Role of fine-needle aspiration cytology in human immunodeficiency virus–associated lymphadenopathy: a cross-sectional study from northern India

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ABSTRACT

Objective: To evaluate the role of fine-needle aspiration cytology in the diagnosis of human immunodeficiency virus (HIV)–associated lymphadenopathy.

Design: Case series.

Setting: Tertiary care teaching hospital, India.

Patients: Fifty consecutive HIV-positive patients, who presented with lymphadenopathy at the out-patient department and antiretroviral therapy clinic.

Results: Tubercular lymphadenitis was the most common diagnosis, reported in 74% (n=37) of patients; 97.2% of them were acid-fast bacilli–positive. Reactive lymphadenitis and fungal lymphadenitis were present in 10 and 1 cases, respectively. The most common cytomorphological pattern of tubercular lymphadenitis was necrotising suppurative lymphadenitis, present in 43.2% (n=16) of patients. Of eight biopsies done in reactive cases, six turned out to be tubercular lymphadenitis. Fine-needle aspiration cytology had a sensitivity of 83.7% for diagnosing tubercular lymphadenitis.

Conclusion: Necrotising suppurative lymphadenitis should be recognised as an established pattern of tubercular lymphadenitis. Reactive patterns should be considered inconclusive rather than a negative result, and re-evaluated with lymph node biopsy. Fine-needle aspiration cytology is an excellent test for diagnosing tubercular lymphadenitis in HIV-associated lymphadenopathy.

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New knowledge added by this study

- Necrotising suppurative lymphadenitis should be recognised as an established pattern of tubercular lymphadenitis.
- In advanced human immunodeficiency virus (HIV) disease, reactive lymphadenitis should be considered inconclusive rather than a negative result, and re-evaluated with lymph node biopsy.

Implications for clinical practice or policy

- As lymphadenopathy is common in all stages of HIV disease, judicious use of fine-needle aspiration cytology can be helpful in diagnosing associated opportunistic infections and other pathological conditions.

Introduction

Human immunodeficiency virus (HIV) infection is an important worldwide public health problem. Developing nations, where resources are limited, are the worst affected nations. Until curative treatment for HIV infection becomes available, the crux of management is early diagnosis and treatment with highly active antiretroviral therapy.

As HIV is a lymphotropic virus, lymphoid tissues are the major anatomical site where the virus establishes itself during early infection. These lymphoid tissues act as reservoirs for the virus in the asymptomatic phase of infection. In the late stage, HIV disseminates from these sites to cause a full-blown acquired immunodeficiency syndrome (AIDS).[1] Thus, lymph node involvement is found in all stages of infection. The cause of lymph node enlargement is often difficult to establish by history, physical examination, radiographic studies, and routine laboratory tests. Surgical biopsy is the gold standard for diagnosis. However, it has several drawbacks: costly, time-consuming, and requiring

more elaborate precautions. Fine-needle aspiration cytology (FNAC) does not have any of these limitations, and is also comparatively less invasive. Furthermore, the cost of aspiration cytology is only 10% to 30% of that of surgical biopsy.[2]

We performed FNAC to establish the aetiological diagnosis in our study subjects with HIV infection. To detect false-negative results, biopsy was done in cases diagnosed as reactive lymphadenitis. The aims of the study were to assess the accuracy of FNAC and to correlate the findings with clinical and laboratory parameters like CD4 counts.

Methods

The study was conducted in the Departments of Medicine and Pathology, PGIMER and Dr RML Hospital, New Delhi, India, from January 2009 to December 2009. The study protocol and proforma were approved by the ethics committee of the institute. Informed written consent was obtained from all patients. Fine-needle aspiration cytology was performed in 50 consecutive HIV-positive patients presenting with lymphadenopathy at the antiretroviral clinic, or the out-patient or in-patient services. Detailed history was taken and examination of the patients was performed. Clinical stage (as per the World Health Organization [WHO] classification) and CD4 counts were recorded for all patients. Fine-needle aspiration cytology was performed by the clinician on the largest non-inguinal lymph node using standard precautions. The area was cleaned and draped. A 10-mL syringe and 23-gauge needles were used. If the sample was insufficient, another sample was taken from a different lymph node. Slides for Papanicolaou and Periodic-acid Schiff (PAS) stains were fixed with 95% ethanol immediately after preparing the smear; others were air dried. A total of six slides were prepared from each aspirate and were immediately processed by staining with Giemsa stain, Papanicolaou's stain, Ziehl-Neelsen (ZN) stain for acid-fast bacilli (AFB), PAS stain for fungi, and Gram stain. Cases that were AFB-positive on ZN staining were diagnosed as tubercular lymphadenitis; otherwise, they were retained as suspected cases. Based on the presence or absence of granulomas, caseation (necrosis) and neutrophilic infiltration, tubercular lymph nodes were classified into four cytomorphological categories: granulomatous lymphadenitis (GL), necrotising granulomatous lymphadenitis (NGL), necrotising lymphadenitis (NL), and necrotising suppurative lymphadenitis (NSL). Lymph node biopsies were performed in cases which showed a reactive pattern or suspected tubercular lymphadenitis on FNAC. Sensitivity, specificity, and positive and negative predictive values were calculated for FNAC as a diagnostic modality compared with biopsy. Statistical analysis for association between FNAC findings and various parameters was done using univariate and multivariate logistic regression analyses. Data analysis was performed by the Statistical Package for the Social Sciences (Windows version 19.0; SPSS Inc, Chicago [IL], US). A P value of less than 0.05 was regarded as statistically significant.

與人類免疫缺陷病毒相關的淋巴結腫中細針穿刺細胞學檢查的角色：印度北部的一個橫斷面研究

Naveen Kumar, BB Gupta, Brijesh Sharma, Manju Kaushal, BB Rewari, Deepak Sundriyal

目的：評估與人類免疫缺陷病毒（HIV）相關的淋巴結腫中細針穿刺細胞學（FNAC）檢查的角色。

設計：病例系列研究。

安排：印度一所提供第三層醫療服務的教學醫院。

患者：連續50名有淋巴結腫並到門診部和抗逆轉錄病毒療法診所的HIV患者。

結果：研究發現結核性淋巴結炎是最常見的診斷（37例，74%）；其中97.2%抗酸菌培養的結果呈陽性。反應性淋巴結炎有10例，另真菌性淋巴結炎有1例。結核性淋巴結炎最常見的細胞形態學模式為壞死性化膿性淋巴結炎（16例，43.2%）。活躍的8個活檢病例中，有6個為結核性淋巴結炎。FNAC檢查用作診斷結核性淋巴結炎的敏感性為83.7%。

結論：壞死性化膿性淋巴結炎應被界定為淋巴結結核的一個定性格局。其反應模式可視作為非決定性的，但不是一個陰性結果；而且須以淋巴結活檢作重新評估。FNAC對於與HIV相關的淋巴結病患者作診斷結核性淋巴結炎是一個很好的測試。

Results

A total of 50 patients (43 men and 7 women) were included in the study. The mean age of the patients was 32.4 years. Cervical region was the most common site of lymphadenopathy (n=39; 78%) followed by axillary and inguinal regions. The lymph nodes were matted and generalised in 62% (n=31) and 48% (n=24) of cases, respectively. Generalised lymphadenopathy was present in 54% (n=20) of cases with tubercular lymphadenitis and 40% (n=4) of cases with reactive lymphadenitis. Nature of aspirate was bloody in 21 (42%) cases, caseous in 24 (48%), and mixed (with blood and caseation) in the remaining patients. The CD4 count ranged from 12 cells/μL to 353 cells/μL, with a mean count of 131 cells/μL. Most of the patients were in WHO clinical stage 3 (n=31; 62%).

The most common cytological diagnosis was tubercular lymphadenitis (n=37; 74%) followed by reactive pattern (n=10; 20%). Only one FNAC was diagnosed as fungal lymphadenitis showing PAS-positive spores of *Histoplasma capsulatum* (Fig 1). In two cases, the cytologies were suggestive of

thyroid tissue and lipoma; these were treated as failed FNACs. Tubercular lymphadenitis was further categorised into four cytomorphological patterns, as shown in Table 1. All tubercular cases were AFB-positive, except one which was a AFB-negative GL on FNAC. Subsequently, this was shown to be AFB-positive tubercular lymphadenitis on biopsy. Of the 10 cases reported as reactive lymph nodes on FNAC, eight gave consent for biopsy. Biopsy showed AFB-positive fibrocaseous tubercular lymphadenopathy in six out of these eight cases; in the remaining two cases, biopsy findings matched with the FNAC findings.

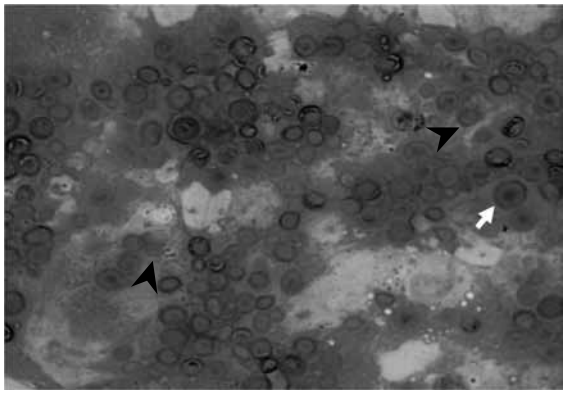

FIG 1. Histoplasma lymphadenitis: Periodic-acid Schiff–positive oval yeast cells with thick capsule (white arrow), both extracellular and intracellular (black arrow heads) in location (x 100)

All cases diagnosed as having mycobacterial disease on FNAC and those who underwent biopsy were included in the analysis. Hence 45 cases were analysed: 36 cases diagnosed as mycobacterial (tubercular) lymphadenitis on FNAC, one case of GL which was AFB-positive fibrocaseous tubercular lymph node on biopsy, and eight cases of reactive lymphadenopathy that underwent biopsy (Table 2). The sensitivity and negative predictive value of FNAC for diagnosing tubercular lymphadenitis were 83.7% and 22.2%, respectively. As AFB positivity was the requisite criterion for diagnosing tubercular lymphadenitis, it was expected that there would be no diagnosis of tuberculosis (TB) in any case which

TABLE 1. Cytomorphological patterns of tubercular lymphadenitis

Serial No.	Finding	No. of cases	No. of cases with biopsy	Results in biopsy	Mean CD4 count (cells/μL)
1	Tubercular lymphadenitis*				
	Granulomatous lymphadenitis	1	-	-	153
	Necrotising granulomatous lymphadenitis	7	-	-	112
	Necrotising lymphadenitis	12	-	-	119
	Necrotising suppurative lymphadenitis	16	-	-	92
2	Suspected tubercular lymphadenitis				
	Granulomatous lymphadenitis, AFB-negative	1	1	1-FCTL	-
3	Reactive lymphadenitis	10	8	6-FCTL, 2-Reactive	196
4	Fungal lymphadenitis	1	-	-	114
5	Non-representative†	2	-	-	-
	Total	**50**	**9**	**-**	**-**

Abbreviations: AFB = acid-fast bacilli; FCTL = fibrocaseous tubercular lymph node

* Cases were diagnosed as tubercular on fine-needle aspiration cytology only if they were AFB-positive on Ziehl-Neelsen staining

† There were no lymph node tissue; they turned out to be thyroid tissue and lipoma

TABLE 2. Analysis of 45 cases

	Mycobacterial infection (AFB +ve) by FNAC or biopsy*	No mycobacterial infection by both biopsy and FNAC
Mycobacterial infection (AFB +ve) by FNAC	36	0
No mycobacterial infection (AFB -ve) by FNAC	7† (6 Reactive and 1 GL turning FCTL on biopsy)	2 (Reactive on FNAC as well as biopsy)
Total	**43**	**2**

Abbreviations: AFB = acid-fast bacilli; FCTL = fibrocaseous tubercular lymph node; FNAC = fine-needle aspiration cytology; GL = granulomatous lymphadenitis

* All AFB-positive cases were treated with anti-tubercular drugs and they responded to therapy with regression of lesions and absence of symptoms

† Seven cases were missed by FNAC but later diagnosed as AFB-positive FCTL on biopsy

was AFB-negative on FNAC; thus, the specificity and positive predictive value were 100%.

We performed logistic regression analysis with tubercular lymphadenitis as the dependent variable and four parameters as covariates. On univariate analysis, CD4 count (P=0.016), nature of aspirate (P=0.013), and matted nodes on examination (P=0.028) were associated with tubercular aetiology on FNAC; lymph node distribution did not show any such association (P=0.401). However, in multivariate analysis, none of these factor was associated with tubercular aetiology on FNAC. Moreover, none of these factors was associated with the severe form (NL or NSL) of tubercular lymphadenitis either on univariate or multivariate analysis.

Discussion

Lymphadenopathy in HIV patients is very common; it can be a presenting feature in about 35% of patients with AIDS.[3] Causes can be varied, depending on the stage of the disease, and may include persistent generalised lymphadenopathy, lymphoid malignancies, and opportunistic infection. All these can be easily and efficiently diagnosed by aspiration study of these lymph nodes. These causes of lymphadenopathies are important causes of death in AIDS patients. In this study, we aimed to investigate the performance of FNAC for the accurate diagnosis of lymphadenopathies. We also compared our results with those from similar Indian and western studies (Table 3[1,4-16]).

Tuberculosis is the most frequent opportunistic infection in HIV patients.[17,18] Lymph nodes are the commonest site of extra-pulmonary TB in patients with AIDS.[19,20] Using FNAC as the diagnostic modality, we also found tubercular lymphadenitis to be the most common cause of lymphadenopathy, present in 74% of our patients. Similar conclusion was drawn in other Indian studies; however they reported a prevalence of 34.2% to 60% (Table 3). The high prevalence of tubercular lymphadenitis in our series may be related to the low immunity of the majority of patients; 41 out of 50 patients had CD4 counts of <200 cells/μL.

There are two specific pathological criteria for diagnosing tubercular lymphadenitis—caseation and granuloma formation. Both are less likely to be present in tubercular lymphadenitis associated with advanced HIV disease. This is because T-cell function, which is suppressed in advanced HIV disease, is required for granuloma formation. On the basis of these two findings, tubercular lymphadenitis is classified into three categories[21,22]: GL, NGL, and NL.

The GL pattern can occur due to several causes. However, in a country like India, where TB is very common, this pattern is considered to be due to TB until proven otherwise. We found this pattern in 5.4% (2 out of 37 cases with tubercular lymphadenitis) of TB cases, a finding similar to that in other previous studies where it ranged from 4.3%

TABLE 3. Comparison of our FNAC results with those from previous studies[1,4-16]

Serial No.	Study	Total No. of FNAC	Conclusive (%)	Reactive (%)	TB (%)	Fungus (%)	Malignancy (%)	Other (%)
1*	Martin-Bates et al[4]	27	100	40.7	22.2	7.4	22.2	7.4
2*	Shapiro and Pincus[5]	26	84.6	46	15	4	0	19
3*	Jayaram and Chew[6]	39	92.3	25.6	53.8	7.7	2.5	10.4
4*	Reid et al[7]	65	66.15	38.5	15.4	1.5	10.8	0
5*	Bottles et al[8]	121	100	50	17	0	33	0
6*	Llatjos et al[9]	57	96.4	59.6	36.8	0	0	0
7*	Lowe et al[10]	73	68.5	34	3	0	12	19
8†	Nayak et al[11]	32	100	31.2	46.8	0	6.2	15.6
9†	Shenoy et al[12]	48	100	36	48	0	12	4
10†	Saikia et al[13]	25	96	40	36	12	8	0
11†	Gill et al[14]	25	100	32	60	0	0	8
12†	Shobhana et al[15]	54	100	55.5	41	0	3.7	0
13†	Vanisri et al[16]	36	100	36.1	58.3	0	2.7	2.7
14†	Satyanarayana et al[1]	196	80.1	42.3	34.2	1	2.6	0
15†	Present study	50	96	20	74	2	0	0

Abbreviations: FNAC = fine-needle aspiration cytology; TB = tuberculosis

* Western data

† Indian data

TABLE 4. Cytomorphological patterns in tubercular lymphadenitis: comparison with previous studies[6,9,11,12,16,23]

Serial No.	Study	Total No. of FNAC	TB lymph node No. (%)	AFB +ve* (%)	GL* (%)	NGL* (%)	NL* (%)	NSL* (%)
1	Nayak et al[11]	32	15 (46.9)	53.3	13.3	26.6	40.0	20.0
2	Shenoy et al[12]	48	23 (47.9)	43.4	4.3	74.0	8.6	13.0
3	Vanisri et al[16]	36	21 (58.3)	47.6	28.5	47.6	19.0	0
4	Rajasekaran et al[23]	16	16 (100.0)	56.2	0	62.5	37.5	0
5	Jayaram and Chew[6]	39	21 (53.8)	95.2	4.7	0	28.5	66.6
6	Llatjos et al[9]	57	21 (36.8)	76.1	19.0	33.3	57.1	0
7	Present study	50	37 (74.0)	97.2	5.4	18.9	32.4	43.2

Abbreviations: AFB = acid-fast bacilli; FNAC = fine-needle aspiration cytology; GL = granulomatous lymphadenitis; NGL = necrotising granulomatous lymphadenitis; NL = necrotising lymphadenitis; NSL = necrotising suppurative lymphadenitis; TB = tuberculosis

* % Of total tubercular lymph nodes

to 28.5% (Table 4).[6,9,11,12,16,23] The NGL pattern, with both caseation and epithelioid granulomas, is the most typical pattern of tubercular lymphadenitis. It was present in 18.9% (7 out 37 cases of tubercular lymphadenitis) of our cases; other studies have reported it in the range of 26.6% to 74% (Table 4).[9,11,12,16,23] Necrotising lymphadenitis represents the most severe cytomorphological pattern of tubercular lymphadenitis. There is complete necrosis with only 'acellular' debris. It is not labelled as 'purulent' because there are no degenerated polymorphonuclear cells. Complete necrosis reflects impaired cell-mediated immunity in this group of patients. Cases of NGL can be wrongly labelled as NL if material is aspirated from that part of the node which contains only caseation. This was the second most common pattern reported in our study (32.4%; 12 out of 37 cases of tubercular lymphadenitis). In other studies, the reported prevalence rates range from 8.6% to 57.1% (Table 4).[6,9,11,12,16,23]

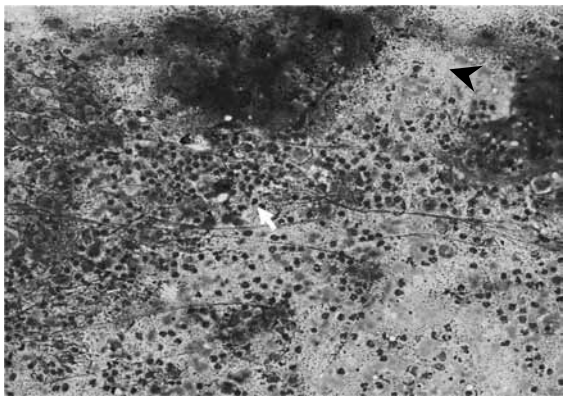

FIG 2. Liquefied necrotic material (black arrow head) with infiltration of polymorphs (white arrow), giving impression of suppurative lymphadenitis. No epithelioid cells or giant cells are seen (Giemsa staining, x 40)

The NSL pattern of tubercular lymphadenitis (Fig 2) was the most common cytomorphological picture, seen in 43.2% (16 out of 37 cases of tubercular lymphadenitis) of patients. This pattern was reported in 20% and 13% cases of tubercular lymphadenitis by Nayak et al[11] and Shenoy et al,[12] respectively (Table 4). Jayaram and Chew[6] reported this pattern in 67% of their TB cases in Kuala Lumpur, Malaysia. Although reported in these case series, unlike the other three patterns, the NSL pattern is not yet a well-recognised cytomorphological type of tubercular lymphadenitis. However, this pattern is important, especially in HIV patients. If ZN staining is not done, the thin caseation commonly present in these cases can be mistaken for pus, and the case wrongly labelled as pyogenic lymphadenitis. Similar observations have been made in some studies.[6,11,12,24]

Studies have shown that FNAC is more sensitive for the diagnosis of TB in HIV-positive patients than in seronegative patients.[25] In our series, AFB positivity rate in TB cases was 97.2% (n=36/37), which was higher than that in previous studies (43.4% to 95.2%).[6,9,11,12,16] This could be due to the fact that the disease was quite advanced in our group of tubercular lymphadenitis patients (mean CD4 count of 108 cells/μL). Moreover, as the cytomorphological pattern deteriorated and necrosis appeared, AFB positivity increased from 50% to 100%. This was in agreement with data from earlier studies.[6,9,11,12,16] Chances of detecting AFB were least in lymph nodes showing GL pattern: four out of five studies[6,9,11,12,16] did not report any AFB-positive case with this pattern of lymphadenopathy. Further, although TB is very common in HIV subjects, *Mycobacterium avium* complex (MAC) is not frequently seen in India. Its chance further decreases by adding MAC prophylaxis of azithromycin to the patient's treatment regimen.

A reactive lymphadenitis was observed in

only 20% of cases in our study. Most of the western studies reported it as the most common lymph node pathology, observed in 25.6% to 59.6% of cases (Table 3). One case of histoplasmosis was detected in our study (Fig 1). On Giemsa staining, the lymph node showed reactive lymphoid cells, histiocytes, areas of granuloma formation, along with sheets of *Histoplasma capsulatum* organism, located both extracellularly and intracellularly, which were positive on PAS staining. Hence, although the finding of GL without AFB in HIV-infected patients in India is taken as TB unless proven otherwise, causes like fungal infection (by PAS staining) should be excluded, especially if the CD4 count is low.

We performed a lymph node biopsy in 18% of our cases (Table 5). Among these, the findings were different from those in FNAC in 77.8% of the cases. False-negative rate in our study was 16.3% (7 out of 43 cases of TB; Table 2). The false-negative rate in other studies ranges from 2% to 9.2%.[1,4,7,8] Of these seven false-negative cases, six were diagnosed as reactive nodes on FNAC which later showed fibrocaseous nodes on biopsy. Possible reasons for discordance could be focal tubercular involvement of the nodes. On FNAC, the tubercular area could have been missed and, hence, wrongly labelled as reactive cases. Also, different nodes in the same area can enlarge due to different pathologies. Hence, a report of reactive pattern in advanced disease, like in our group of patients (mean CD4 in reactive group being 196 cells/μL), does not have much value, and should not be the end of further assessment. It should be considered an inconclusive result rather than a negative one. It emphasises the importance of performing a biopsy in this group of patients.

A falling CD4 count in our group of patients was associated with increasing risk of tubercular lymphadenitis. However, CD4 counts did not predict the severity of cytomorphological forms of tubercular lymphadenitis. Of note, 41 out of 50 patients had CD4 counts of <200 cells/μL. Hence, we did not have a group of patients with higher CD4 counts in whom less severe forms of tubercular lymphadenitis were more common. This association should be studied further by recruiting patients with a wide range of CD4 counts.

In univariate analysis, a matted lymph node on examination (P=0.028) and caseous material (P=0.013) on aspiration were found more often in TB cases versus reactive cases. Hence, apart from routine cytology stains, these observations guide us for ordering special staining like ZN staining. However, their association with cytomorphological pattern of TB was not significant on univariate analysis, as the whole spectrum of pattern can have caseation on aspiration (except GL) and matted nodes on examination, although cytomorphologically these are of increasing severity.

TABLE 5. Comparison of lymph node biopsy results with those from previous studies[1,4,7,8]

Serial No.	Authors	Total No. of FNAC	No. (%) of biopsies	FNAC = biopsy (%)†
1	Martin-Bates et al[4]	27	16 (59.3%)	87.5
2	Reid et al[7]	65	16 (24.6%)	50
3	Bottles et al[8]	121	5 (4.1%)	0
4	Satyanarayana et al[1]	196	13 (6.6%)	53.8
5	Present study*	50	9 (18.0%)	22.22

Abbreviation: FNAC = fine-needle aspiration cytology

* We performed a biopsy in 8 cases reported as reactive lymphadenitis and 1 case of AFB-negative granulomatous lymphadenitis on FNAC

† % Of cases in which biopsy result matches FNAC

Conclusion

Tuberculosis is the most common aetiology of HIV-associated lymphadenopathy in India. Acid-fast bacilli positivity is very high in HIV-associated tubercular lymphadenitis. We recommend routine AFB staining for all lymph nodes undergoing FNAC in HIV patients. Lymph nodes showing AFB-negative GL pattern on FNAC should be stained for fungus, especially if CD4 count is low. If a patient's CD4 count is low, a reactive FNAC pattern should be taken as an inconclusive result and is an indication for biopsy. All lymph nodes showing NSL pattern on FNAC should undergo ZN staining in HIV-positive patients. It should be recognised as a tubercular cytomorphological pattern, especially in patients with low immunity like those with AIDS. Fine-needle aspiration cytology of lymph nodes is a valuable test for diagnosing tubercular lymphadenitis in HIV-associated lymphadenopathy.

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