

Diagnostic yield of fine needle aspiration biopsy in HIV-infected adults with suspected mycobacterial lymphadenitis

R Razack,¹ MB ChB, MScMedSc (Cytopathology); M Louw,¹ MB ChB, MMed (Anat Path), MScMedSc (Cytopathology); C A Wright,^{1,2} MB BCh, MMed (Anat Path), FCPATH (SA), FRCPath (UK), FIAC, PhD

¹ Division of Anatomical Pathology, Faculty of Medicine and Health Sciences, Stellenbosch University, and National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa

² National Health Laboratory Service, Port Elizabeth, South Africa

Corresponding author: R Razack (rubina@sun.ac.za)

Background. Fine needle aspiration biopsy (FNAB) has been shown to be the diagnostic procedure of choice for superficial lymphadenitis in tuberculosis endemic regions.

Methods. We conducted a retrospective laboratory-based study to determine the bacteriological yield of clinically suspected mycobacterial tuberculous lymphadenitis following FNAB in adults, and specifically HIV-positive patients, to determine the need for the introduction of automated nucleic acid amplification tests (NAATs) such as the Xpert MTB/RIF assay as the initial diagnostic modality.

Results. A diagnostic yield of 80% was achieved, significantly higher in HIV-positive v. HIV-negative patients (84% v. 52%, respectively; $p < 0.001$).

Conclusion. The results justify using automated NAATs such as the Xpert MTB/RIF assay as the initial diagnostic modality to expedite management in HIV-infected patients.

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Tuberculous lymphadenitis (LAD) is the most common form of extrapulmonary tuberculosis (TB), accounting for 30 - 52% of cases of peripheral lymphadenopathy in developing countries with a high TB incidence.^[1-3] In high-incidence countries, it is usually considered a disease of childhood,^[4] while the peak age of tuberculous LAD in developed countries such as the USA has now been shown to be 30 - 40 years.^[5]

In tuberculous LAD, fine needle aspiration biopsy (FNAB) has proved to be the diagnostic procedure of choice, with diagnostic yields varying from 42% to 83%, the highest yield in any extrapulmonary specimen investigation.^[1,2,6] Although FNAB is simple, cost effective and safe, cytomorphology is not specific and microbiological cultures for speciation and drug sensitivity are required. The literature reports a variable detection rate of mycobacteria on cultures acquired by FNAB, with figures ranging between 35% and 83%.^[1-3] In South Africa (SA), bacteriological confirmation defined as the identification of mycobacterial organisms, either by positive Ziehl-Neelsen stain, Papanicolaou autofluorescence and/or culture from aspirates in children is high, at 77.1%.^[7] Comparative figures for aspirates in the adult population in SA are few and have small sample numbers.^[8,9]

With this background, a retrospective laboratory-based study was conducted to determine the bacteriological yield of clinically suspected mycobacterial LAD in adults, and specifically, HIV-positive patients, to determine the need for introduction of automated nucleic acid amplification tests (NAATs), such as the Xpert MTB/RIF assay as the initial diagnostic modality.

Methods

The study was conducted from May 2007 to March 2010 at the Tygerberg Hospital FNAB clinic. Ethical approval was received from the Stellenbosch University Health Research Ethics Committee (ref. no. S12/07/202). The study population included adults, ≥ 14 years of age (as defined in SA), referred to the FNAB clinic for suspected

mycobacterial LAD, where cytomorphology was consistent with mycobacterial disease.

FNABs were performed by the trained sister or pathologist using a 23 G or 25 G needle attached to a 10 ml syringe. Two aspirates were performed, and the syringe rinsed in Mycobacterial Growth Indicator Tube (MGIT) medium for mycobacterial culture. Samples inoculated into MGIT were cultured according the standard operating procedure in the automated BACTEC MGIT 960 system (Becton Dickinson, USA). Cultures were incubated at 37°C for up to 50 days or until flagged positive.

A positive cytology diagnosis included cytomorphological features consistent with mycobacterial infection and confirmation of the organism on Ziehl-Neelsen stain or Papanicolaou autofluorescence.

Results

A total of 368 patients were included. Of these, 226 (61%) were HIV-positive, 25 (7%) HIV-negative and in 117 (32%) patients the HIV status was unknown. The numbers of women and men in the study population were 233 (63.3%) and 134 (36.4%), respectively. The gender of 1 (0.3%) patient was not recorded. Mycobacterial LAD (bacterial confirmation) was confirmed in 293 (79.6%) patients. Of these, 228 (77.8%) had positive MGIT cultures while in 65 (22%) cases with negative MGIT cultures, 64 (22%) were diagnosed on Ziehl Neelsen stain, and 1 (0.4%) on Papanicolaou autofluorescence. The average time to culture was 18.6 days (range 4 - 50).

A significant difference was found between the diagnostic yield in the HIV-positive and -negative populations (84% v. 52%, respectively; $p < 0.001$). The yield in the HIV-unknown population was 77%. Of the 228 positive cultures, 226 were *Mycobacterium tuberculosis*, 1 *M. avium-intracellulare*, and 1 *M. szulgai*. The non-tuberculous organisms were both in HIV-positive patients. A positive culture for *M. tuberculosis* was obtained in 29/84 (34.5%) patients in whom a sputum sample had been submitted. The HIV status of 2 of these patients was unknown, while 27 patients were HIV-positive.

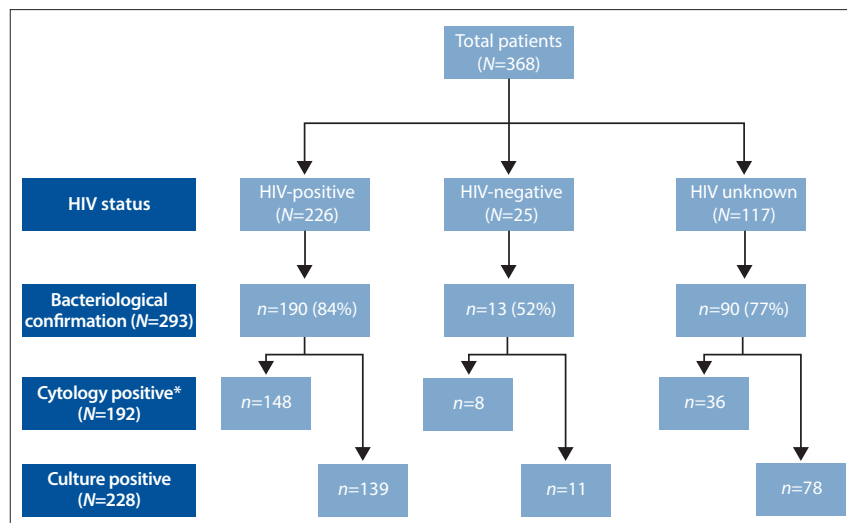


Fig. 1. Study flow diagram. *Cytology = cytomorphology and identification of organism on Ziehl-Neelsen stain or Papanicolaou autofluorescence.

The mean age of patients diagnosed with mycobacterial LAD was 31.9 years (range 14 - 71); with the mean age in the HIV-positive population being 32.6 years and in the HIV-negative population 28.5 years.

Multivariate logistic regression analysis showed positive HIV status to be significantly associated with a positive bacteriological yield ($p=0.005$), independent of other variables included in the model, namely gender, age and site. The odds ratio indicates that an HIV-positive patient has 4.86 times higher odds of having a positive bacteriological yield (95% confidence interval 1.65 - 9.75) than an HIV-negative patient.

Discussion

The relationship between HIV and TB is bidirectional.^[1,2] TB is a catalyst in the progression of HIV, and HIV infection is associated with an increased risk of developing TB. HIV alters the clinical presentation of TB such that TB progresses more rapidly and aggressively in HIV-infected individuals. Sputum smears, which are the cornerstone of diagnosis in resource-limited settings, are usually negative in HIV-associated TB, attested to by the 34.5% sputum culture yield in this study. This contributes to the diagnostic delay in treatment.^[1,2] Extrapulmonary TB can occur either alone or in association with pulmonary TB in 40 - 60% of cases.^[1,2] FNAB provides a means of easy access to diagnostic material in many of these pulmonary cases.

This study shows that the bacteriological yield of FNAB in suspected mycobacterial LAD in adults is comparable to, and higher than, that found in children in TB-endemic areas.

Compounding the problem of HIV and TB co-infection is immune reconstitution inflammatory syndrome (IRIS) where the initiation of antiretroviral treatment (ART) 'unmasks' the clinically silent disease.^[10] *M. tuberculosis* is estimated to account for about one-third of HIV-related IRIS events.^[10] To avoid IRIS complications, ART is ideally initiated once mycobacterial infection has been excluded, but diagnosing TB using current diagnostic modalities has limitations. In this study, the average time to culture was excellent at 18.6 days, but this delay in initiating treatment increases the contagious risk, particularly in resistant disease. In endemic areas, patients with granulomatous inflammation are often treated empirically with anti-TB drugs, contributing to the generation of multidrug-resistant TB. The heavy burden of TB, and HIV, in countries such as SA places a strain on scarce resources, which can be alleviated with a rapid diagnosis that reduces the number of follow-up visits.

Conclusion

Given the high diagnostic yield of mycobacterial LAD in HIV-infected adult patients on FNAB, and the pressure to expedite diagnosis, we feel this justifies

recommending new automated NAATs such as the Xpert MTB/RIF test to be used as first-line diagnostic modalities. The Xpert MTB/RIF test has been shown to be of value in the diagnosis of extrapulmonary TB, including tuberculous LAD.^[11,12] The advantages include minimal sample size, and ease and rapidity of diagnosis. The rapid turnaround time will, in turn, reduce the need for hospitalisation, reduce the contagious risk and decrease morbidity and mortality associated with the high TB burden in SA.

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References

- Reuter H, Wood R, Schaaf HS, Donald PR. Overview of Extrapulmonary Tuberculosis in Adults and Children. In: Schaaf HS, Zumla A, eds. Tuberculosis: A Comprehensive Clinical Reference. Atlanta: Saunders Elsevier, 2009;(34):377-380.
- Nacheha JB, Maartens G. Clinical Aspects of Tuberculosis in HIV-infected Adults. In: Schaaf HS, Zumla A, eds. Tuberculosis: A Comprehensive Clinical Reference. Atlanta: Saunders Elsevier, 2009;(51):524-525.
- Singh K, Muralidhar M, Kumar A, et al. Comparison of in house polymerase chain reaction with conventional techniques for the detection of *Mycobacterium tuberculosis* DNA in granulomatous lymphadenopathy. J Clin Pathol 2000;53(5):355-361. [http://dx.doi.org/10.1136/jcp.53.5.355]
- Mohapatra PR, Janmeja AK. Tuberculous lymphadenitis. J Assoc Physicians India 2009;57:585-590.
- Fontanilla JM, Barnes A, von Reyn F. Current diagnosis and management of peripheral tuberculous lymphadenitis. Clin Infect Dis 2011;53(6):555-562. [http://dx.doi.org/10.1093/cid/cir454]
- Monkongdee P, McCarthy D, Cain K, et al. Yield of acid-fast smear and mycobacterial culture for tuberculous diagnosis in people with human immunodeficiency virus. Am J Respir Crit Care Med 2009;180(9):903-908. [http://dx.doi.org/10.1164/rccm.200905-0692OC]
- Marais BJ, Wright CA, Schaaf HS, et al. Tuberculous lymphadenitis as a cause of persistent lymphadenopathy in children from a tuberculous-endemic area. Pediatr Infect Dis J 2006;25(2):142-146. [http://dx.doi.org/10.1097/01.inf.0000199259.04970.d1]
- Wright CA, Hoek KGP, Marais BJ, van Helden P, Warren R. Combining fine-needle aspiration biopsy and high-resolution melt analysis to reduce diagnostic delay in mycobacterial lymphadenitis. Diag Cytopathol 2010;38(7):482-488. [http://dx.doi.org/10.1002/dc.21223]
- Wright CA, Bamford C, Prince Y, et al. Mycobacterial transport medium for routine culture of fine needle aspiration biopsies. Arch Dis Child 2010 95(1):48-50. [http://dx.doi.org/10.1136/adc.2009.164038]
- Colebunders R, John L, Huyst V, Kambugu A, Scano E, Lynen L. Tuberculosis immune reconstitution inflammatory syndrome in countries with limited resources. Int J Tuberc Lung Dis 2006;10(9):946-953.
- Hilleman D, Rusch-Gerdes S, Boehme C, Richter E. Rapid molecular detection of extrapulmonary tuberculosis by the automated GeneXpert MTB/RIF system. J Clin Microbiol 2011;49(4):1202-1205. [http://dx.doi.org/10.1128/JCM.02268-10]
- Ligthelm LJ, Nicol MP, Hoek KG, et al. Xpert MTB/RIF for rapid diagnosis of tuberculous lymphadenitis from fine-needle aspiration biopsy specimens. J Clin Microbiol 2011;49(11):3967-3970. [http://dx.doi.org/10.1128/JCM.01310-11]

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