EFFICACY OF FINE-NEEDLE ASPIRATION TECHNIQUE, ZIEHL-NEELSEN STAINS AND CULTURE (BACTEC) IN DIAGNOSIS OF TUBERCULOUS LYMPHADENITIS IN A TERTIARY CARE HOSPITAL, GAYA, INDIA

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ABSTRACT

BACKGROUND

Tuberculous lymphadenitis is the commonest form of extrapulmonary tuberculosis and tissue diagnosis is the mainstay in the diagnosis of extrapulmonary tuberculosis. This study was conducted to compare cytology, ZN staining, fine-needle aspiration technique and culture findings of clinically suspected tuberculous lymphadenitis cases.

MATERIALS AND METHODS

This is a descriptive study. Total 300 patients of lymphadenopathy referred to the Department of Microbiology, Anugrah Narayan Magadh Medical College, Gaya, Bihar and Associated Hospital of Bihar between May 2014 and May 2017, were included. Using solid culture (BACTEC) as the gold standard, we assessed the sensitivity, specificity, positive predictive value (PPV) and negative predictive value of the FNAC for detecting MTB and ZN staining for acid-fast bacilli (AFB) respectively.

RESULTS

A total of 300 fine-needle aspirated specimens from lymph nodes were included in the study. Out of 300 cases, 140 aspirates were reported as cytomorphology suggestive of tuberculous lymphadenitis. The age ranged from 1 to 70 years, with the mean age of 35.5 years. Female preponderance was noted accounting for 57.14% (80/140) of cases. Maximum number of patients were from age group of 10–29 years comprising 42.15% of the group (59/140). Out of 300 cases, 68(48.57%) had lymphadenitis other than tuberculosis, and 16 (11.43%) had malignant lymphadenopathy, including 04 (02.84%) cases of primary malignancy (i.e., lymphoma) and 13 (09.28%) of secondary metastasis to lymph nodes. Though cytology suggestive of tuberculous lymphadenitis was found in 140 (46.67%) cases out of total 300 cases,Ziehl-Neelsen stain demonstrated acid-fast bacilli (AFB) in 60 (20.00%) cases and BACTEC isolated mycobacteria in 80 (26.67%) cases. When culture (BACTEC) is taken as the gold standard, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the FNAC in the diagnosis of TB lymphadenitis results was 96.55%, 96.38%, 95.89% and 96.96% as per this study and if ZN stain is taken as the standard for diagnosis, the sensitivity, specificity, PPV and NPV were 95.23%, 99.17%, 96.77% and 98.76% respectively.

CONCLUSION

FNAC is an assay which has high sensitivities when optimally selected is efficient and one of the most accurate frontline method for the diagnosis of Tuberculous Lymphadenitis. It is effectively supplemented by Ziehl-Neelsen Staining which is the most simple, quicker, reliable and relatively cheap diagnostic tool . Culture methods (BACTEC) can be reserved to obtain more accurate diagnosis.

KEYWORDS

Tuberculosis, Lymphadenopathy, Fine-Needle Aspiration Cytology, Ziehl-Neelsen Stain, BACTEC.

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BACKGROUND

Tuberculosis is a very ancient disease and evidence of its existence was seen in Egyptian mummies and statuaries in the form of Pott`s disease of spine.[1] Tuberculosis waxed and waned in Europe during 18th and 19th centuries. During industrial revolution it claimed millions of lives in Europe and so was called as `The White Plague'.[2] Robert Koch wrote that tuberculosis killed one third of Europeans of middle age. According to WHO, tuberculosis still kills three million people every year in underdeveloped countries.[2] Tuberculosis still ravages in India even 100 years after the discovery of tubercle bacillus, with an annual incidence of 100/100,000 and a prevalence four times the incidence.[3]

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Tuberculosis continues to be a major health problem in developing countries. Tuberculosis is one of the oldest diseases known to affect humans and lymphadenopathy is one of the most common presentation of extrapulmonary tuberculosis.[4,5] Tuberculous lymphadenitis can be presumptively diagnosed morphologically on fine-needle aspiration cytology of lymph node. Fine-needle aspiration cytology is now widely utilised as a first line diagnostic procedure in the diagnosis of palpable masses, including peripheral lymphadenopathy. Its value in the diagnosis of mycobacterial lymphadenitis in adults is well documented.

In extrapulmonary tuberculosis, the most common presentation is cervical lymphadenopathy, especially among the Asian populations.[6,7] Lymph node enlargement could be due to tuberculosis, other inflammatory disease or fungal infection, or some underlying malignancy.[8] In general, tuberculous (TB) lymphadenitis is diagnosed using conventional methods such as histopathology on basis of caseous necrosis and granuloma formation. The chances of acid-fast bacilli (AFB) identification in tissue section are less because xylene and formalin affect the sensitivity of Ziehl–Neelsen (ZN) method to detect Mycobacterium tuberculosis in histopathology sections.[9]

FNAC is accurate, inexpensive, quick & simple method that is used for diagnosis of lymphadenopathy. FNAC is the first line investigation for lymphadenopathy. ZN stain is the used simple, quicker, reliable, minimally invasive, and relatively cheap diagnostic modality with minimal risk of complications in the demonstration of acid-fast bacteria belonging to the genus Mycobacterium tuberculosis. Mycobacteria are slow growing and hence culture is not done routinely in all laboratories, but BACTEC system is a recent development for rapid detection of mycobacteria based on radiometric monitoring. It has added a new dimension to diagnostic microbiology.[10]

Aims and Objectives

The aims and objective of this prospective study were (1) to describe presentation pattern of TB lymphadenitis and (2) to compare results of Culture (BACTEC), FNAC and ZN stain in the diagnosis of TB lymphadenitis.

MATERIALS AND METHODS

Study Design: The study is design is descriptive study. Total 300 patients of lymphadenopathy referred to the Department of Microbiology, Anugrah Narayan Magadh Medical College, Gaya, Bihar and Associated Hospital of Bihar between May 2014 and May 2017, included in the study. The study protocol was approved by the hospital ethics committee.

Patients Inclusion Criteria- Patients attending the Department of Microbiology, Anugrah Narayan Magadh Medical College, Gaya, Bihar and Associated Hospital of Bihar between May 2014 and May 2017, having fever, night sweats, cough for more than 3 weeks with sputum, loss of appetite, loss of weight, chest pain, haemoptysis and/ or radiological evidence of tuberculosis were included.

Sample Collection- A total of 300 Fine needle aspirates were obtained from patients who presented with signs and symptoms of Tuberculosis after consent was given. Early morning sputum samples were collected in clean, sterile, leak proof, wide mouth containers.

Sample Processing- (i) FNA material from lymph nodes was applied to prior labelled slides directly and direct smears prepared for ZN staining.

(ii) Leftover material in the hub of the needle was rinsed in one millilitre (mL) normal saline and transferred into Bijou bottles. To this, one mL of 3.5% NaOCl was added and the mixture incubated at room temperature for 15 minutes while shaking at regular intervals. One half of 1 mL of xylene was added and the mixture let to stand for 15 minutes undisturbed to float the bacilli. The creamy layer was carefully scooped using a wire loop and smears prepared on ii prior labelled, albumin-coated microscope slides. The slides were air-dried, heat fixed and stained by the ZN method. Remaining material was inoculated in BACTEC (Middlebrook 7H12B) vial taking care to have at least 0.5 mL volume of test material in the vial.

Direct ZN- FNA material obtained were smeared on slides and directly stained with strong Carbol fuchsine and steamed for five minutes. The slides were then washed with tap water and decolourised with 1% acid alcohol until clear. Subsequent rinsing in tap water followed. Counter staining was done in Methylene blue for three minutes and finally rinsed in tap water and left to air dry. Examination was done using high power (X100) and reported using WHO format.

Total 300 clinically diagnosed patients of lymphadenopathy referred to the Department of Microbiology, Anugrah Narayan Magadh Medical College, Gaya, Bihar and Associated Hospital of Bihar between May 2014 and May 2017, were included in this study. The variables included in the study were age, sex, and site of lesion. Relevant history and examination of nodes were recorded.

Cytology smears and ZN stain smears were examined in Department of Microbiology, Anugrah Narayan Magadh Medical College, Gaya, Bihar. BACTEC vial containing aspirated material was sent to Department of Microbiology, PMCH, Patna without delay where first medium was supplemented with mixture of antimicrobials called PANTA, which contains polymyxin –B, amphotericin-B, nalidixic acid, trimethoprim and azlocillin to reduce the contamination. Then initial reading Growth Index (GI) was taken and then incubated at 37^0C. Readings of GI were taken on day 1, 3, 5, 7,9,12 for first 15 days and then weekly up to 45 days.

Multiple smears were prepared with part of aspirated material; two to three smears were stained with haematoxylin and eosin (H & E) stain and ZN staining was performed on separate slide. All data were grouped and analysed. Smears stained with H&E stain (Figure 1. Granuloma formation, H&E stain, 40×) were examined under microscope for the presence of granuloma, necrosis Langhans giant cells, plasma cells, lymphocytes,

macrophages, and neutrophils. Smears stained with ZN stain (Figure 2. Acid-fast bacilli in ZN stain, ZN stain, 100×) were examined under oil immersion objective for AFB.

Presence of sheets of epithelioid cells with lymphocytes and plasma cells with or without multinucleated giant cells were diagnosed as granulomatous lymphadenitis, and eosinophilic granular material containing inflammatory cells and necrotic cell debris was defined as caseous necrosis.[11] The TB abscess was described as degenerate caseous necrosis and/or liquefied necrotic material with marked degenerating and viable inflammatory cell infiltration without epithelioid granuloma.[12]

Data was recorded and statistically analysed using Specificity, sensitivity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Kappa value and using solid culture (BACTEC) as the gold standard, we assessed the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the FNAC for detecting MTB and ZN staining for acid-fast bacilli (AFB) respectively.

Statistical Analysis- Statistical analysis was performed with commercially available software (SPSS 16.0; SPSS, Inc.).

RESULTS

A total of 300 fine-needle aspirated specimens from lymph nodes were included in the study. Out of 300 cases, 140 aspirates were reported as cytomorphology suggestive of tuberculous lymphadenitis. The age ranged from 1 to 70 years, with the mean age of 35.5 years. Female preponderance was noted accounting for 57.14% (80/140) of cases (Table 1). 42.15% (59/140) of the cases with suggestive cytomorphology of tubercular lymphadenitis were in the range of 10-29 years of age. Depending upon cytomorphological features, granuloma 105 (75%), necrosis 85 (60.71%), lymphoid background 40 (28.57%), acute inflammation 35 (25%), giant cell 25 (17.86%) were found in tuberculous lymphadenitis (Table 3). In present study, the most common site of involved lymph nodes was of the cervical region in 70% (98/140) of the cases (Table 2).

TB lymphadenitis was found in 68 (48.57%) cases, inflammatory lymphadenitis other than tuberculosis in 68 (48.57 %), and malignant lymphadenopathy in remaining 16 (11.43%) cases, consisting 04 (02.84%) cases of primary malignancy (i.e., lymphoma) and 13 (09.28%) of metastasis to lymph node (Table 4). Of 140 cases of lymphadenitis, ZN stain was found to be positive for AFB in 60 (42.85%) cases (Table 5).

The cytology suggestive of tuberculous lymphadenitis was found in 140 (46.67%) cases out of total 300 cases. Ziehl-Neelsen stain demonstrated acid-fast bacilli (AFB) in 60 (20.00 %) cases and BACTEC isolated mycobacteria in 60 (26.67%) cases (Table-6).

When setting the results Culture (BACTEC) as the gold standard, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the FNAC in the diagnosis of TB lymphadenitis results were 96.55 %, 96.38%, 95.89% and 96.96% respectively. In addition, when compared with of ZN stain in the diagnosis of TB lymphadenitis results, the sensitivity, specificity, PPV and NPV of were 95.23%, 99.17%, 96.77% and 98.76% respectively (Table 7).

Age (Years)	Male	Female	Total	Percentage
0–09	5	9	14	10.00
10-19	12	18	30	21.43
20-29	13	16	29	20.72
30-39	9	8	17	12.14
40-49	8	6	14	10.00
50-59	6	8	14	10.00
60-69	5	9	14	10.00
More than 70	2	6	8	05.71
Total	**60**	**80**	**140**	**100**
Percentage	**42.86**	**57.14**	**100**	**100**

Table 1. Age- and Sex-wise Distribution of Cases of Lymphadenopathy

Site	Number of Percentage
Cervical lymph node	98 (70%)
Axillary lymph node	12 (8.57%)
Supraclavicular lymph node	8 (5.71%)
Submandibular	2 (1.42%)
Submental	9 (6.42%)
Chest	4 (2.85%)
Inguinal lymph node	2 (1.42%)
Other	5 (3.57%)
Total	**140 (100)**

Table 2. Site Distribution of Tubercular Lymph Node

Cytomorphological Patterns	Number	Percentage
Granuloma	105	75%
Necrosis	85	60.71%
Lymphoid background	40	28.57%
Acute inflammation	35	25%
Giant cell	25	17.86%
No documented	10	7.14%

Table 3. Cytomorphological Patterns

Type of Lesion	Cytomorphological Diagnosis	Number of Cases	Percentage
Non-neoplastic (inflammatory lymphadenitis)	Tuberculous lymphadenitis	68	48.57
	Chronic nonspecific lymphadenitis	39	27.86
Acute lymphadenitis		16	11.43
Neoplastic (malignant lymphadenopathy)	Metastasis to lymph node	13	9.28
	Hodgkin's lymphoma	2	1.42
Non-Hodgkin's lymphoma		2	1.42
Total		**140**	**100**

Table 4. Various Cytomorphological Picture in Cases of Lymphadenopathy

Cytomorphological Picture	AFB Positive Cases	AFB Negative Cases	Total	Percentage
Epithelioid granuloma with caseous necrosis	28	27	55	39.28
Necrosis only without inflammatory cells	07	02	09	6.42
Necrosis with polymorphs	22	14	36	58.80
Neither necrosis nor granuloma	03	37	40	28.60
Total	**60**	**80**	**140**	**100**
Percentage	42.86	57.14	100	100

Table 5. AFB Positivity in Various Cytomorphological Subpatterns in Cases of Lymphadenitis

Cases	Number of Positive Cases	Percentage of Positive Cases
Cytology suggestive of tuberculous lymphadenitis	140	46.66
ZN staining demonstrating AFB	60	20.00
Culture isolating mycobacteria	80	26.66
Total cases	300	

Table 6. Correlation Between Cytology, ZN Staining and Culture Findings

	Cytology Percentage	ZN Smears Percentage
Sensitivity	96.55 %	95.23 %
Specificity	96.38%	99.17%
Positive Predictive Value (PPV)	95.89%	96.77%
Negative Predictive Value (NPV)	96.96%	98.76%

Table 7. Comparison of Cytology and Smear in Diagnosing Tuberculous Lymphadenitis when Culture was taken as Gold Standard

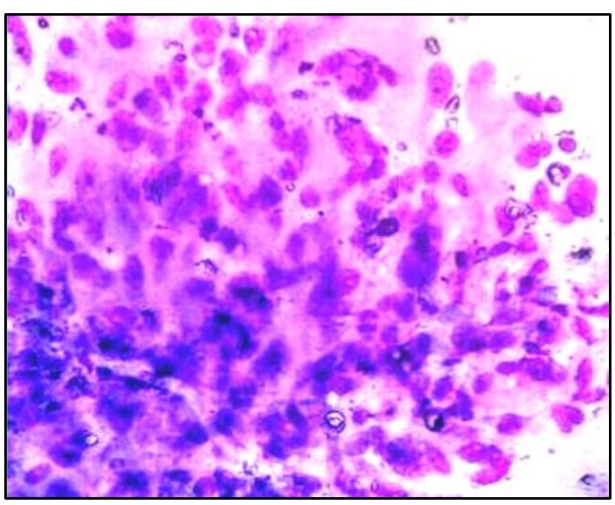

Figure 1. Granuloma Formation, H&E Stain, 40×

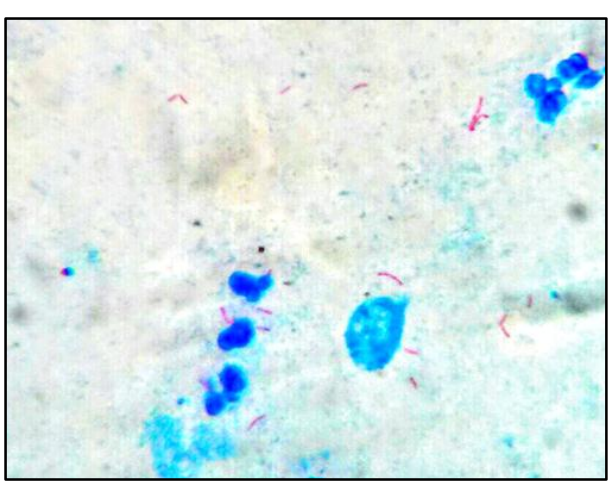

Figure 2. Acid-fast Bacilli in ZN Stain, ZN Stain, 100×

DISCUSSION

The diagnosis of TB is still based on poorly validated symptom-based algorithms, often not resulting in a definitive diagnosis. The clinical presentation of tuberculosis is usually fever, night sweat, weight loss, anorexia. But sometimes, delay in diagnosis has often been attributed to atypical clinical presentation and radiological presentation. The diagnosis of tuberculosis by cytomorphology is not new. It is a necrotising granulomatous infection, which cytologically demonstrates the microscopic equivalent of caseous necrosis, granular-appearing necrotic background, together with mature lymphocytes, epithelioid histiocytes and multinucleated Langhans type histiocytes. Several conditions, including mycosis, bacterial and viral adenitis can present the same cytology as does mycobacterium tubercular adenitis does. Laboratory tests may be essential to establish the cause of such adenopathy correctly, because treatment and prognosis may differ. Demonstration of Mycobacterium tuberculosis in fine needle aspirates becomes necessary for an early and accurate treatment. Fine needle aspiration cytology provides a rapid and definitive tissue diagnosis in the superficial lymphadenopathy. This study demonstrates that it also permits confirmation of the presence of mycobacteria with AFB stain in microscopy. The diagnosis of tuberculosis is confirmed by the demonstration of tubercular bacilli. Mycobacteria are slender rod shaped, non-motile, non-sporing, aerobic bacterium measuring 2 to 10 um in length. India has the highest TB burden as shown in the 2011 World Health Organization (WHO) statistics.[3] The diagnosis of extrapulmonary tuberculosis still remains to be more of a clinical decision. Not many clinically sensitive tests are available in India to assist the treating physician. For accurate diagnosis of M. tuberculosis, isolation and culture of organism is gold standard, but as M. tuberculosis is a slow growing organism, culture on conventional Lowenstein–Jensen medium takes 6–8 weeks. Middlebrook medium isolates growth of organism comparatively more rapidly. Mean duration to yield positive culture is about 3 weeks. But for the disease such as tuberculosis, this is too long to wait for results of culture as it is necessary to start treatment at the earliest. Therefore, comparatively rapid diagnostic strategies need to be established for diagnosis of TB

lymphadenitis.[13] FNAC is a well-established diagnostic technique for lymphadenopathy evaluation. It is cost effective, safe, minimally invasive, and a rapid method of diagnosing not only TB lymphadenitis but also other pathologies. It also avoids the possible physical and psychological complications of an excision biopsy.[13,14]

In this prospective study, we have examined 300 cases of lymphadenopathy referred to the Department of Pathology. The finding that the majority of the patients 42.15% (59) were from 10–29 years age group correlates with those of the other studies conducted by Bezabih and Mariam,[8] Lobo et al,[15] Teklu et al,[16] Hart et al[17] and Majeed and Bukhari.[18]

Most common site involved was cervical region in 98 (70%) cases, which also correlates with the findings of other studies carried out by Bezabih et al,[8] Lau et al,[11] and Chen et al.[19] ZN stain was found to be positive for AFB in 60 (42.85%) cases, which correlates with the findings of other studies conducted by Majeed and Bukhari,[18] Kheiry and Ahmed,[20] and Rajwanshi et al,[21] which reported ZN positivity of 37.4%, 59.4%, and 40% respectively. Most common cytological pattern observed was epithelioid granuloma with caseous necrosis and with or without Langhans giant cells in 37 (37%) cases, which is similar to the study conducted by Gupta et al.[22] Highest AFB positivity was seen in 119 (33.90%) cases with necrosis with or without granuloma and inflammatory cells. Few cases (54; 15.38%) with necrosis and granuloma showed AFB negativity whereas 36 (10.25%) smears that showed necrosis and polymorphs were reported as suppurative lymphadenopathy and 105 (29.62%) cases that did not show necrosis or granuloma and also were negative for AFB were reported as chronic nonspecific lymphadenitis, which is also similar to the study conducted by Gupta et al.[22] AFB were mostly visible in purulent aspirate whether acellular or accompanied by granuloma, and in the absence of ZN staining, case can be misinterpreted as an acute lymphadenitis.[23] When Culture (BACTEC) was taken as the gold standard, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Kappa value the of FNAC in the diagnosis of TB lymphadenitis results were 96.55%, 96.38%, 95.89% and 96.96% respectively. Sensitivity of FNAC was higher and diagnostic accuracy was comparable with other studies.

The diagnostic difficulties encountered were parallel to those experienced by different authors[24,25,26] working on similar projects, a case in point being false negative cytology diagnosis in case with purulent aspirate which calls for ZN staining in every case suspected of tuberculous in origin.

CONCLUSION

Compared to AFB smear, FNAC assay has high sensitivity, is efficient, accurate, inexpensive, quick & simple for the diagnosis of Tuberculous Lymphadenitis .Cytomorphological features of FNAC on H&E stain have significant diagnostic yield. FNAC is effectively supplemented by Ziehl-Neelsen Staining, which is a simple, quicker, reliable and relatively cheap diagnostic tool. Culture methods (BACTEC) can be reserved for accurate diagnosis and those with strong suspicion but negative on FNAC.

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