

Clinical and Cytomorphological Patterns of Granulomatous Inflammation and its Correlation with Ziehl–Neelsen Staining

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Abstract

Introduction: Tuberculosis (TB) is one of the leading causes of mortality and morbidity in India, and extrapulmonary cases from the lymph nodes account for one-fifth of the overall disease burden. TB is known for its varied clinical presentations as well as different sites (organs) of involvement. Fine-needle aspiration cytology (FNAC) plays an important role in diagnosing a significant number of cases which present as granulomatous lesions. Here, we study the cytomorphological and clinical presentation of swellings showing granulomatous pattern of inflammation and correlate them with acid-fast bacilli (AFB) positivity. **Materials and Methods:** A retrospective study of 3-years duration was done from January 2018 to December 2020 in a tertiary care hospital. Slides of 356 cases showing epithelioid granulomas on cytology were taken out. The clinical data were collected from patient requisition forms. All the available clinical and cytological findings were recorded. The slides were re-examined and characterized into specific patterns of granulomatous inflammation on the basis of predominant background population of cells, necrosis, and hemorrhage. These were correlated with the presence of positive AFB staining on Ziehl–Neelsen (ZN) stain. Chi-square test was used for comparison between groups and $P < 0.05$ was taken to be statistically significant. **Results:** The mean age of presentation was 25 years (ranging from 5 months to 75 years) with a slight female preponderance (male-to-female ratio being 0.9:1). The cervical lymph nodes were the most common site. The sites of presentation were varied. The aspirates were gray–white to blood mixed on gross and cytological examination in 186 cases (52.25%). On microscopy, the suppurative pattern was seen in 202 cases (56.74%) and necrosis was seen in 182 cases (51.12%). The AFB positivity on ZN staining was seen in 96 (26.96%) cases in FNAC smears. There was a significant association of positive AFB staining with younger age group (<25 years), larger sized swellings (>2 cm), fixed and matted swellings, longer duration of symptoms (>2 weeks), and absence of pain and fever. The whitish/purulent aspirates on gross examination as well as suppurative and necrotic patterns on cytomorphology on microscopic examination showed a highly significant positive correlation with AFB staining. **Conclusion:** The gross and microscopic patterns of suppuration and necrosis on FNAC in combination with clinical signs and symptoms are highly suggestive of TB. ZN staining on cytology smears is a very simple and useful investigation, especially in suppurative and necrotic patterns of cytology, for clinching an early diagnosis, which goes a long way in the management of tuberculosis.

Keywords: Acid-fast bacilli, cheesy aspirate, clinicopathological, granuloma, necrosis, reactive, tuberculous

INTRODUCTION

Tuberculosis (TB) is a chronic granulomatous disease which is a significant cause of morbidity and mortality, especially in the developing countries of the world. It is among the top ten causes of death globally. Since 2011, TB is the leading cause of death due to a single infectious agent (surpassing HIV), with an estimated 1.2 million deaths in 2018 among HIV-negative people and another 0.25 million in HIV-positive people with TB. The case fatality ratio, though in high-income countries, is 5%, it still continues to be around 20% in high-burden

countries, out of which India accounts for the outstandingly maximum number of cases.^[1] Extrapulmonary TB accounts for 15%–20% of all cases of TB. Tuberculous lymphadenitis and cutaneous TB account for up to 35% and 1.5% of these cases, respectively.^[2–4] TB is known for the varied type of clinical presentations and diverse sites of involvement, so much so that, it has been reported to affect almost every organ

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Submitted: 12-Sep-2021 Revised: 19-Nov-2021

Accepted: 21-Nov-2021 Published: 30-Dec-2021

Access this article online

Quick Response Code:



Website:
www.actamedicainternational.com

DOI:
10.4103/amit.amit_145_21

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How to cite this article: Bohara S, Das R, Tripathi N, Verma L. Clinical and cytomorphological patterns of granulomatous inflammation and its correlation with Ziehl–Neelsen staining. *Acta Med Int* 2021;8:88–93.

except hair, nail, and teeth.^[5] The high cost of TB diagnostics is a major drawback in high burden countries, besides lack of comprehensive training, quality assurance, implementation planning, and support for maintenance.^[6]

Fine-needle aspiration cytology (FNAC) is the most popular, economical, and rapid cytological diagnostic technique, which is routinely done in cases of swelling or lymph nodal enlargement at accessible locations. It has a sensitivity and specificity ranging between 88% and 96%.^[3] FNAC along with ZN staining has been recommended as a standard diagnostic algorithm in suspected tuberculous patients.^[7] Studies have shown up to 2–5 times greater acid-fast bacilli (AFB) positivity on cytology smears compared to histopathology;^[8,9] hence, it seems reasonable to say that cytomorphological examination on FNAC along with Ziehl–Neelsen (ZN) staining (to detect AFB) is very useful in the evaluation of suspected tuberculous swellings. In a developing country with limited resources and high disease burden, the presence of epithelioid cell granulomas is still looked on as a reliable evidence of TB. With this background, we aimed to study the clinical and cytomorphological presentation of swellings showing granulomatous patterns of inflammation and to correlate them with AFB positivity on ZN stain.

MATERIALS AND METHODS

A retrospective study of 3-year duration was done from January 2018 to December 2020 in the department of pathology, tertiary care hospital. Ethical clearance was obtained from the Institutional Review Board (IEC/IRB No: HIMS/IRB/2021-22/3761. Dated: September 25, 2021).

A total of 356 cases of cytology reported as granulomatous lesions were included in the study. The clinical and demographic parameters of age, sex, site of swelling, presence or absence of pain or fever, and duration of symptoms were retrieved from the available requisition forms. In cases of indoor patients, the clinical data were taken from the patient case files in the medical record department of the institution. Examination details of the swelling such as size, number of swellings, mobility, presence or absence of discharging sinus, and the nature of discharge were also recorded from the same.

The FNAC findings of the type of aspirate and cytomorphological findings of epithelioid cell granulomas with accompanying necrosis, acute suppurative inflammation, hemorrhage, or type of accompanying cell population were noted after re-evaluation of all the stained slides. All the cases were characterized into specific patterns of granulomatous inflammation on the basis of predominant background population of suppuration, necrosis, reactive lymphoid cells, or hemorrhage. These details were correlated with the presence of positive AFB staining on ZN stain, which was routinely being performed along with routine Leishman, hematoxylin, and eosin and Papanicolaou staining, in evaluation and final diagnosis of granulomatous lesions. The presence of fungi as a causative etiology was excluded by taking only periodic acid–Schiff-negative cases

of granulomatous inflammation. All the cases reported as granulomatous inflammation in malignancies (lymphomas, sarcomas, and metastatic carcinomas), parasitic infestations, foreign body, and in those on antitubercular treatment were also excluded from the study.

All the above clinicopathological parameters were correlated for the presence of AFB positivity. The categorical variables of age, gender, site, size, number, mobility of the swelling, duration of the swelling, and its association with pain and fever were grouped into two categories in each and correlated with the presence of AFB. The gross examination findings and microscopic findings were also compared, forming groups. Chi-square test was used for comparison between categorical variables and $P < 0.05$ was considered statistically significant. The sample size was calculated taking α (Type I) error as 5%, the confidence interval of 95%, and the power of the study as 80%. Statistical analysis of data was performed using the SPSS version 20.0 (SPSS Inc., Chicago IL, USA) software.

RESULTS

A total of 356 cases of granulomatous lesions were included in the study. The majority of cases (75.8%) presented as neck swelling. The mean age of presentation was 25.04 years (ranging from 5 months to 75 years) with a slight female preponderance (male-to-female ratio being 0.9:1). The cervical lymph nodes were the most common site. Cervical lymph nodes were involved in 154 cases (43.25%) and soft-tissue abscess (cold abscess) in the neck was seen in 38 cases (10.67%). The supraclavicular, infraclavicular, submandibular, submental, and preauricular and postauricular group of lymph nodes constituted up to 78 (22%) cases [Table 1]. The sites of presentation were varied. The aspirates were gray–white to blood mixed on gross and cytological examination in 186 cases (52.25%). On microscopy, the suppurative pattern was seen in 202 cases (56.74%) and necrosis was seen in 182 cases (51.12%). The AFB positivity on ZN staining was seen in 96 (26.96%) cases in FNAC smears.

Difference between categorical variables revealed a statistically significant correlation with AFB positivity in age <25 years, size of the swelling >2 cm, fixed/matted swelling, painless swellings, and longer duration (>2 weeks) of symptoms. The cheesy white/purulent-looking aspirates on gross examination revealed statistically significant AFB positivity when compared with hemorrhagic/grayish aspirates [Table 2]. Sinus tract formation was observed in eight patients (2.25%) in our study, which complained of watery and purulent discharge in five and three cases, respectively.

Among six cases of granulomatous mastitis, none showed AFB positivity. Among all the cutaneous soft-tissue granulomatous lesions (total 61 cases), only 18 (29.50%) showed AFB.

On cytomorphology (predominant background population/material), smears revealed smears with necrotic background (Group I) in 117 (32.86%), suppurative background (Group II)

in 85 (23.87%), reactive background (Group III) in 144 (40.44%), and hemorrhagic background (Group IV) in

Table 1: Distribution of site of various swellings

Site of FNAC	Frequency (%)
Cervical lymph nodes	154 (43.25)
Submental lymph nodes	12 (3.37)
Axillary lymph nodes	54 (15.1)
Supraclavicular lymph nodes	28 (7.86)
Infraclavicular lymph nodes	8 (2.24)
Preauricular lymph nodes	4 (1.12)
Postauricular lymph nodes	8 (2.24)
Submandibular lymph nodes	18 (5.05)
Neck swelling	38 (10.67)
Inguinal swelling	12 (3.37)
Forearm swelling	2 (0.5)
Groin swelling	2 (0.5)
Thigh swelling	4 (1.12)
Occipital swelling	2 (0.5)
Hip swelling	2 (0.5)
Breast lump	6 (1.68)
Anterior chest wall swelling	2 (0.5)
Total	356 (100)

The cervical lymph nodes were the most common site of involvement (43.25%), followed by axillary (15.1%) and neck swelling (10.67%). FNAC: Fine-needle aspiration cytology

10 (2.80%) cases [Table 3]. On grouping these cases and comparing with its AFB positivity, the difference revealed statistically significant correlations ($P < 0.001$) between necrotic and nonnecrotic, suppurative and nonsuppurative, as well as nonreactive and reactive groups [Figure 1 and Table 4].

No significant correlations were found with respect to gender ($P = 0.662$), cervical site ($P = 0.247$), and number of swellings ($P = 0.693$) and presence or absence of multinucleated giant cells on cytomorphological examination ($P = 0.634$).

All the cases were graded according to Kumar *et al.*^[10] classification. In Grade 1+ pattern, AFB were scanty in amount and seen after thorough search. In Grade 2+ pattern, AFB were singly scattered, and in Grade 3+, they were numerous in collections and could be seen under $\times 100$. Majority of cases in our study (89 out of 96 cases [92.7%]) revealed Grade 1+ AFB positivity, while only five cases showed 2+ (5.2%) and two cases showed 3+ positivity (2.0%). All the cases with Grade 2+ and 3+ positivity showed necrotic background with degenerated cellular morphological patterns. All of these cases were painless with a duration of symptoms >2 weeks. Up to 5 out of 7 cases (5.2%) were also associated with fever and weight loss. None of these patients were known cases of HIV infection.

Table 2: Comparison between categorical variables of age, gender, site, size, number, mobility of the swelling, duration of the swelling, and its association with pain and fever revealed significant association with acid-fast bacilli positivity in age <25 years, size of the swelling >2 cm, fixed/matted swelling, painless swellings, and longer duration (>2 weeks) of symptoms. The cheesy white/purulent looking aspirates on gross examination were significantly associated with acid-fast bacilli positivity

Clinical parameters	AFB positive	AFB negative	Chi-square test
Age <25 years with AFB positivity	61	120	$P=0.003$ (HS)
Age >25 years with AFB positivity	35	140	
Male with AFB positivity	46	114	$P=0.493$ (NS)
Female with AFB positivity	50	146	
Cervical site with AFB positivity	58	176	$P=0.247$ (NS)
Noncervical site with AFB positivity	38	84	
Weight loss present	16	25	$P=0.06437$ (NS)
No weight loss	80	235	
Size of the swelling <2 cm	21	88	$P<0.0296$ (S)
Size of the swelling >2 cm	75	172	
Single swelling/lymph node	51	132	$P=0.693$ (NS)
Multiple swellings/lymph nodes	45	128	
Mobile swelling	7	121	$P<0.001$ (HS)
Fixed/matted swelling	89	139	
Swelling associated with pain	15	96	$P<0.001$ (HS)
Painless swelling	81	164	
Swelling associated with fever	19	83	$P=0.0246$ (S)
Swelling not associated with fever	77	177	
Duration of symptoms <2 weeks	29	113	$P=0.0234$ (S)
Duration of symptoms >2 weeks	67	147	
Cheesy/purulent aspirate	82	92	$P<0.001$ (HS)
Greyish or hemorrhagic aspirate	14	168	

AFB: Acid-fast bacilli, S: Significant, NS: Not significant, HS: Highly significant

DISCUSSION

FNAC is a simple, reliable, cheap, and noninvasive investigation and is widely used for rapid diagnosis of TB in developing countries like India. A quick cytomorphological diagnosis is essential in starting antituberculous treatment. Demonstration of AFB on ZN stain helps in confirmation and confidently rendering a diagnosis of tuberculous lymphadenitis/lesion. TB has been known to affect varied age groups of patients ranging from early to advanced age. In the present study, the age group of patients diagnosed with suspected tuberculous granulomatous lesions ranged from 5 months to 75 years, though the majority of patients were in their second to fourth decade. The mean age was 25.04 years. This was similar to previously reported data by various authors.^[11-16] Statistically significant association of AFB positivity was noted in younger age group.

Slight female preponderance in the present study (male-to-female ratio of 1:1.2) is similar to Mitra *et al.*^[11] and Fatima *et al.*^[17] and has been attributed to poor nutritional status and possibly lower standard of living in India,^[11] though there was no statistically significant difference with respect to gender when AFB positivity was compared. Contrary to these studies, male predominance was noted by Bezabih *et al.*,^[18] where male-to-female ratio of 1.3:1 was reported.

The cervical region was the most common site attributing a total of 270 cases (75.8%), similar to previously reported

Table 3: Among 356 cases, cytomorphology (predominant background population/material), smears revealed cases with necrotic (with or without suppuration) background in 56.74%, reactive background in 40.44%, and hemorrhagic background in 2.80% of cases

Patterns	n (%)	AFB positivity (%)
Necrotic background	117 (32.86)	47 (40.17)
Suppurative background	85 (23.87)	38 (44.70)
Reactive background	144 (40.44)	11 (7.63)
Hemorrhagic background	10 (2.80)	0
AFB: Acid-fast bacilli		

Table 4: Comparing the acid-fast bacilli positivity, difference between necrotic and nonnecrotic background, suppurative and nonsuppurative background as well as difference between reactive and nonreactive background were statistically highly significant ($P<0.01$). The acid-fast bacilli positivity was not seen in any of the cases having a hemorrhagic background

Groups	Features	Positive	Negative	Chi-square test
I	Necrotic background with AFB positivity	47	70	$P<0.001$ (HS)
	Nonnecrotic background with AFB positivity	49	190	
II	Suppurative background with AFB positivity	38	47	$P<0.001$ (HS)
	Nonsuppurative background with AFB positivity	58	213	
III	Reactive background with AFB positivity	11	133	$P<0.001$ (HS)
	Nonreactive background with AFB positivity	85	127	
IV	Hemorrhagic background with AFB positivity	0	10	-
	Nonhemorrhagic background with AFB positivity	96	250	

AFB: Acid-fast bacilli, HS: Highly significant

80% of cases by Mitra *et al.*^[11] and 74.2% of cases by Bezabih *et al.*^[18] There was a statistically significant correlation in comparison with other sites. This may be attributed to the common site of access of the bacteria through the tonsillar lymphoid tissue. Single lymph node was found in 183 (51.4%) patients in our study, whereas Nidhi *et al.*^[13] showed single lymph node enlargement in tuberculous lymphadenopathy in 63.3% cases, whereas Aggarwal *et al.*^[19] found single lymph nodal enlargement in 48.6% of patients. Single lymph node presentation in majority of studies may be due to increased awareness regarding extrapulmonary TB among the masses.

Aggarwal *et al.*^[19] and Singh *et al.*^[20] noted matting in 26.8% and 32.8% of cases, respectively, whereas our study showed fixity to surrounding skin and matting of lymph nodes in a total of 228 cases (64.04%). This finding showed highly

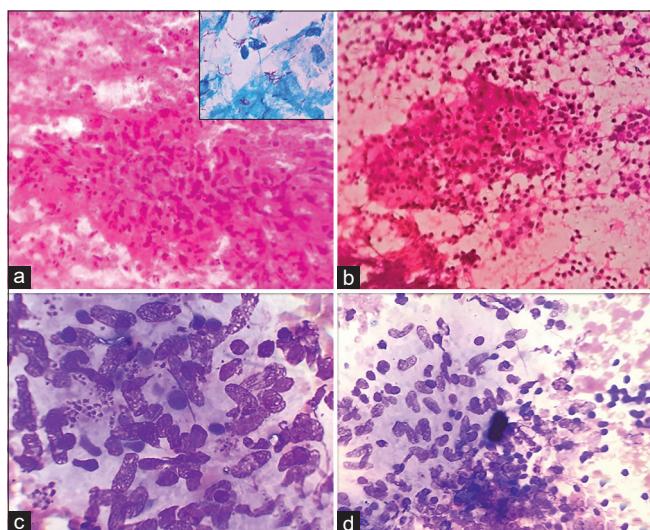


Figure 1: (a) Photomicrograph shows granulomatous inflammation with necrotic background (H and E; $\times 400$). Inset shows acid-fast bacilli in Ziehl-Neelsen stain; $\times 1000$. (b) Photomicrograph shows granulomatous inflammation with reactive background (H and E; $\times 400$). (c) Photomicrograph shows a collection of slipper-shaped epithelioid cells with platelet clumps in a hemorrhagic background (May Grunwald Giemsa stain; $\times 1000$). (d) Photomicrograph shows epithelioid

significant statistical correlation with AFB positivity. Jones and Campbell^[21] classified peripheral tuberculous lymph nodes into five stages. Stage 1 is characterized by enlarged, firm, mobile, and discrete nodes showing nonspecific reactive hyperplasia followed by Stage 2 of large rubbery nodes fixed to surrounding tissue due to periadenitis. Stage 3 shows central softening with abscess formation. In Stage 4, there is formation of collar-stud abscess and in the last stage (Stage 5), sinus tract is formed.

Clinical features vary with the stage of the disease. The lymph nodes are nontender unless associated with secondary bacterial infection, rapidly enlarging nodes, or coexisting HIV infection. In few cases, lymph node abscess may burst to form chronic nonhealing sinus and ulcer formation. These sinuses usually show thin, bluish, undermined edges and scanty watery discharge.^[22] In a study by Tadesse *et al.*,^[23] cases of suspected TB showed scarring of overlying skin and were 2.5 times more likely to yield positive results on the concentration method as compared to those patients without scar. In our study, scarring was noted in only 5 patients (1.40%), all of which were AFB positive on ZN staining. In the infectious process, caseous material perforates the deep fascia and escapes into the superficial fascia resulting in collar-stud abscess which may present with persistent discharging sinus and development of scar.

Difference between categorical variables in our study revealed a statistically significant correlation with AFB positivity in age <25 years, size of the swelling >2 cm, fixed/matted swelling, painless swellings, and longer duration (>2 weeks) of symptoms, concordant with the above. Sinus tract formation was observed in only 8 patients (2.25%) showing watery discharge in 5 of them (62.5%). Sinus tract formation was observed in eight patients (2.25%) in our study, which complained of watery and purulent discharge in five and three cases, respectively. Similar to our study, systemic symptoms such as fever and weight loss were seen in only a few cases of tuberculous lymphadenopathy in the previous studies.^[24]

The common causes of cutaneous TB are scrofuloderma, lupus vulgaris, and TB verrucose cutis. The most common site is the neck region,^[25] as was also seen in our study in 38 cases (62.29%). Besides the characteristic cytomorphological features of TB, necrosis is found more in cytology of cutaneous TB, possibly due to a larger sampling area within the swelling which could be accessed in FNAC and also because of ease of aspiration of soft necrotic material. In the present study, AFB positivity was seen in 18 cases (29.5%) of granulomatous cutaneous swellings. Kathuria *et al.*^[19] have reported more than five times AFB positivity on cytopathology compared to histopathology and an overall correlation of 92.9% on cytopathology compared to histopathology.

In developing countries, FNAC with identification of pink beaded rod-shaped AFB on ZN stain remains the cornerstone for providing accurate and timely diagnosis of TB since culture is not routinely done in health facilities mainly due to slow growth of bacteria and lack of equipment required for the

test. AFB positivity was seen in 96 cases (26.96%) among all showing granulomatous pathology in the present study, while it has been reported to be between 35.6% and 55.2% of cases in the previous studies^[26,27] to a wide range as 10%–70% in others.^[28] AFB positivity depends on many factors such as choosing the right smear with representative and appropriate sample (more necrotic particles show greater positivity), use of proper staining techniques, subjective variation of the examining pathologist such as time spent on each slide on examination, level of alertness, and experience. These may be the reasons for the wide variations in the AFB positivity seen in published literature.^[29]

In cases where the aspirates were purulent/whitish, AFB positivity was as high as 82 (47.13%), which accounted for 85.41% of all AFB-positive cases. Prasoon^[30] has also described association of purulent aspirates with bacillary load. It is emphasized that it is important to understand the chance of finding AFB which is high in necrotic lesions, as its detection varies according to the evolution of granulomatous inflammation in the pathophysiology of TB.^[31] It is a common tendency to diagnose purulent aspirates as suppurative lesions; however, due to the high rate of AFB positivity in such cases, it is highly recommended to thoroughly search for epithelioid granulomas and perform ZN staining. The absence of characteristic features due to mixed inflammatory bacterial superinfections may be the reason for misdiagnosis of TB as suppurative abscess.^[24]

Mycobacterium TB elicits a delayed Type IV hypersensitivity immunological response which is seen 2–4 weeks after the primary infection. The activated macrophages secrete tumor necrosis factor- α and Th1 cell express cytokines (γ -interferon), forming granulomatous lesions centered around the infected foci so as to effectively neutralize the bacilli without causing further tissue destruction. Caseous necrosis is seen in the central part and when the macrophage activation is weak, further tissue destruction occurs. The central necrosis starts liquefying and this contains abundant bacilli. Thus, granulomatous reactions with little or no necrosis would be associated with few bacilli, while reactions with hardly any or no granuloma would be expected to show more AFB.^[26] In our study, a predominant necrotic pattern was seen in 117 cases (32.86%) and showed AFB positivity in 47 cases (40.17%).

Hemalatha *et al.*^[31] and Das *et al.*^[26] have found maximum (35.6% and 67%, respectively) AFB smear positivity in neutrophil-rich aspirates, this was similar to the pattern observed in our study where among 85 (23.87%) cases of suppurative background pattern, 38 (44.70%) showed positive staining. In cases of uncontrolled bacterial multiplication in lymph nodes, they tend to become necrotic and abscess formation is initiated, this may be the reason for increased AFB detection in such cases.^[32]

The classification of AFB staining pattern was proposed by Kumar *et al.* The authors along with Gosavi *et al.* found that the majority of cases show Grade 1 + AFB positivity. However, all of these cases were HIV positive, unlike our study.^[33]

The present study emphasizes on the need to be aware of the clinicopathological pointers of TB. AFB screening is a time taking procedure and suffers from huge subjective variations; hence, the purulent and whitish aspirates on FNAC need extensive screening chiefly in a suppurative and necrotic background to increase the detection of true-positive cases of TB.

CONCLUSION

FNAC is a very safe, convenient, and effective first-line investigation for the diagnosis of tuberculous etiology. The present study highlights that purulent to whitish aspirates and microscopic patterns of suppuration and necrosis on FNAC in combination with clinical scenario of younger age group, large-sized swellings, fixed/matted swelling, and longer duration of symptoms are highly suggestive of TB. ZN staining on cytology smears in the above scenario is very helpful for clinching an early diagnosis in resource-limited settings.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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