

COMPARISON OF FINE NEEDLE ASPIRATION CYTOLOGY WITH HISTOPATHOLOGY IN DETECTING TUBERCULOSIS IN CERVICAL LYMPHADENOPATHY

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ABSTRACT

Objective: To evaluate the sensitivity and specificity of Fine Needle Aspiration Cytology (FNAC) in diagnosing tuberculosis lymphadenitis and to compare FNAC to histopathology of incisional biopsy of the cervical lymph nodes in the same subjects.

Material and Methods: It was a Comparative study conducted in the departments Histopathology of Khyber Teaching hospital and Khyber Medical College, Peshawar, Pakistan. The study period was from January 2013 to January 2014. Our study included 100 patients, clinically suspected to have tuberculous lymphadenitis. The patients of all ages and both sexes who were clinically suspected to have tuberculous lymphadenitis underwent FNAC followed by incisional biopsy to confirm the diagnosis. The relevant laboratory investigations were also recorded in these patients.

Results: In this study, the sensitivity was 95%, specificity was 50%, Positive Predictive Value (PPV) was 91% & Neative Predictive Value (NPV) was 63%. The false negative (FN) rate was 4% and false positive (FP) rate was 8%. The true positive (TP) rate was 81% & true negative (TN) rate was 7%. The inadequate rate was 3%.

Conclusion: The sensitivity and Positive Predictive Value (PPV) is high while specificity and Negative Predictive Value (NPV) is low. Therefore FNAC is a useful screening test however due to low specificity it must be combined with AFB staining or PCR in cases where there is high suspicion of false positive cases. In case of inconclusive results on cytology in patients with a high clinical suspicion of tuberculosis the results must be confirmed by Incisional biopsy.

Key Words: Fine needle aspiration cytology, FNAC, Tuberculous cervical, Incisional biopsy. Lymphadenopathy.

INTRODUCTION

Lymphadenopathy is defined as an abnormal increase in size and changes in consistency of lymph nodes and can be due to infectious, non-infectious and malignant diseases. The number, size and duration varies according to the underlying cause. The approximate number of lymph nodes in the body is 800 and nearly 300 of them are present in the neck.¹ The normal size of lymph node is less than three millimeter. Some studies report that lymphadenopathy less than one centimeter are mostly benign whereas in malignancy the size is usually more than two centimeter.² Malignant lymphadenopathy is reported to be of longer duration than benign causes of lymphadenopathy.³

Tuberculosis is one of the earliest diseases known to mankind. Tuberculosis is caused worldwide by a

group of Mycobacterium species called Mycobacterium tuberculosis complex which includes Mycobacterium tuberculosis, Mycobacterium bovis and Mycobacterium Afranicum.⁴ Tuberculosis is becoming a global disaster accounting for nine million new cases and mortality of three million persons each year with 25% of total deaths in developing countries.⁵

In the list of twenty two high burden tuberculosis countries of the world, Pakistan ranks 6th with an estimated three lakh new cases diagnosed each year, whereas India ranks 1st in tuberculosis burden with two million new cases of tuberculosis diagnosed every year⁶. Russia ranks 12th in terms of high tuberculosis burden with 107/100,000 new cases and 17/100,000 death each year.⁷

Tuberculous lymphadenitis has affected human beings since long. The incidence of mycobacterial lymphadenitis is directly proportional to the increase in the incidence of mycobacterial infection worldwide. It has been observed that in non endemic areas there is increase incidence of tuberculous lymphadenitis in immigrants from South East Asia and India.⁸ Tuberculous lymphadenitis is the most common form

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of extrapulmonary tuberculosis.⁹ Almost 35% of extra pulmonary tuberculosis consists of tuberculous lymphadenitis accounting for 15-20% of total cases of tuberculosis. The most common site of tuberculous lymphadenitis is cervical region where it is reported in 60-90% of patients. Tuberculous lymphadenitis may or may not be associated with pulmonary tuberculosis.¹⁰ It can occur in any age group but is more common in second decade of life.¹³ Most of the studies report that females are almost twice more affected than males.^{11,12} Patients with tuberculous lymphadenitis can have positive sputum smears and cultures results despite normal chest radiographs therefore these patients can transmit tuberculosis to others.¹³ In patients with tuberculous lymphadenitis rupture of swollen lymph node results in production of discharge that contain mycobacteria which is contiguous to others.¹³ Human immune deficiency virus (HIV) is associated with both reactivation of latent tuberculosis infection as well as increase risk of tuberculous lymphadenitis.¹⁴ In patients with HIV the extra pulmonary tuberculosis accounts for 53-62% of total tuberculosis cases.¹⁵

According to studies done on cervical lymphadenopathy in Pakistan, India, Nepal, Saudi Arabia, United States and Africa, the frequency of tuberculous lymphadenitis was recorded to be 70.4%, 70%, 54%, 82.7%, 40.4 and 72.2% respectively.¹⁶⁻²⁰ According to various studies done in Khyber Pakhtunkhwa, the incidence of tuberculous lymphadenitis range from 66%-75%.²¹

Fine Needle Aspiration Cytology (FNAC) has a high degree of accuracy, is relatively cheap with minimal trauma and risk of complications and is also simple, quicker and reliable diagnostic procedure.²² Aspiration of lymph nodes for diagnostic purpose was first done by Griey and Gray in 1904 in patients with sleeping sickness, there after the practice of FNAC developed gradually until 1921 when Guthrie tried to correlate FNAC results with various disease processes.²³

FNAC is of great diagnostic importance in children with persistent peripheral lymphadenopathy especially in areas where tuberculosis is endemic.²⁴ The diagnostic accuracy of FNAC in tuberculous lymphadenitis is 90-94% according to various studies.^{16,17} Sensitivity and specificity of FNAC in Tuberculous lymphadenitis in Pakistan, India, Nepal, Saudi Arabia, Africa and United States are 98% and 100%, 94% and 100%, 77% and 98%, 77% and 70%, 78% and 91%, and 46% and 100% respectively.²⁵⁻²⁹ A recent retrospective study show that FNAC has a higher diagnostic yield (60.8%) compared with respiratory specimen (39.2%) and reduced time of diagnosis i.e. 7 days vs 22 days.³⁰

MATERIAL AND METHODS

It was a Comparative study conducted in the departments Histopathology of Khyber Teaching hospital and Khyber Medical College, Peshawar, Pakistan. The study period was from January 2013 to January 2014. Our study included 100 patients, clinically suspected to have tuberculous lymphadenitis. The patients of all ages and both sexes who were clinically suspected to have tuberculous lymphadenitis underwent FNAC followed by incisional biopsy to confirm the diagnosis. The relevant laboratory investigations were also recorded in these patients.

The following was the Inclusion criteria. The population of interest for this survey was both male and female patients of all ages with cervical lymphadenopathy who are clinically suspected to be tuberculous. Patients with following signs, symptoms and laboratory findings are suspected to have tuberculous lymphadenopathy:-

1) Presence of fever, malaise, night sweats, anorexia, weight loss and family history of TB. 2) Presence of discrete or matted lymph nodes involving different groups of cervical lymph nodes and mostly in the posterior triangle of neck. 3) Raised ESR, lymphocytosis on FBC and strongly positive tuberculin test.

All patients with cervical lymphadenopathy who are clinically suspected to have lymphadenopathy due to following causes:- 1) Associated with sore throat or ear infection. 2) Neoplastic causes either primary (lymphoma, leukemia) or secondary (from lung, breast, thyroid and stomach). 3) BCG vaccine associated lymphadenopathy, were excluded from the study. Before performing the procedure the participants were briefed regarding the research topic and its significance, and they were also advised to answer the questions asked by the researcher so that the questionnaire can be filled as properly as possible and if they have any problem they could either ask the team members or the researcher in person. All the patients were screened for HBs Ag and Anti HCV antibodies.

The study had four parts. In first part a detailed history and clinical examination was carried out. In the second part laboratory investigation required to confirm clinical suspicion of tuberculosis were obtained from the records of patient. This included Total leukocyte count (TLC) and Differential leukocyte count (DLC), ESR, Montoux test, X-ray chest and AFB staining.

In the third part, FNAC was carried out on these patients. The smears were stained and examined under microscope and the results were noted. Finally, in the fourth part of the study biopsy of the lymph node was carried out by the surgeon. The biopsy samples were processed and examined under the microscope. The histological findings were recorded.

Continuous variables were analyzed using means and standard deviations while categorical variables were analyzed using proportions. All the data was analyzed in SPSS version 16. The clinical, laboratory, cytological and histological variables were categorized and correlated by applying Chi-square test i.e. Pearson's Chi-square. Statistical significance was taken at the 5% level i.e. $P < 0.05$. The data on FNAC and histopathology results were then used to calculate the sensitivity, specificity, predictive values, false positive/negative cases and true positive/negative cases.

RESULTS

It is a hospital based descriptive comparative study of 100 patients clinically suspected to have tuberculous lymphadenitis. In this study of 100 patients the age range was 5-50 years. The patients were grouped into three according to their ages. In first group the age range was 1-15 years, in 2nd group it was 16-40 years while in 3rd group it was above 40 years. The maximum number of patients (61%) were found in the 2nd group with an age range from 16-40 years. This is followed by (32%) patients in the 1st group with age range from 1-15 years while minimum number of patients (7%) were seen in the age group above 40 years. The genderwise distribution was males 33% and females 67%. Thirty-four percent of patients belonged to Rural areas and 66% were found Urban areas. Most of the patients i.e 66% were from poor socio-economic class and 74% of patients were uneducated while 26% had a secondary grade education. The history of Tuberculosis in the patients and in the family is shown in Table 1. The

Table 1: Past and family history of tuberculosis

Past history	No. of patients with percentage
Present	22(22%)
Absent	78(78%)
Family history of tuberculosis	
Present	48(48%)
Absent	52(52%)

Table 2: Location of Lymphadenopathy

Site	No. of cases with percentage
Anterior Triangle	24(24%)
Posterior Triangle	43(43%)
Supraclavicular	11(11%)
Submental	2(2%)
Submandibular	10(10%)
Postauricular	10(10%)

Table 3: Types of cells on FNAC and Biopsy

Types of cell		FNAC	Biopsy
Lymphocytes	Yes	99	100
	No	01	0
Plasma cells	Yes	79	79
	No	21	21
Epithelioid cells	Yes	89	89
	No	11	11
Langhans' giant cells	Yes	14	83
	No	86	17
Fibroblasts	Yes	86	86
	No	14	14
Macrophages	Yes	81	81
	No	19	19
Neutrophils	Yes	31	28
	No	69	72
Necrosis	Caseating	69	69
	Non-caseating	19	19
	Absent	12	12

Table 4: Overall Results

Parameters	Percentages
Sensitivity	95%
Specificity	50%
Positive Predictive Value(PPV)	91%
Negative Predictive Value(NPV)	63%
False positive rate	8%
False negative rate	4%
True positive rate	81%
True negative rate	7%
Inadequate rate	3%

Table 5: Results of FNAC and Histopathology

Cytological results	No. of patients with percentages
Positive for tuberculosis	89(89%)
Negative for tuberculosis	11(11%)
Histopathological results	
Positive for tuberculosis	85(85%)
Negative for tuberculosis	15(15%)
Results	
Relevant	85(85%)
Conflicting	15(15%)

distribution of neck nodes are shown in Table 2. In 88% of patients a Chronic granulomatous inflammation most likely tuberculosis was observed. The types of cells on the basis of FNAC and Biopsy is shown in Table 3. The sensitivity, specificity, PPV, NPV are shown in Table 4. The results of cytology and histopathology are shown in Table 5.

DISCUSSION

Fine needle aspiration cytology has a high degree of diagnostic accuracy, is relatively cheap with minimal trauma and risk of complications and is also simple, quicker and reliable diagnostic procedure.²² In Pakistan the burden of tuberculosis is increasing due to poor socioeconomic conditions, inappropriate health care delivery system and poor level of education. The recent rise in HIV/AIDS has further complicated the situation due to increase incidence of tuberculosis in HIV positive patients. The conventional methods are slow and time consuming and therefore there is a need to establish newer diagnostic techniques that are rapid, easy, safe and cost effective.

FNAC is a well established technique with a high degree of accuracy in diagnosing tuberculous lymphadenitis especially in endemic areas like Pakistan where the diagnosis of tuberculosis can be made with confidence when its cytomorphological criteria is met.¹²

In this study the results of cytology and histopathology were tabulated and compared. Although many other aspects of patients clinical profile and laboratory investigations were also compared with the other studies but the important aspect of this study was to compare the sensitivity and specificity of FNAC results with the histological results and to find out the conclusion. These findings are concordant with other studies which also revealed that the peak incidence of tuberculous lymphadenitis is seen in the age group between 20-40 years.³⁰⁻³³

Females were more affected (67%) than males (33%) with male to female ratio of 1:2 in this study. Female predominance is observed in most of the other studies conducted on tuberculous lymphadenitis roughly up to 64% of the total patients which is in accordance with our results.³⁴

Most patients (66%) were from urban areas while only 34% belong to rural areas in this study. This is due to the fact that tuberculosis is common in people living in close communities. Similar findings were observed in a study done in Ethiopia by Abebe et al, and Fazali-Wahid et al, showed that 47% of the patients were from urban areas. Most of our patients (66%) were from poor socioeconomic class. This is due to the increase incidence of tuberculosis in this class not only due to

poor living conditions and under nutrition but also due to limited access to this group to health facilities. This result was in accordance with a study done in Karachi by Ahmed et al 2010. Another study done in Peshawar showed that 60% of the patients with tuberculous lymphadenopathy belonged to poor class.³⁴

The past history of tuberculosis was recorded in 22% of the patients in this study while a study done by Kanlikama et al showed that 16.1% had suffered from pulmonary TB in the past. In this study family history of tuberculosis was seen in 48% of the patients while the study done by Kanlikama et al, showed that 21.8% of the patients had history of contact. This showed that in this study the history of contact was present in twice as much patients compared to the study done by Kanlikama.⁴⁰

The commonest group of lymph nodes affected by tuberculosis in this study was posterior triangle nodes involved in 43% of the cases followed by anterior triangle nodes in 24% cases, supraclavicular in 11%, submandibular in 10%, postauricular in 10% and submental in 2% of the patients respectively. This findings were comparable to the study done by Maharjan et al., who observed involvement of posterior triangle nodes in 42% patients followed by upper and lower deep cervical in 22%, submandibular in 15%, supraclavicular in 9%, submental in 4% and postauricular in 4% of the cases respectively. The involvement of posterior triangle lymph nodes in majority of the patients with tuberculous lymphadenitis is also noted by Prasad et al and Dandapat et al.^{37,39}

In this study fine needle aspiration showed epithelioid cells in 89% of the cases, Langhans giant cells in 14%, fibroblasts in 86%, macrophages in 81% and caseating necrosis in 69% of the cases. These findings were in accordance with the study done by Surase et al., 2009 in which epithelioid cells were observed in 84%, langhans' giant cells in 8%, fibroblasts in 80% and caseating necrosis in 71%. In a study done by Ahmed et al., 2011 caseating necrosis was seen in 68% cases while Fatmi and Jamal reported caseating necrosis in 62% of cases.

In this study, the Positive Predictive Value (PPV) for cytology was 91% while the Negative Predictive Value (NPV) was 63%. In a study done by Derese et al., the PPV for cytology was 78.6% while NPV was 54.2%. This indicates that our findings were consistent with other studies.⁴²

The false positive rate in this study was 8% while false negative rate was 4% and inadequate rate was 3%. Among the 8 false positive cases two came out to be Hodgkin's lymphoma, two non- Hodgkin's

lymphoma and four reactive hyperplasia on histopathology. Out of the 4 false negative cases which proved to be tuberculous on histopathology one was inadequate on cytology, two were reported as chronic non specific inflammation while one was reported as acute non specific inflammation on cytology. Out of the three cases which were inadequate on cytology, one turned out to be tuberculous while two were reported as reactive hyperplasia on histopathology. In a study done by Lee et al, it was illustrated that inadequacy rate were lower (3.8%) in FNAC samples aspirated by experienced aspirator. These findings were comparable to our results. In the study by Lee et al, it was found that when a general practitioners performed the FNAC the inadequacy rate was recorded to be 16%. Therefore the skill of the operator is the most important factor in reducing inadequate sample rates.

In this study the sensitivity of FNAC was 95% while specificity was 50%. In a study done by Derese et al., 2012 the sensitivity was found to be 81% while specificity was 50%. However in most other studies much higher specificity is noted compared to our study. The range of sensitivity was 77-98% while the range of specificity was 70-100% in most studies.²³⁻²⁸ In this study the cytology lacked specificity but had a higher sensitivity because non tuberculous granulomatous patients could also be diagnosed as tuberculous lymphadenitis.

CONCLUSION

Sensitivity of FNAC for tuberculous lymphadenitis is high however the specificity is very low therefore FNAC can be used as a useful screening test especially in endemic countries like Pakistan.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

Nadeem S: Idea & Data Collection.

Munir AH: Typing.

Khan SK: Bibliography.

Ashraf Z: Statistics.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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