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Original Research Article

CORRELATION OF VARIOUS CYTOMORPHOLOGICAL PATTERNS OF GRANULOMATOUS LYMPHADENITIS WITH ANCILLARY TECHNIQUES – ZN STAIN & CBNAAT

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Abstract

Background: Granulomatous lymphadenitis is a chronic inflammatory condition that can be associated with lymphoproliferative disorders, infectious and autoimmune diseases. **Aim:** The present study is aimed to evaluate the diagnostic yield and accuracy of fine needle aspiration cytology (FNAC) in association with ancillary techniques i.e., ZN stain and CBNAAT in patients with Granulomatous lymphadenitis. **Materials and Methods:** The present research was a retrospective study conducted for a period of 1 year from February 2022 to February 2023 at a tertiary care centre, Gandhi Medical college, Hyderabad, Telangana State.A total of 210 cases with lymphadenopathies diagnosed as granulomatous lymphadenitis with various cytomorphological patterns were included in the study. Clinical data such as history of fever, cough, cold, contact with Tuberculosis (TB) patient, past history of TB, site of aspiration, type of aspiration such as Blood mixed aspirate(BMA), Cheesy, pus, blood mixed with cheesy material or pus were obtained from medical records. Cytological evaluation was performed on material obtained from FNA. Smears prepared were fixed in Ethanol and stained with haematoxylin and eosin stain, Further, a ZN-Stain was performed on air dried smears and sample for CBNAAT collected simultaneously. **Result:** A total of 210 granulomatous lymphadenitis cases were evaluated and correlated with ZNstain for AFB and CBNAAT, positivity for Mycobacterium tuberculosis was 82.85% by CBNAAT and 65.71% by conventional ZN staining method. **Conclusion:** The study revealed the diagnostic yield and accuracy of FNAC is in correlation with ancillary techniques, further study also revealed that FNAC findings of granulomatous lymphadenitis cases were in more association with CBNAAT than conventional ZN Stain.

INTRODUCTION

Granulomatous lymphadenitis is a chronic inflammatory condition that can be associated with lymphoproliferative disoders, infectious and autoimmune diseases.[1] Among infections Tuberculosis is the most common etiological factor for Lymphadenopathy. Tuberculosis is one of the most persistent communicable disease according to the Global tuberculosis report-2014 of World health organization.[2,3] Tuberculosis is caused by Mycobacterium tuberculosis. A total of 1.6 million people died from Tuberculosis in 2021 (including 1,87,000 people with HIV) worldwide. TB is the 13th leading cause of death and second leading cause of death after Covid-19(Above HIV/AIDS).[3] In developing countries like India, where the prevalence and incidence of disease burden are highest, FNAC has proved to be valuable in the diagnosis of TB Lymphadenitis and provides an easy way for collecting material for bacteriological examination.[4,5] FNAC is one of the cost-effective and most reliable first line investigation performed for evaluating the cause of Lymphadenopathy.
Lymphadenopathy is a predominant condition which is characterized by a spectrum of granulomatous

inflammation in lymph nodes.[6]These granulomas are a consequence of human body's endeavor to wall off or offending impurity, be it a foreign body, chronic infection or necrotic fat.[7] The most widely recognized infections related to granulomatous lymphadenitis are Mycobacterium tuberculosis (M. tuberculosis) and non-tuberculous mycobacteria (NTM). Different etiologies require explicit treatments and identifying the causative microbe is important to understand and treat the patient. Furthermore, recognizing irresistible and non-irresistible reasons for granulomatous lymphadenitis is critical, as it fundamentally influences the treatment and response of patient.[8]

Cytological assessment of LN aspiration gives significant knowledge about the morphology of granulomatous lesions. Cell types frequently seen in granulomatous lymphadenitis incorporate epithelioid histiocytes, multinucleate giant cells(both langhans and/or foreign body type), lymphocytes, plasma cells. It is essential to take a note that the cytological appearance of granulomas can be variable in morphology.[9]However, FNAC has several limitations especially in the absence of Acid-Fast Bacilli (AFB). To overcome these demonstrative difficulties, auxiliary methods have been acquainted with supplement cytological assessment and improve the precision. Among normally utilized techniques, Ziehl-Neelsen (ZN) stain and Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) are the most commonly used ones.[10] The ZN stain is an exemplary microbiological method that helps to identify Acid Fast Bacilli (AFB) for cytological identification based on their interesting cell wall organization. A positive ZN stain is reminiscent of a mycobacterial contamination, showing the requirement for additional species-explicit testing and medication weakness profiling. Further, the CBNAAT, otherwise called the GeneXpert MTB/RIF assay, has risen as a quick and exceptional for identifying M.tuberculosis and surveying protection from the basic anti-TB drug, rifampicin. The test depends on the Amplification of mycobacterial DNA using polymerase chain reaction (PCR), empowering the identification of even low bacterial loads and giving outcomes within a couple of hours.[11]

Various studies have observed the concordance between cytological elements seen in granulomatous lymphadenitis and the outcomes got from ZN stain and CBNAAT. While ZN staining stays a vital modality, its responsiveness might be restricted, particularly in paucibacillary situations where a couple of mycobacteria are available. In such conditions, CBNAAT has shown to be especially favorable, offering further developed responsiveness and explicitness in recognizing M. tuberculosis, even with low bacterial load.[12]Fine needle aspiration cytology and Z-N staining is an initial diagnostic tool in resource poor countries. ZN staining is a rapid diagnostic technique but has very low sensitivity due to its Paucicellular nature.[13]The present study is aimed to evaluate the diagnostic yield and accuracy of fine needle aspiration cytology (FNAC) in association with ancillary techniques i.e., ZN stain and CBNAAT in patients with Granulomatous lymphadenitis.

MATERIALS AND METHODS

Study Design

The present research is a retrospective study conducted for a period of 1 year from February 2022 to February 2023, at a tertiary care centre, Gandhi medical college/Gandhi Hospital, Hyderabad, Telangana state.

Inclusion Criteria

Patients of all ages, both males & females, HIV Positive cases are included in the study. Lymphadenopathy cases on FNAC diagnosed as granulomatous lymphadenitis with or without caseous necrosis and suppurative granulomatous lymphadenitis are included. Ziehl-Neelsen (ZN) stain for acid fast bacilli (AFB) positive or negative cases were included in the study.

Exclusion Criteria

Lymphadenopathy cases with malignant / metastatic deposits. Any other swellings apart from lymph nodes are excluded.

Study Population

A total of 210 cases with lymphadenopathies diagnosed as granulomatous lymphadenitis with various cytomorphological patterns were included in the study.

Clinical History

Clinical data such as history of fever, cough, cold, contact with Tuberculosis (TB) patient, past history of TB, site of aspiration, type of aspiration such as Blood mixed aspirate (BMA), Cheesy, pus, blood mixed with cheesy material or pus was retrieved from medical records.

Cytological Evaluation

FNA was performed by using 22G needle. Two alcohol fixed smears prepared, stained with routine haematoxylin & eosin for cytological evaluation, another two air-dried smears prepared, stained by ZN for AFB, Simultaneously sample for CBNAAT was collected in a sterile container with 1-2 ml of normal saline.

CBNAAT

Cartridge based nucleic acid amplification test (CB-NAAT, GeneXpert,) is an automated cartridge-based molecular approach that identifies both Mycobacterium Tuberculosis and rifampicin resistance/sensitive within two hours. In a pre-sterile container, the aspirate was combined with buffer in 1:2 ratio and incubated at room temperature for 30 minutes. Using a Pasteur pipette, 2 ml of the above prepared sample mixture was transferred to an Xpert cartridge, which was then loaded onto GeneXpert machine (Trueprep, Autov2). CBNAAT results were

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reported as detected or not detected and Rifampicin resistant or sensitive.

Statistical Analysis

The statistical analysis was performed using IBM-SPSS 28.0 software. Descriptive statistics were employed for obtaining the frequencies and percentages. Chi-square test was done to understand the significance in the qualitative variables. P-value less than 0.05 was considered as significant.

RESULTS

Out of 210 cases Mantoux test was done in 113 (53.8%) patients. Among these 113 cases 70 (61.9%) were found to be positive for Mantoux test (Mycobacterium tuberculosis infection). In the present study age group ranging between 2-77 years and the mean age being 30.68 years. Age group between 21-30 was found to be predominant with 31.9% and children below 10 years and elderly were found to be least affected. Females are predominantly affected, male to female ratio is 1:1.9. The demographic details are depicted in [Table 1].

Most common site of lymphadenopathy is cervical region followed by axillary, Supraclavicular and Inguinal region and the results about the sites of lymph nodes involved are mentioned in the [Table2].

Clinical presentation

More than half of the patients had fever as a predominant clinical symptom, other symptoms like cough, cold, loss of appetite and weight loss were also observed in the patients under study. Further, past history of tuberculosis and history of contact with tuberculosis patients were also observed, wherein few of them have completed the anti-tuberculosis treatment and few were defaulters. In some cases other infectious diseases like HIV and Pott's spine was also observed. The detailed information about the clinical presentation of the patients under study is mentioned in the [Table3].

The nature of material aspirated from the patients are described below in [Table4]. The most common type of material aspirated on FNA was blood mixed aspirate accounting for 108(51.43%) cases followed by Cheesy aspirate 64 (30.48%). Least common type of aspirate was pus.

Further, four different types of cytomorphological patterns were observed in patients with granulomatous lymphadenitis. Most of the cases were found to be caseating granulomatous lymphadenitis seen in 100 (47.62%) cases, followed by granulomatous lymphadenitis without caseous necrosis in 77 (36.65%) cases and least number was observed with suppurative granulomatous lymphadenitis in 15 (7.14%) cases. The distribution of the cytomorphological patterns is depicted in [Table5].

Comparison of cytomorphological features with ZN staining and CBNAAT

The positivity for Mycobacterium tuberculosis was 82.85% by CBNAAT and 65.71% by conventional ZN staining method. About 17.14% cases which were negative for AFB on ZN stain were positive for tuberculosis on CBNAAT. Among the 174 cases that were positive for CBNAAT, 124 were found to be sensitive and 50 were resistant for rifampicin. However, these susceptibility pattern varied based on the cytomorphological feature from type-A to D. The results of the comparison between ZN staining and CBNAAT testing are depicted in [Table 6].

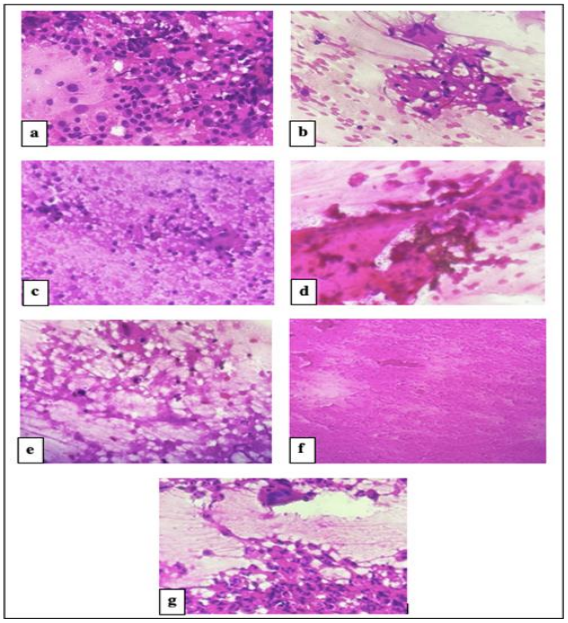

Figure 1: Cytosmear shows - a) Polymorphous population of lymphocytes in various stages of maturation admixed along with histiocytes and transforming histiocytes; b) Well-formed granulomas composed of epithelioid cell clusters; c) Lymphocytes in various stages of maturation along with multinucleate giant cell in a caseous necrotic background; d) Cluster of epithelioid cells in a caseous necrotic background; e) Individually scattered epithelioid cells in a necrotic background; f) Extensive areas of necrosis; g) sheets of neutrophils admixed along with histiocytes, cyst macrophages, cluster and individually scattered epithelioid cells in a fibrinopurulent background

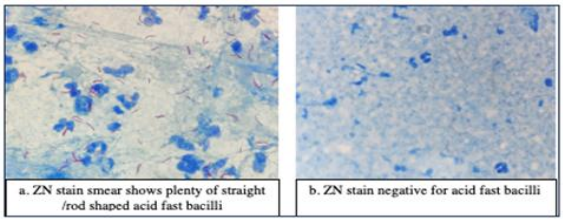

Figure 2: cytosmear shows a) ZN stain demonstrating AFB; b) ZN stain negative for AFB

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Table 1: Demographic details of the subjects under study

S. no	Age group (years)	Male	Female	Total
1	1-10	1	7	8 (3.8%)
2	11-20	14	33	47 (22.38%)
3	21-30	19	48	67 (31.90%)
4	31-40	18	25	43 (20.48%)
5	41-50	10	10	20 (9.52%)
6	51-60	7	13	20 (9.52%)
7	61-70	2	2	4 (1.9%)
8	71-80	1	0	1 (0.47%)
	Total	72 (34.28%)	138 (65.72%)	210

Table 2: Sites of lymph nodes involved in Granulomatous lymphadenitis

S. no	Site of lymphadenopathy	Frequency	Percentage
1	Cervical	153	72.86%
2	Supraclavicular	19	09.05%
3	Axillary	31	14.76%
4	Inguinal	7	03.33%

Table3: Clinical presentation of the patients under study

S.no	Clinical presentation	Number of cases (n=210)
1	Fever	119
2	Cough	72
3	Cold	8
4	Loss of weight	88
5	Loss of appetite	72
6	H/o contact with TB	60
7	Past h/o TB	39
8	Complete course of ATT treatment	27
9	Defaulter of ATT treatment	10
10	HIV positive	4
11	Past h/o pulmonary TB	7
12	Past h/o Pott's spine	4
13	Past h/o knee joint TB	2

Table4: Nature/type of material aspirated on FNAC

S. no	Type	Frequency	Percentage
1	Cheesy	64	30.48%
2	Blood mixed with cheesy material	13	6.19%
3	Pus	11	5.24%
4	Pus mixed with blood	14	6.66%
5	Blood mixed aspirate (BMA)	108	51.43%

Table 5: Cytomorphological patterns of granulomatous lymphadenitis diagnosed on FNAC

S.no	Group / Type	Number	Percentage
1	Type - A: Caseating granulomatous lymphadenitis	100	47.62%
2	Type-B:Granulomatous lymphadenitis without caseous necrosis	77	36.66%
3	Type - C: Caseous necrosis without granulomas	18	8.57%
4	Type - D: Suppurative granulomatous lymphadenitis	15	7.14%

Table6: Comparison between ZN staining and CBNAAT testing

S.no	Group / Type	Number of cases	ZN Stain positivity	CBNAAT positivity	Rifampicin sensitive	Rifampicin resistance
1	Type-A:Caseating granulomatous lymphadenitis	100 (47.62%)	80 (80%)	90 (90%)	60	30
2	Type-B: Granulomatous lymphadenitis without caseous necrosis	77 (36.66%)	40 (51.94%)	55 (71.42%)	44	11
3	Type-C:Caseous necrosis without granulomas	18 (8.57%)	10 (55.55%)	16 (88.88%)	10	6
4	Type-D : Suppurative granulomatous lymphadenitis	15 (7.14%)	8 (53.33%)	13 (86.66%)	10	3
Total		210	138 (65.71%)	174 (82.85%)	124	50

P-value for CBNAAT and FNAC is 0.03 and it is significant, chi square value is 15.4. For ZN staining and FNAC P-value is not significant with value being 0.15 and chi square value 0.3. So CBNAAT is better than ZN stain.

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Table 7: Comparison of age group predominantly affected, age range, mean age and gender wise distribution of cases with other studies

S.no	Study	Age group m/c(% of cases affected)	Age Range	Mean Age	M:F Ratio
1	Present Study	11-30 years (54.28%)	2 yrs-77yrs	30.68 yrs	1:1.9
2	Arora S et al	20-40 years (71.2%)	5yrs-71yrs	-	1:1.27
3	Shaila K Mitra	20-40 years (74.4%)	6 Mon-69yrs	25.08	1:1.5
4	Divya Shetty et al	20-40 years (59%)	6yrs-73yrs	26.3 yrs	1:2.7
5	Siddegowda et al	16-30 years (35%)	8Mon-75yrs	-	1:1
6	Manju MD et al		-	28.42 yrs	2.15:1

Table 8: Comparison of site of lymph nodes involved with other studies

S.no	Study	Cervical	Axillary	supraclavicular	Inguinal	Other swellings
1	Present study	72.86%	14.76%	9.05%	3.33%	-
2	Arora S et al	80.3%	7.6%	10.6%	1.5%	-
3	Divya Shetty et al	89%	10%	-	1%	-
4	Siddegowda et al	84%	9%	-	3%	4%

Table 9: Comparison of type of aspirate with other studies

S.no	Study	Blood mixed/ Hemorrhagic	Cheesy /caseous	Blood mixed cheesy	Pus / Purulent	Blood mixed with pus
1	Present study	51.43%	30.48%	6.19%	5.24%	6.66%
2	Arora S et al	33.3%	22.7%	-	44%	-
3	Divya Shetty et al	44%	7%	-	49%	-
4	Suresh Masilamani et al	84.4%	3.3%	-	12.3%	-
5	Shaila K Mitra et al	33.5%	25.5%	-	41%	-

Table 10: Comparison of cytomorphological patterns with other studies

S.no	Study	Caseous necrosis with granulomatous lymphadenitis	Granulomatouslymphadenitis without Caseous necrosis	Caseous necrosis Without granulomas	Suppurative granulomatous lymphadenitis	Non caseating non granulomatous
1	Present study	47.62%	36.66%	8.5%	7.14%	Nil
2	Arora S et al	40.9%	31.8%	Nil	27.3%	Nil
3	Divya Shetty et al	59%	22%	14%	Nil	5%
4	Siddegowda et al	13%	22%	12%	21%	Nil
5	Shaila K Mitra et al	40.0%	29.5%	30.5%	Nil	Nil

Table 11: Comparison of ZN Stain and CBNAAT positive results with other studies

S.no	Study	ZN Stain (%)	CBNAAT(%)
1	Present study	65.75%	82.85%
2	Arora S et al	54.5%	57.6%
3	Divya Shetty et al	34%	60%
4	Suwarna B Patil et al	46.35%	55.20%
5	Manju MD et al	23.08%	79.49%
6	Suresh Masilamani et al	55.7%	Not done
7	Shaila K Mitra et al	51.6%	Not done

DISCUSSION

Granulomatous lymphadenitis is a typical condition Characterized by the presence of granulomas in lymph nodes. Cytomorphological assessment of lymph node aspiration has been the conventional first-line demonstrative methodology for granulomatous lymphadenitis.[10]Though there are conventional methods for the diagnosis, they are laborious, time consuming, with less accuracy. Further, sample collection from the patient might also plays a vital role in proper diagnosis. The present study was an attempt to evaluate the diagnostic yield and accuracy of fine needle aspiration cytology (FNAC) in association with ancillary techniques i.e., ZN stain and CBNAAT in patients with Granulomatous lymphadenitis.

Total sample positivity in the present study is 82.85% by CBNAAT and 65.71% by Z-N staining, which is in concordance with Manju et al., with CBNAAT positivity of 79.49%.[14] A sample positivity of 17.6% was found in a study carried out by Sanjay et al which is very less than that observed in the present study.[15]The reason could be that the present study has included only the suspected cases of tuberculosis. Further the present study showed more accuracy when compared to other studies,[16-18] which might be because of multidisciplinary approach. In this study, CBNAAT was found to be more accurate when compared to ZN staining.

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The age range in the present study was 2-77 years, with an average of 30.68 years and the male and female ratio was 1:1.9, which was similar to the studies conducted elsewhere [Table7].[19-23]

The sites of lymph node involvement like cervical, axillary, supraclavicular, inguinal were in correlation with the study conducted by Arora et al.,[19] [Table 8] whereas in other studies the supraclavicular regions were omitted for aspiration.[20,21] The nature of aspirate obtained on FNA in the present study such as, Blood mixed aspirate, cheesy or Pus aspirate was concordant with other studies[Table 9].[19,20,22,24]

The most common cytomorphological pattern observed in this study is Caseous necrosis with granulomatous lymphadenitis (47.62%), followed by granulomatous lymphadenitis without Caseous necrosis (36.66%), Caseous necrosis without granulomas (8.5%) and Suppurative granulomatous lymphadenitis (7.14%), where showing similar distribution pattern as in other studies[Table 10].[19,20,22,24]Further, the study also revealed the varied distribution of rifampicin resistance among different cytomorphological features. In addition to these, when the ZN staining and CBNAAT were compared, CBNAAT found to be accurate for diagnosis and the present study found to show the accuracy in both ZN staining and CBNAAT when compared to other studies[Table 11],[19,20,22,24] which might be due to comprehensive collection of sample for ancillary tests (ZN & CBNAAT) at the same time of FNA . However, FNAC stands to be an efficient and cost-effective diagnostic tool which can be adapted and employed easily, where the CBNAAT is not available.

CONCLUSION

Tuberculous lymphadenitis is a common presentation of Extra Pulmonary Tuberculosis in developing countries like India. The one-time collection of sample with FNAC for routine cytology, ZN staining for AFB & CBNAAT for detection of Mycobacterium tuberculosis provides a best comprehensive approach to achieve the best patient care & rapid detection of tuberculous lymphadenitis. Molecular testing for MTB by CBNAAT- Xpert MTB /RIF is the sensitive test and a rapid technique in clinically suspected cases of Tuberculous lymphadenitis, even in the absence of caseating granulomas in cytology & AFB in ZN stain. This can diagnose more number of samples in lesser time which will be beneficial for quick and accurate diagnosis. Additionally, it gives critical data on rifampicin resistance, helping with the early identification of multidrug-safe tuberculosis and directing proper treatment systems. Further we can avoid unnecessary surgical excision of lymph nodes.

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