Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 8s, https://carcinogenesis.com/

Cytomorphological Patterns of Tuberculous Lymphadenitis: Experience from a Tertiary Centre

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ABSTRACT

Introduction: Lymphadenitis is the most common extra pulmonary manifestation of tuberculosis (TB). Tuberculous lymphadenitis is seen in nearly 35% of extra pulmonary TB. In human immunodeficiency virus (HIV) infection, extra pulmonary TB constitutes almost 53-62% of TB. Fine needle aspiration cytology (FNAC), demonstration of acid fast bacilli (AFB) by ZiehlNeelson (ZN) stain, auramine rhodamine stain, polymerase chain reaction, culture and histopathological examination of excised node are the various diagnostic modalities for tubercular lymphadenitis. FNAC is a routinely done, economical, rapid and sensitive cytological technique for diagnosis of tuberculous lymphadenitis. Diagnosis on cytomorphology along with acid fast staining will avoid unnecessary surgical intervention.

Objectives:

1. To determine frequency of cytomorphological patterns in tuberculous lymphadenitis.

2. To correlate Acid Fast Bacilli positivity and burden with cytomorphological patterns.

Material and Methods: Study was conducted at the department of Pathology, Shimoga Institute of Medical Sciences for 2 years. FNAC was done on patients presenting with lymph node enlargement and cytology smears stained with May Grunwald Giemsa, Papanicalaou & Hematoxylin & Eosin were studied. Cytologically, all cases of tuberculous lymphadenitis were categorized into 5 patterns A to E. Correlation between patterns with ZN positivity and burden was assessed.

Results: Tuberculous lymphadenitis predominantly affected individuals in the 2nd & 3rd decades of life (30%), with slight female preponderance (65.7%). Cervical region was the most common lymph node involved (61.5%). Most frequent cytomorphological pattern was epithelioid granuloma with necrosis-Pattern B (47.1%), followed by epithelioid granuloma without necrosis pattern A (18.6%). Overall AFB positivity was observed in 54.2% of cases. Statistical analysis showed significant association between cytomorphological patterns & ZN stain findings (p=0.032). Notably, cases with necrosis & neutrophilic infiltrate had a higher proportion of 3+ ZN positivity (p=0.048).

Conclusion: FNAC is a simple, reliable, & well-accepted procedure for diagnosing tuberculous lymphadenitis. Combining cytomorphology with ZN staining improves diagnostic accuracy. Integrating conventional & newer diagnostic techniques enhances sensitivity for early TB diagnosis in paucibacillary specimens.

Keywords: *FNAC, Tuberculous lymphadenitis, Epithelioid granuloma, Cytomorphological patterns, Ziehl Neelson stain*

How to Cite: Susmitha MS, Veena S , Shilpa N, Syeda Shifana Anjum, Vani Y, Khadeeja B, (2025) Cytomorphological Patterns of Tuberculous Lymphadenitis: Experience from a Tertiary Centre, *Journal of Carcinogenesis*, *Vol.24, No.8s*, 714-722

1. INTRODUCTION

Lymphadenitis is the most common extra pulmonary manifestation of TB. Tubercular lymphadenitis is seen in nearly 35% of extra pulmonary TB. It is the leading cause of death from a curable infectious disease. Though India is running stringent National control programs, there is resurgence in immunocompromised AIDS cases. In human immunodeficiency virus (HIV) infection, extra pulmonary TB constitutes almost 53-62% of TB.[1,2,3,4] Fine needle aspiration cytology (FNAC), demonstration of acid fast bacilli (AFB) by Ziehl Neelson (ZN) stain, auramine rhodamine stain, polymerase chain reaction, culture and histopathological examination of excised node are the various diagnostic modalities for tubercular lymphadenitis. FNAC is a routinely done, economical, rapid and sensitive cytological technique for diagnosis of tuberculous lymphadenitis. Diagnosis on cytomorphology along with acid fast staining will avoid unnecessary surgical intervention.

2. OBJECTIVES:

1. To determine frequency of cytomorphological patterns in tuberculous lymphadenitis.

2. To correlate AFB burden with cytomorphological patterns.

3. MATERIAL AND METHODS

A cross sectional study was conducted at Department of Pathology Shimoga institute of medical sciences Shimoga for 2 years, after obtaining ethical clearance from Institutional ethical committee. Clinically suspected for tuberculous lymphadenitis patients were referred to Pathology Department for FNAC. FNAC on palpable peripheral group of lymph nodes was done using 22-23 G needle and 5ml syringe. Cytology smears stained with May Grunwald Giemsa, Papanicaloau stains, Hematoxylin and Eosin stain, ZN stain were studied

Inclusion criteria:

1. FNAC reported as Tuberculous lymphadenitis.

2. FNAC with diagnosis of granulomatous lymphadenitis and AFB negativity were included only if available histopathology/ culture/ CBNAAT/ Mantoux test showed tuberculosis.

Cytologically, all cases of tuberculous lymphadenitis were categorized into 5 patterns A to E.

Pattern A – Epithelioid granuloma without necrosis.

Pattern B – Epithelioid granuloma with caseous necrosis.

Pattern C – Necrosis with neutrophilic infiltrate without epithelioid granuloma.

Pattern D - Numerous macrophages.

Pattern E - Caseous necrosis only.

ZN stained smears were studied and AFB screening was done under 100X(oil immersion) objective and graded as follows.

3+ Cases with numerous bacilli singly dispersed or arranged in bundles detected.

2+ Cases with singly scattered AFB

1+ Cases with occasional AFB.

Findings including various patterns, ZN positivity and grades were tabulated. Correlation between patterns with ZN positivity and burden was assessed. Significance of correlation between cytomorphological patterns with AFB positivity and burden was assessed by Fisher's Exact Test.

4. RESULTS

Of the total of 2998 FNAC done in the department, 70 cases were diagnosed as Tubercular lymphadenitis and included in the study.

Tubercular lymphadenitis was seen most frequently in third decade of life (32.8%). Age ranged from 1year to 91 years.(Figure 1). Slight female preponderance (65.7 %) was observed with Female:Male ratio of 1.9:1.(Figure 2). Cervical

lymph node was most commonly involved (85.71%), followed by axillary(12.8%), inguinal (1.42%) nodes.

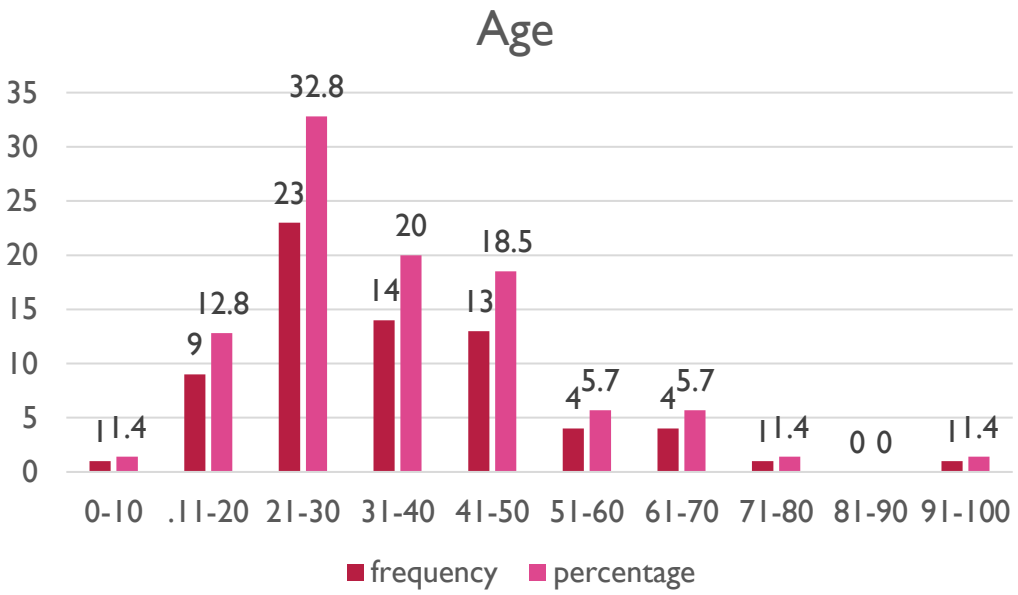

Figure 1. Age distribution of tuberculous lymphadenitis

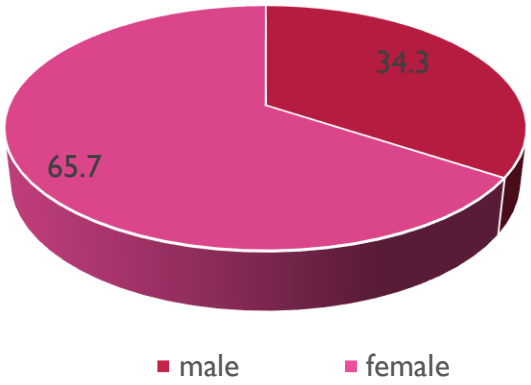

Figure 2. Gender Distribution of Tuberculous Lymphadenitis

Out of 5 cytomorphological patterns, epithelioid granuloma with necrosis was the most frequent pattern (pattern B) in 47.1%, followed by epithelioid granuloma without necrosis: pattern A (18.6%)(Table 1). Overall AFB positivity was seen in 51.42%. The association between the pattern and ZN findings was statistically significant, as indicated by Fisher's Exact Test ($p = 0.032$)(Table 2)

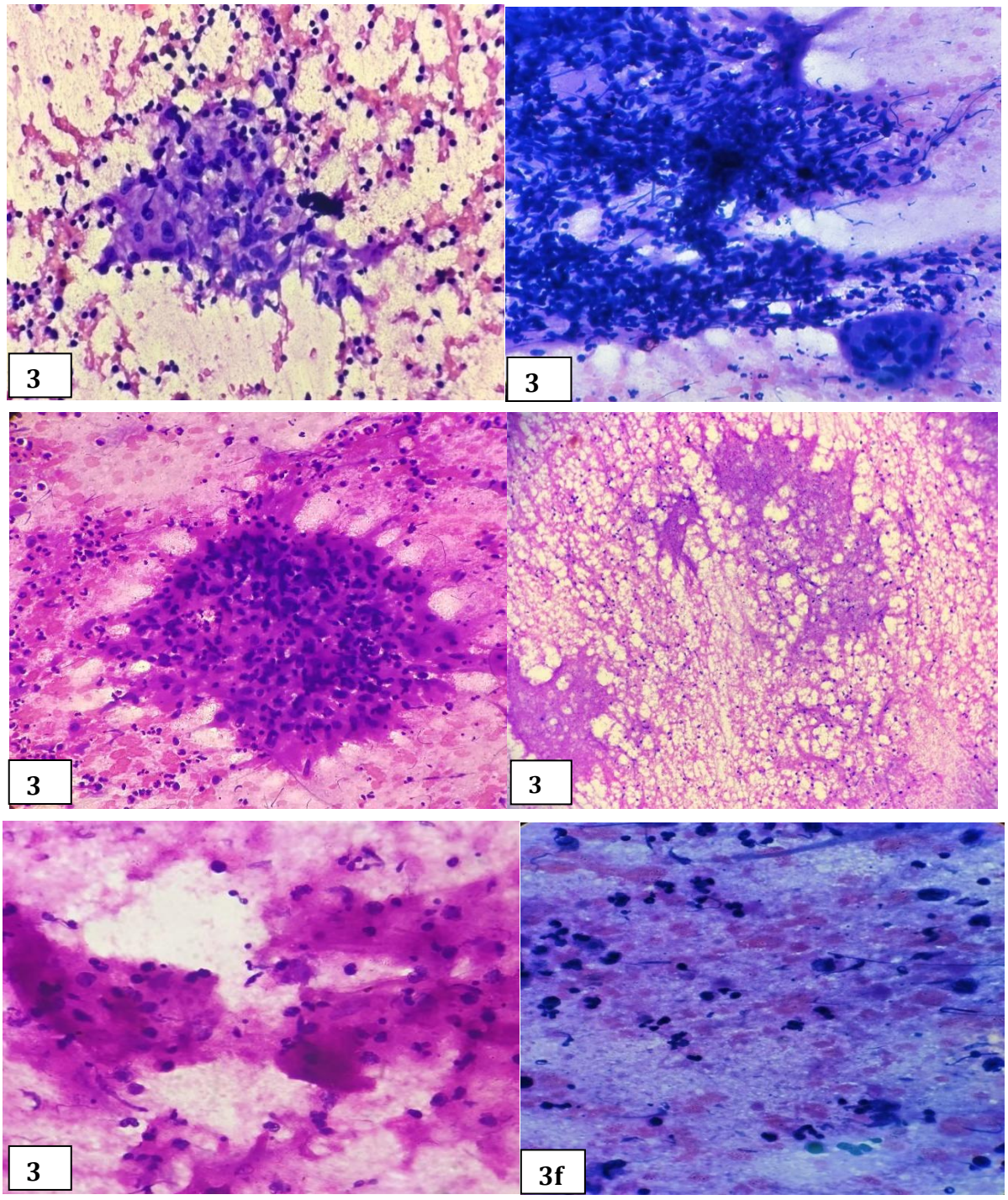

Fig. 3a,3b- Epithelioid cell cluster without necrosis (H&E, MGG stain;40x). 3c – Epithelioid cell cluster with necrosis & 3d- Only necrosis, (H&E, 40X) 3e,3f – Necrosis wth neutrophils (H & E stain, MGG stain 40x).

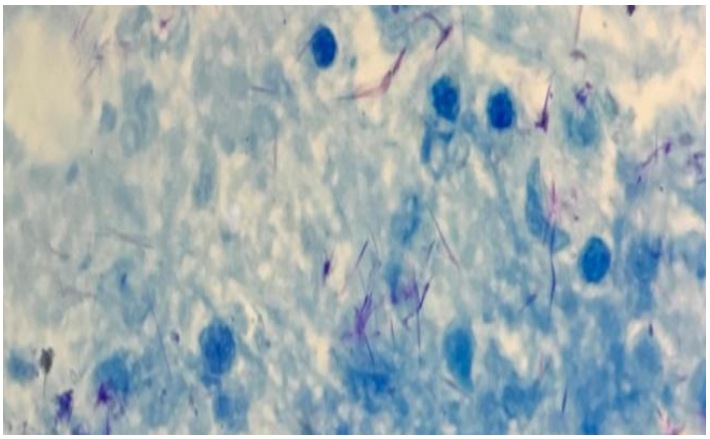

Figure 4 Micrograph showing Acid fast bacilli 3+ (Ziehl- Neelsen stain; 1000x)

Table 1. Frequency of Cytological Patterns and AFB

Cytological Features	Number	Percentage	AFB positivity
Pattern A- Epithelioid granuloma without caseous necrosis	13	18.6%	(3) 23.1%
Pattern B- Epithelioid granuloma with caseous necrosis	33	47.1%	(20) 60.6%
Pattern C- Necrosis with neutrophilic infiltrate without Epithelioid granuloma	10	14.28%	(8) 80%
Pattern D-Macrophages predominant	4	5.7%	(1) 25%
Pattern E- Caseous necrosis only	10	14.28%	(4) 40%

Table 2. Association between patterns and ZN findings in TB lymphadenitis

Pattern	ZN findings [number(%)]		Total	p value
	Positive	Negative		
A	3 (23.1)	10(76.9)	13	0.032
B	20(60.6)	13(39.4)	33	
C	8(80)	2(20)	10	

D	1(25)	3(75)	4
E	4(40)	6(60)	10
Total	36(51.4)	34(48.6)	70

The association between the pattern and ZN findings was statistically significant, as indicated by Fisher's Exact Test (p = 0.032)

Statistical Significance (p value = 0.032): This suggests a significant association between the presence of neutrophilic infiltrate with necrosis and ZN grading.(Table 2) Specifically, cases with neutrophilic infiltrate show a higher proportion of 3+ ZN positivity compared to cases without it. This indicates that neutrophilic infiltrate is associated with higher ZN grading. (Table 3)

Table 3. Association between patterns and ZN findings

AFB /ZN stain	**Pattern A (N= 13) 18.6%**	**Pattern B (N= 33) 47.1%**	**Pattern C (N= 10) 14.3%**	**Pattern D (N= 4) 5.7%**	**Pattern E (N= 10) 14.3%**	**Total (N=70) 100%**	p value
Negative	10 (29.4%)	13 (38.2%)	2 (5.9%)	3 (8.8%)	6 (17.6%)	34 (100%)	0.024
1+	3 (11.5%)	16 (61.5%)	3 (11.5%)	0 (0%)	4 (15.4%)	26 (100%)	
2+	0 (0%)	3 (60%)	2 (40%)	0 (0%)	0 (0%)	5 (100%)	
3+	0 (0%)	1 (20%)	3 (60%)	1 (20%)	0 (0%)	5 (100%)	

The association between the patterns and ZN grading was statistically significant, as indicated by Fisher's Exact Test (p = 0.024)

5. DISCUSSION

TB lymphadenitis constitutes 31.7% of lymphadenitis in India. Few western studies have reported very low incidence of tuberculosis lymphadenitis (1.6%).[4,5] Cytodiagnosis of tuberculosis depends on demonstration of epithelioid cells, Langhans giant cells and lymphocytes with or without accompanying necrosis. The characteristic necrotic background comprising of eosinophilic granular material containing nuclear debris was described as 'tubercular diathesis'[1].

In the present study tubercular lymphadenitis was seen most frequently in third decade of life (32.8%). Female preponderance (65.7 %) was observed with Female:Male ratio of 1.9:1. The possible reason being low socioeconomic status, reproductive age group, low immune status. Cervical lymph node was most commonly involved (85.71%), followed by axillary(12.8%), inguinal (1.42%) nodes. In study by Bhatta et al, most commonly involved lymphnode was cervical(82.53%) followed by inguinal lymphnode(9.52%).[6]

5 cytomorphological patterns were noted in our study. Epithelioid cells have been considered most important for the diagnosis of tuberculosis. To some extent it denotes immune status of the individual, the duration of infection and the nature of causative organism. In the present study they were present in 46 cases (65.71%). Pattern B- Granulomas with caseous necrosis was the most common pattern although ZN positivity was high in Pattern C- Necrosis with neutrophils and without granulomas. In Nidhi et al study, Pattern neutrophils with necrosis was the most common pattern, but AFB positivity percentage was highest in Pattern granulomas with necrosis.[7] In Shilpa et al study, the most frequent pattern was only necrosis and ZN positivity was also highest in same pattern.[8] The studies have revealed varied results. In study conducted by Mitra et al, AFB positivity was seen in 51.6% cases, and out of that maximum AFB positivity was present in cases with necrosis only without epithelioid granulomas (78.1%) and least (37.7%) in cases with epithelioid granuloma with caseous necrosis.[9] Chand P et al study revealed that among the four cytological patterns on FNAC, maximum cases demonstrated caseous necrotic material with degenerated inflammatory cells. In their study, overall AFB positivity was 44.54% and maximum AFB positivity was seen in cases having caseous necrosis only.[10] Swetha Rana et al study found that pattern with necrotizing lymphadenitis showed highest ZN positivity of 81.0%.[11] Masilamani S et, Hemalatha et al and Sowmya et al studies found that necrosis without epithelioid granuloma pattern had the highest AFB positivity of 77.1%, 73.5% and 34.5% respectively.[12, 13,14]

Pattern with polymorphs and necrosis showed highest positivity of 75% and 100% in Gupta R et al and Gain M et al studies.[15,16] In the present study, it was found that absence of granulomas, presence of necrosis and neutrophils were associated with high ZN positivity. Immune response in TB is of Type IV hypersensitivity. Macrophages activated to epithelioid cells will destroy bacilli and hence the load of AFB is less. Whereas, if macrophages are not activated to epithelioid cells, tissue destruction occurs, central necrosis liquefies and such cases have high bacillary load. Approximately 10,000- 100,000 mycobacterial organism/ml of sample should be present for smear AFB positivity [2,7]

FNAC sample can be used for AFB detection, as well as culture and molecular biologic studies of Mycobacterium tuberculosis. In studies involving multiple sites, AFB positivity by Z-N or fluorochrome stain ranged from 23% to 45% with an average of 35.5%. The positive rate of mycobacterium culture from FNA sample ranges from 20.8% to 83% with an average of 57.6%.[17]

Table 4.Comparison of patterns, AFB positivity in various studies

Patterns	Present study n= 70	Nidhi et al[7] n= 318	Shilpa G et al[8] n= 457	Vimal et al [5] n= 117
Epithelioid granuloma without necrosis				
% of cases	18.6%	14.3%	16.7%	34.1%
AFB positivity	23.1%	4%	4.4%%	32.5%
Epithelioid granuloma with necrosis				
% of cases	47.1%	16.4%	18.3%	33.3%
AFB positivity	60.6%	69.5%	39.4%	64.1%

Necrosis with neutrophils				
% of cases	14.3%	53%	27.2%	26.4%
AFB positivity	80%	42%	81.6%	67.7%
Numerous macrophages.				
% of cases	5.7%	-	-	-
AFB positivity	25%	-	-	-
Only necrosis				
% of cases	14.3%	39.2%	37.8%	5.9%
AFB positivity	40%	59%	83.8%	71.4%

Differential diagnoses for granulomas include tuberculosis, sarcoidosis, leprosy, mycosis, post vaccinations lymphadenitis, Cat scratch disease. In western countries, demonstration of epithelioid cells in lymph node aspirates may suggest sarcoidosis as first possible diagnosis, but in India, this finding would suggest tuberculosis unless proved otherwise, since the incidence is high. But with the rise of AIDS cases worldwide, TB has to be ruled out in all granulomatous lesions. However, diagnosis is confirmed by demonstration of AFB by ZN stain or ancillary tests like CBNAAT, Culture, histopathology. Mudduwa LKB et al studied 43 TB cases, using FNAC, ZN stain, Culture and PCR, concluded that the presence of epithelioid cells either with caseation or positive Ziehl Neelsen stain had very good agreement with the gold standard and high positive and negative predictive values.[2]

Khateeb Y et al study analyzed the different cytomorphological patterns of tuberculous lymphadenitis and compared the role of Ziehl–Neelsen (ZN) stain, Auramine–Rhodamine (AR) stain, Mycobacterium Growth Indicator Tube Culture (MGIT), and Cartridge-Based Nucleic Acid Amplification Testing (CBNAAT) in the detection of Mycobacterium tuberculosis.They concluded that smear positivity of ZN and AR stain is low and can confirm the diagnosis only in a few cases. CBNAAT and MGIT have a higher detection rate, which is greatly increased when both methods are used.[18] Atnafu A et al observed a strong concordance between Pattern having abundant caseous necrosis with few epithelioid macrophages with GeneXpert and MGIT culture. [19]

6. CONCLUSION

FNAC is a simple outpatient department (OPD) procedure which is simple quick and reliable method effectively used as a first line investigation for diagnosing tuberculous lymphadenitis at places with limited resources. Epithelioid granuloma with necrosis was the most frequent pattern. Though the Cytology findings favoured TB in many cases, overall AFB positivity was seen in 51.42%. Necrosis with neutrophilic infiltrate without Epithelioid granuloma had the highest AFB positivity and bacterial load. A combination of conventional techniques and newer diagnostic techniques can be applied for early and rapid diagnosis of TB in paucibacillary specimens to achieve maximum sensitivity.

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