61%	57%	0.74
Both lungs affected	6%	5%	0.69
Mean no. of zones	2.1	2.3	0.38
Mean ratio†	0.50	0.49	0.95
Mediastinal shift	26%	29%	0.76
Upper lobe infiltrates	6%	19%	0.10
Lower lobe infiltrates	6%	17%	0.15
Cavitary disease	0	3%	0.35
Hilar or mediastinal adenopathy	3%	5%	0.73

* Four X-rays were not available for analysis: 2 HIV-negative, 2 HIV-positive.
† Length affected lung/length healthy lung. This ratio could not be calculated for 3 HIV-negative and 6 HIV-positive case in whom both lungs were affected.

fluid using BACTEC was more sensitive than culture on LJ medium for both HIV-positive and HIV-negative patient groups (Table 3).

To determine whether BACTEC gave better results because it uses an enriched liquid medium, a comparison was made between BACTEC (which employs liquid Middlebrook broth) and solid Middlebrook 7H-10 agar-based medium, and between BACTEC and liquid Kirchner medium, for pleural fluid culture. This was done in a subgroup of 40 subjects, of whom seven were HIV-negative and 33 were HIV-positive (Table 5). Culture positivity was similar between Middlebrook 7H-10 and LJ solid media. The diagnostic yield was improved using both BACTEC and Kirchner liquid media compared to solid media. Kirchner liquid medium had almost as high a sensitivity as BACTEC culture; however, the mean time until positive culture was significantly lower using BACTEC medium and radiometric detection methods than simple Kirchner medium (3.5 weeks vs. 6.7 weeks, $P < 0.001$).

Sputum samples were available for two-thirds of all participants. Sputum cultures were positive in one-quarter, with no difference between HIV-positive and -negative patients.

Table 3 Outcome of diagnostic investigations in relation to HIV status in pleural tuberculosis

	Proportion (%) positive		
	HIV− (n = 33)	HIV+ (n = 109)	P value
Histology	15/29 (52%)	49/86 (57%)	0.78
Biopsy, BACTEC culture	14/25 (56%)	66/82 (81%)	0.27
Biopsy, Middlebrook 7H-10 culture	5/24 (21%)	41/73 (56%)	0.006
Fluid, BACTEC culture	8/33 (24%)	82/109 (75%)	<0.001
Fluid, Löwenstein-Jensen	4/33 (12%)	47/109 (43%)	0.002
Sputum smear*	2/33 (6%)	16/109 (15%)	0.24
Sputum culture†	5/33 (15%)	29/109 (27%)	0.26

* Sputum smear was available for 26 HIV-negative and 63 HIV-positive subjects.
† Sputum culture was available for 26 HIV-negative and 61 HIV-positive subjects.

Table 4 Time to positive on BACTEC culture for HIV-negative and HIV-positive patients with pleural tuberculosis

	Mean time to positive BACTEC culture in days (range)		P value (t-test)
	HIV−	HIV+	
Pleural biopsy tissue	n = 13 18 (1–26)	n = 60 15 (1–40)	0.25
Pleural fluid	n = 8 26 (18–41)	n = 80 22 (2–40)	0.26

DISCUSSION

In this study we examined adults with initial episodes of suspected tuberculous pleurisy who were referred to a large public tuberculosis centre in Uganda. By studying a large number of HIV-negative and HIV-positive subjects, we were able to confirm and extend the findings of several previous studies.[4,11–18] First, our data were in keeping with earlier studies indicating the superiority of liquid over solid media for culture of pleural tissue and fluid specimens.[6,19,20] Second, comparison of HIV-negative and HIV-positive subjects demonstrated clear differences in the duration of symptoms and yield of pleural fluid and pleural biopsy cultures between the two groups.

The diagnostic yield for histological examination of pleural biopsy specimens was similar for HIV-negative and HIV-positive subjects, in keeping with several previous studies.[11,12,16,18] Pleural biopsy and pleural fluid culture gave a higher yield in HIV-positive subjects, with the highest proportion positive among those with the lowest CD4 counts. This differs from earlier reports of predominantly HIV-negative patients in which histology of the biopsy tissue gave the highest yield.[19,21] Our findings were largely due to the high sensitivity of BACTEC culture for pleural samples from HIV-positive subjects. Using BACTEC liquid media, the yield of pleural biopsy culture was also slightly higher than pleural biopsy histology for HIV-negative patients. Comparisons between culture media were limited by differences in the volumes of homogenised tissue, fluid or sediment inoculated; however, BACTEC liquid media was clearly superior to both LJ and Middlebrook 7H-10 solid media for culture of both biopsy tissue and pleural fluid. The

Table 5 Comparison of solid and liquid culture media for isolation of *Mycobacterium tuberculosis* from pleural fluid for 40 subjects (7 HIV-negative, 33 HIV-positive)

Medium	Positive n (%)	P value*	Mean weeks to positive	P value†
BACTEC	30 (75)		3.5	
Kirchner	26 (65)	0.46	6.7	<0.001
Löwenstein-Jensen	18 (45)	0.01	4.7	0.01
Middlebrook	14 (35)	<0.001	Not done	

* χ^2 test for comparison with BACTEC.
† t-test for comparison with BACTEC.

liquid culture media were investigated further by comparing BACTEC and Kirchner media. The sensitivity was comparable for these liquid media, although the mean time to positivity for Kirchner medium was 3 weeks longer. The slight superiority of BACTEC may have been due to the more enriched medium and more rapid detection of positive cultures using a radiometric system where the cultures were checked daily. However, the procedure differed for culture in BACTEC and Kirchner in that the pleural fluid was directly inoculated into the BACTEC medium at the bedside, whereas inoculation into Kirchner medium was done in the laboratory 2–3 hours later and after centrifugation. Delay in inoculation for Kirchner could have significantly reduced the yield for this medium, as there is evidence that immediate inoculation into liquid media produces better results.[20–22] Bedside inoculation of Kirchner medium may offer similar sensitivity to BACTEC, without the expense and waste disposal issues of a radiometric system. This requires further study.

Seventy-seven per cent of the patients with tuberculous pleurisy in our study were HIV-positive. This is higher than recent reports in Ethiopia (22%), Kenya (42.3%) and Tanzania (58%), but similar to those in Zambia (81%), Rwanda (83%) and Zimbabwe (85%).[3,4,13,15,16,18] As observed elsewhere, the HIV-positive patients presented with more severe illness and had a longer duration of symptoms than HIV-negative patients.[13,15,18] The size of the pleural effusion was not affected by HIV co-infection. However, several studies have indicated a possible association between HIV and atypical X-ray findings in pleural tuberculosis.[4,11,13,15,17] We also observed that concomitant pulmonary infiltrates were present in a higher proportion of HIV-positive patients with tuberculous pleurisy, but this finding was not statistically significant.

Previous reports have suggested a higher frequency of positive culture for *M. tuberculosis* in pleural fluid from HIV-positive cases,[11,12,14] although this difference was not statistically significant in larger studies.[11,12] Our results show a highly significant difference. The more frequent isolation of *M. tuberculosis* from pleural fluid and biopsy specimens of HIV-positive patients may indicate that HIV-related immunosuppression (as evidenced by decreased mononuclear cell counts) may favour extension of *M. tuberculosis* infection from the lung to the pleural space. The higher viral load in the pleural fluid compared to plasma in HIV-positive patients supports the hypothesis that there is higher replication of the virus at the site of *M. tuberculosis* infection.[23,24] High levels of virus in the pleural fluid may influence the local immune response and may determine HIV progression following treatment for tuberculosis.

The causes of pleural effusions among HIV-negative and HIV-positive patients vary geographically.[25–27] In this study, 79% of the HIV-negative patients and 96% of the HIV-positive patients were found to have tuberculosis. This probably reflects referral bias in favour of tuberculosis in our study population; however, our findings were very similar to those from Rwanda, Tanzania and Zimbabwe. In these studies patients were referred after excluding other clinically obvious diagnoses such as cardiac failure, renal or hepatic failure or empyema.[4,12,13,18] Thus, despite possible bias in referral, the findings suggest that, after excluding other clinically obvious conditions, it is appropriate for clinicians in East and Central Africa to treat patients with lymphocytic pleural effusions for tuberculosis without further investigations when diagnostic facilities are limited. This is especially true for HIV-positive cases. Among the HIV-negative cases malignancy was the second most common diagnosis and should be considered in older patients.

Acknowledgements

We thank the staff of the Uganda-Case Western Reserve University Research Collaboration at Mulago Hospital, Kampala, the Department of Medicine New Mulago Hospital and The AIDS Support Organisation (TASO), Entebbe, for referral and care of the study participants. We are indebted to all the patients who participated in the study and to Steven Kyaligonza and Safina Nakanwagi for field work and nursing.

The study was funded by a Wellcome Trust Career Development Fellowship to Dr Alison Elliott (grant number 044199/Z/95/Z/140/CSD).

References

1 Pitchenick A E, Burr J, Suarez M, Fertel D, Gonzalez G, Moas C. Human T-cell lymphotropic virus III (HTLV-III) seropositivity and related disease among 71 consecutive patients in whom tuberculosis was diagnosed. Am Rev Respir Dis 1987; 135: 875–879.
2 Raviglione M C, Harries A D, Msiska R, Wilkinson D, Nunn P. Tuberculosis and HIV: current status in Africa. AIDS 1997; 11: S115–S123.
3 Elliott A M, Luo N, Tembo G, et al. The impact of human immunodeficiency virus on tuberculosis in Zambia: a cross-sectional study. Br Med J 1990; 301: 412–415.
4 Batungwanayo J, Taelman H, Allen S, Bogaerts J, Kagame A, Van de Perre P. Pleural effusion, tuberculosis and HIV-1 infection in Kigali, Rwanda. AIDS 1993; 7: 73–79.
5 Frye M D, Pozsik C J, Sahn S A. Tuberculous pleurisy is more common in AIDS than in non-AIDS patients with tuberculosis. Chest 1997; 112: 393–397.
6 Berger H W, Mejia E. Tuberculous pleurisy. Chest 1973; 63: 88–92.
7 Karnofsky D A, Burchenal J H. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C M, ed. Evaluation of chemotherapeutic agents. New York: Columbia University Press, 1949: 191–205.
8 Abrams L D. A pleural-biopsy punch. Lancet 1958; 1: 30–31.
9 Kirch C M. A modified Abrams needle biopsy technique. Chest 1995; 108: 982–986.
10 Siddiqi S H. BACTEC tuberculosis system product and procedure manual. Sparks, MD: Becton Dickinson, 1995.
11 Relkin F, Aranda C P, Garay S M, Smith R, Berkowitz K A, Rom W N. Pleural tuberculosis and HIV infection. Chest 1994; 105: 1338–1341.

12 Richter C, Perenboom R, Swai A B M, et al. Diagnosis of tuberculosis in patients with pleural effusion in an area of HIV infection and limited diagnostic facilities. Trop Geogr Med 1994; 46: 293–297.
13 Richter C, Perenboom R, Mtoni I, et al. Clinical features of HIV-seropositive and HIV-seronegative patients with tuberculous pleural effusion in Dar es Salaam, Tanzania. Chest 1994; 106: 1471–1475.
14 Gil V, Cordero P J, Greses J V, Soler J J. Pleural tuberculosis in HIV-infected patients. Chest 1995; 107: 1775–1776.
15 Aderaye A G, Melaku B K, Zenebe C G. Pleural tuberculosis in patients infected with HIV in Addis Ababa. Cent Afr J Med 1996; 42: 337–340.
16 Owino E A, Mcligeyo S O, Gathua S N, Nyong' O A. Prevalence of immunodeficiency virus infection: its impact on the diagnostic yields in exudative pleural effusions at Kenyatta National Hospital, Nairobi. East Afr Med J 1996; 73: 575–578.
17 Trajman A, Neto E B, Belo M T, et al. Pleural tuberculosis and human immunodeficiency virus co-infection. Int J Tuberc Lung Dis 1997; 1: 498–501.
18 Heyderman R S, Makunike R, Muza T, et al. Pleural tuberculosis in Harare, Zimbabwe: the relationship between human immunodeficiency virus, CD4 lymphocyte count, granuloma formation and disseminated disease. Trop Med Int Health 1998; 3: 14–20.
19 Levine H, Metzger W, Lacera D, Kay L. Diagnosis of tuberculous pleurisy by culture of pleural biopsy specimen. Arch Intern Med 1970; 126: 269–271.
20 Cheng A F, Tai V H, Li M S, et al. Improved recovery of *Mycobacterium tuberculosis* from pleural aspirates: bedside inoculation, heparinised containers and liquid culture media. Scand J Infect Dis 1999; 31: 485–487.
21 Valdes L, Alvarez D, San Jose E, et al. Tuberculous pleurisy. A study of 254 patients. Arch Intern Med 1998; 158: 2017–2021.
22 Maartens G, Bateman E D. Tuberculous pleural effusions: increased culture yield with bedside inoculation of pleural fluid and poor diagnostic value of adenosine deaminase. Thorax 1991; 46: 96–99.
23 Goletti D, Weissman D, Jackson R W, et al. Effect of *Mycobacterium tuberculosis* on HIV replication. Role of immune activation. J Immunol 1996; 157: 1271–1278.
24 Garrait V, Cadranel J, Esvant H, et al. Tuberculosis generates a microenvironment enhancing the productive infection of local lymphocytes by HIV. J Immunol 1997; 159: 2824–2830.
25 Marel M, Stastny B, Melinova L, Svandova E, Light R W. Diagnosis of pleural effusions. Experience with clinical studies, 1986 to 1990. Chest 1995; 107: 1598–1603.
26 Hamm H, Matthys H. Pleural disease in patients with AIDS. Curr Opin Pulm Med 1997; 3: 315–318.
27 Miller R F, Howling S J, Reid A J, Shaw P J. Pleural effusions in patients with AIDS. Sex Transm Infect 2000; 76: 122–125.

RÉSUMÉ

CADRE : Centre National du Traitement de la Tuberculose, Hôpital Mulago, Kampala, Ouganda.

OBJECTIFS : Comparer les signes cliniques et radiologiques et les méthodes de diagnostic chez les adultes séropositifs et négatifs pour le virus de l'immunodéficience humaine (VIH), atteints de pleurésie tuberculeuse.

SCHÉMA : Les adultes suspects d'une pleurésie tuberculeuse ont été soumis à un examen clinique, une thoracocentèse et une biopsie pleurale aveugle. Le matériel de biopsie a été cultivé sur milieu solide 7H-10 de Middelbrook et dans des flacons radiométriques BACTEC 12B. Le liquide pleural a été cultivé sur des tubes de Löwenstein-Jensen et sur milieux liquides BACTEC et de Kirchner.

RÉSULTATS : Parmi les 156 sujets enrôlés, 142 avaient une tuberculose dont 80% étaient séropositifs pour le VIH. Parmi les patients tuberculeux, l'affection était plus sévère et de plus longue durée chez les patients séropositifs pour le VIH. L'importance des épanchements est similaire chez les séropositifs et négatifs pour le VIH. Des infiltrats parenchymateux apparaissent dans une plus grande proportion des patients séropositifs pour le VIH, mais cette différence n'est pas statistiquement significative. La lymphocytose du liquide pleural est présente chez tous les séronégatifs pour le VIH et chez 97% des patients séropositifs. Les patients séropositifs pour le VIH ont des décomptes lymphocytaires plus faibles dans le liquide pleural. Les cultures du liquide pleural sont plus souvent positives chez les patients séropositifs pour le VIH. Les milieux liquides BACTEC et de Kirchner ont des rendements supérieurs à ceux des milieux solides.

CONCLUSION : Chez les patients atteints de pleurésie tuberculeuse, séropositifs pour le VIH, la maladie donne des signes plus sévères que chez les patients séronégatifs. Les cultures mycobactériennes provenant de patients séropositifs pour le VIH sont plus souvent positives, ce qui suggère une extension mycobactérienne plus importante en provenance des poumons vers l'espace pleural. Les milieux de culture liquide sont supérieurs aux milieux solides en ce qui concerne la rentabilité diagnostique et la durée précédant le diagnostic.

RESUMEN

MARCO DE REFERENCIA : Centro Nacional de Tratamiento de la Tuberculosis, Hospital Mulago, Kampala, Uganda.

OBJETIVOS : Comparar la presentación clínica y radiográfica y los métodos de diagnóstico de los adultos negativos y positivos al virus de la inmunodeficiencia humana (VIH) con pleuresía tuberculosa.

MÉTODO : Se efectuó un examen clínico, toracocentesis y biopsia pleural cerrada a los adultos con sospecha de tuberculosis pleural. El material de la biopsia se cultivó en medio sólido de Middlebrook 7H-10 y en frascos radiométricos BACTEC 12B. El líquido pleural se cultivó en medio de Löwenstein-Jensen, BACTEC y Kirchner.

RESULTADOS : Sobre 156 personas incorporadas, 142 tenían tuberculosis, y de ellos, el 80% eran VIH positivos. Entre los pacientes tuberculosos, los VIH positivos tenían una enfermedad más grave y prolongada. La extensión del derrame era similar entre los pacientes VIH positivos y negativos. Una mayor proporción de pacientes VIH positivos tenían infiltrados parenquima-

tosos, pero esta diferencia no era estadísticamente significativa. La linfocitosis en el líquido pleural estaba presente en todos los VIH negativos y en el 97% de los VIH positivos. Los pacientes VIH positivos tenían menos linfocitos en el líquido pleural. Los cultivos en el líquido pleural eran positivos con más frecuencia en los pacientes VIH positivos. Los medios líquidos BACTEC y Kirchner dieron rendimientos más altos que los medios sólidos.

CONCLUSIÓN: Los pacientes VIH positivos con pleuresía tuberculosa tenían una enfermedad más grave que los VIH negativos. Los cultivos de micobacterias de los pacientes VIH positivos eran positivos con mayor frecuencia, lo que sugiere que existe un mayor pasaje de gérmenes del pulmón a la pleura. Los medios de cultivo líquidos eran superiores a los sólidos en cuanto al rendimiento diagnóstico y al tiempo necesario para el mismo.