



## **Evaluation of Fine Needle Aspiration Cytology Technique for Early Diagnosis of Tubercular Lymphadenitis in Patients Presenting at a Primary Care Setting in India**

**Pradeep Tandon<sup>1\*</sup> and Winie Gautam<sup>2</sup>**

<sup>1</sup>Department of Pathology, Mayo Institute of Medical Sciences, Barabanki, UP, India.

<sup>2</sup>Ama Diagnostic Centre, Lucknow, UP, India.

### **Authors' contributions**

*This work was carried out in collaboration by both authors. Both authors have contributed in study design and analysis of the results. Author PT has managed the literature search and written the first draft of the manuscript. Both authors have read and approved the final manuscript.*

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### **ABSTRACT**

**Aims:** The aim of the present study is to evaluate whether FNAC helps in detecting tubercular lymphadenitis (TB LAN) at an early stage in a primary care setting. Demographic and cytomorphological profile of TB LAN in this part of the country is also analyzed.

**Study Design:** The study is a retrospective analysis of all FNAC procedures carried out in patients of lymphadenopathy (LAP). Cases diagnosed as TB LAN are analyzed further.

**Place and Duration of Study:** All patients of LAP presenting at Ama Diagnostic Centre, Lucknow, Uttar Pradesh, India, between August 2008 to December 2015.

**Methodology:** FNAC procedure was carried out on 780 patients of whom 762 cases yielded

\*Corresponding author: Email: [tandonp72@yahoo.co.in](mailto:tandonp72@yahoo.co.in);

adequate material. Of these, 245 cases were diagnosed as TB LAN based on cytomorphological details and Zeihl Neelsen staining.

**Results:** TB LAN is the second most common cause of lymphadenitis. Lymph nodes of head and neck region are involved most frequently in TB LAN. Majority of TB LAN patients are in 2<sup>nd</sup> and 3<sup>rd</sup> decade of life. The disease tends to occur at a younger age in this part of the country.

**Conclusions:** Cytomorphological profile of the aspirates indicates that use of FNAC helps in detecting TB LAN at an earlier stage of the disease. Majority of the cases of TB LAN are seen between 10-30 years of age. It also occurs at an earlier age in this part of the country. In about 90% of cases TB LAN tends to involve lymph nodes of the head and neck region.

*Keywords: Tuberculosis of lymph nodes; lymph node aspiration cytology; lesions of lymph node.*

## 1. INTRODUCTION

In our country patients often present with lymphadenopathy because of high incidence of acute and chronic infectious diseases and the rising trend of malignant disorders. For example in rural India, the prevalence of tuberculous lymphadenitis in children up to 14 years of age is approximately 4.4 cases per 1000. The general recommendation regarding management of lymphadenopathy (LAP) of recent onset, in case of children is to manage the patient on conservative lines for a period of two weeks. Further investigations are warranted only when LAP fails to regress within 4-6 weeks. The rationale behind this proposal is the fact that in majority of instances, LAP during childhood is reactive in nature and after conservative treatment, shows early resolution [1]. However, this proposal may not always hold true in our country, because LAP in children of reactive nature, can persist for a longer duration, due to widespread nutritional deprivation and the resultant immune deficiency. Recurrent episodes of acute reactive lymphadenitis - as may occur in under nourished kids - often leads to chronic lymph node enlargement. Also because of poor economic status, many patients often do not seek early treatment. This produces a confounding clinical picture making it difficult to distinguish - on clinical examination alone - between chronic reactive LAP and chronic lymphadenitis due to specific disorders like tuberculosis (TB). For LAP of adults over 40 years of age, the recommendation states that it should be investigated as early as possible, especially when it involves supraclavicular, posterior cervical or deep seated lymph nodes. This is based on the fact that in adults, comparatively a higher percentage of enlarged lymph nodes show metastatic deposits [2]. From last three decades, fine needle aspiration cytology (FNAC) is being used astutely all over

the world for investigating LAP. In our country, the procedure can be of great relevance in distinguishing chronic non-specific reactive LAP from chronic lymphadenitis of a more specific nature like TB. The aim of the present study is to evaluate whether use of FNAC in a primary care setting can help in detecting TB LAN at an early stage of the disease. This would lower the cost of management of a patient with TB LAN. Demographic and cytomorphological profile of TB LAN in this part of the country is also analyzed.

## 2. MATERIALS AND METHODS

### 2.1 Study Area

The present study is a retrospective analysis of FNAC carried out for diagnostic purpose in all patients of LAP referred to the Pathology section of Ama Diagnostic Centre, Lucknow, Uttar Pradesh, India. The period of study is from August 2008 to December 2015. FNAC procedure was carried out in a total of 780 patients. As the present study consists only of patients that were referred to a primary care facility and involves 780 cases, it may not be representative of the disease pattern across the general population of this region.

### 2.2 Sample Collection

After explaining the procedure to the patient, consent to undergo the procedure was taken. All risks associated with the procedure – however minor – were explained to the patient. Consent was obtained from the parents, if the patient was under 16 years of age. Following thorough cleansing of the site of aspiration with 70% alcohol and povidone iodine solution, sample was collected using a 10 ml syringe attached to 21 or 23 gauge needle. Multiple air-dried and/or wet-fixed smears were prepared.

### 2.3 Laboratory Procedure

Smears were first stained by May Grunwald Giemsa (MGG) and Papanicolaou technique for preliminary evaluation. If indicated, Zeihl Neelsen stain for acid fast bacteria and Gram staining were also done. All cases were initially segregated into different disease categories as per criteria given in standard text books of cytology. Cases of TB LAN were analyzed further. Diagnosis of tubercular lymphadenitis and their sub-categorization was done based on following criteria:

- Group 1: Epithelioid cell granulomas + caseous necrosis.
- Group 2: Presence of caseous necrosis only +/- demonstration of AFB
- Group 3: Epithelioid cell granulomas against an inflammatory background +/- demonstration of acid fast bacteria.
- Group 4: Suppurative necrosis + demonstration of acid fast bacteria (AFB) on Zeihl Neelsen stain (ZN stain).

Cases showing caseous necrosis only, were also classified as tubercular, because previous studies indicate that very few diseases in India – apart from tuberculosis - produce caseation necrosis.

### 3. RESULTS

Over the period of 7 years and 5 months, a total of 780 patients of LAP underwent fine needle aspiration procedure for diagnostic purposes. Adequate material was obtained in 762 patients. The anatomical distribution of lymph nodes aspirated is shown in Fig. 1. It is seen that cervical lymph nodes were the commonest group to be involved by a disease process (85.6% of cases) followed by inguinal (6.56%) and axillary group (5.9%) of lymph nodes.

The distribution of disease amongst 762 successful aspirates is shown in Fig. 2. It is seen that reactive non-specific lymphadenitis was the commonest diagnosis rendered (45.5% of cases) followed by tubercular lymphadenitis (32.1% of cases). A total of 245 cases of LAP belonged to tubercular lymphadenitis (TB LAN) group.

Distribution of TB LAN in different anatomical groups is shown in Fig. 3. It is seen that cervical group of lymph nodes are involved most often in tuberculosis (88.16% of cases) followed by axillary (6.12% of cases) and inguinal (2.44% of cases) group of lymph nodes.

The age distribution of TB LAN patients is shown in Fig. 4. In our series, maximum numbers of cases of TB LAN are seen in second (34.6% of cases) and third decade (35.5% of cases) of life.

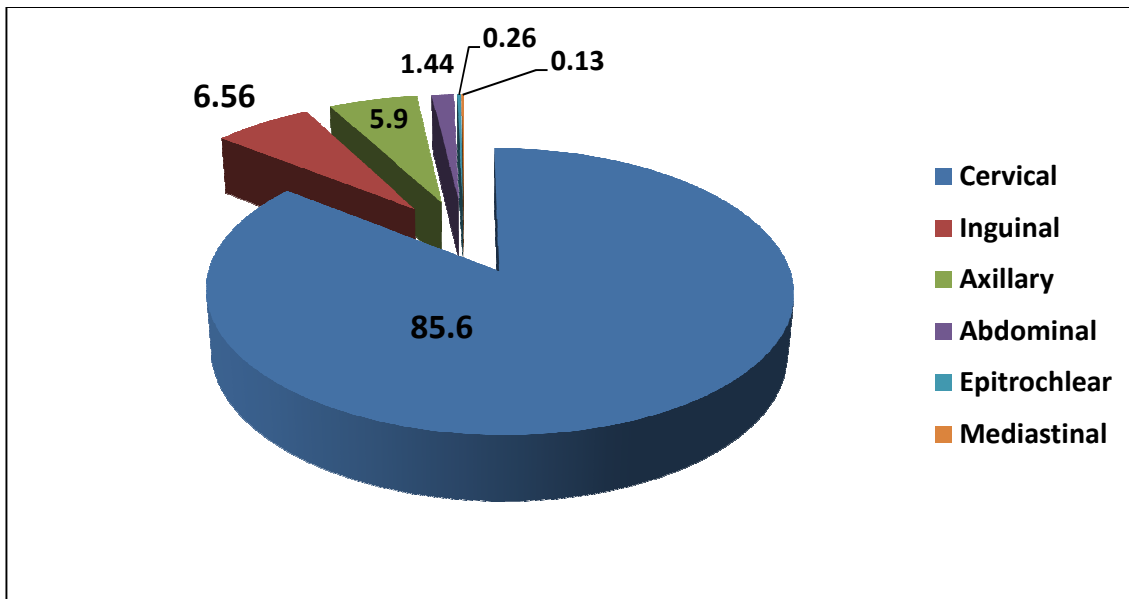


Fig. 1. Distribution of all cases of LAP in different lymph node groups

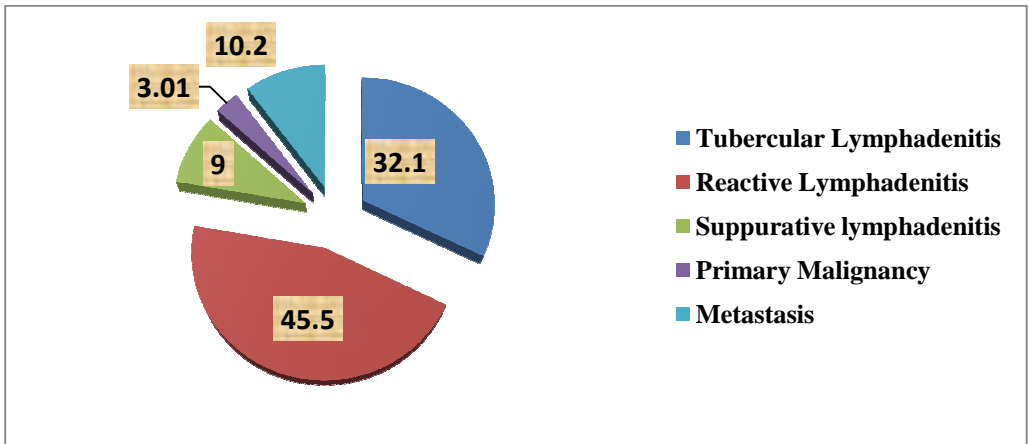


Fig. 2. Distribution of disease amongst all cases of LAP

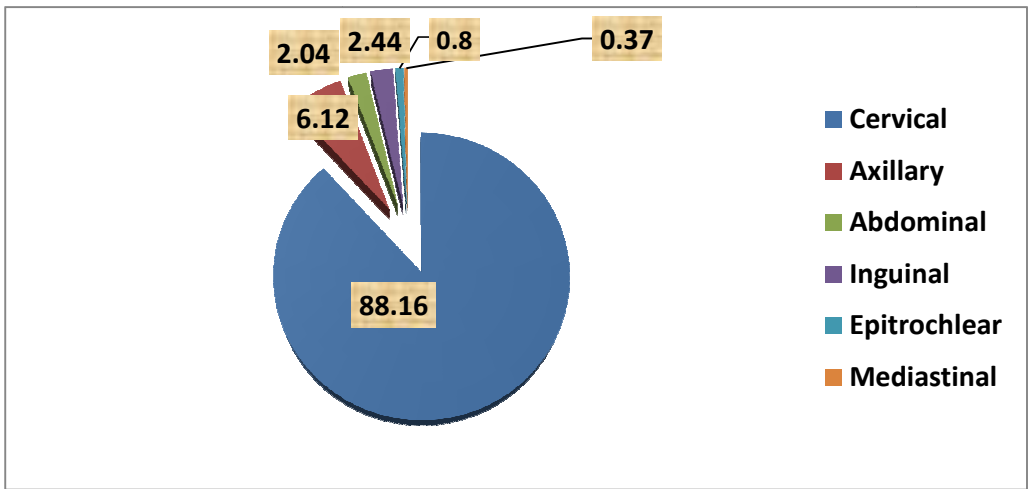


Fig. 3. Distribution of tubercular lymphadenitis in different anatomical lymph node groups

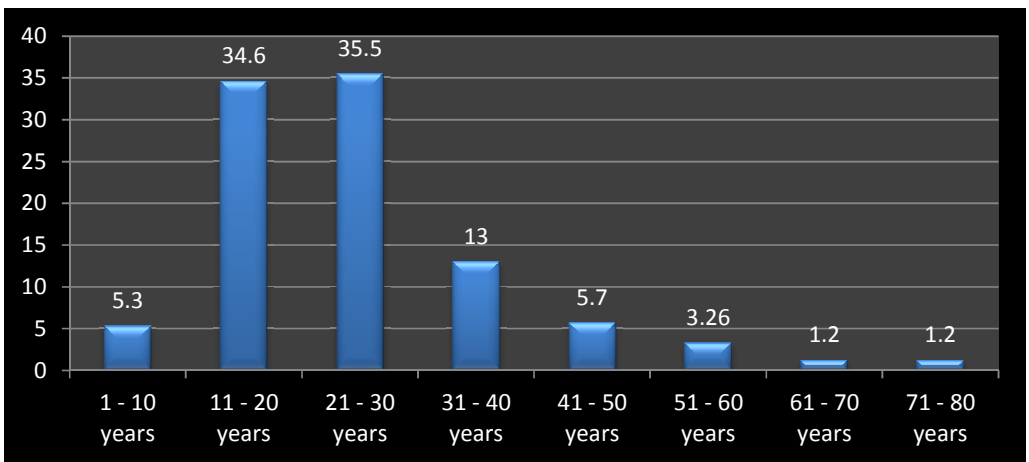


Fig. 4. Age wise distribution of tubercular lymphadenitis

Different cytomorphological features of TB LAN in our series are shown in Fig. 5. It is observed that presence of epithelioid cell granulomas against a background of reactive inflammatory cell population (group 3 patients) was the commonest pattern seen in our series (45.64% of cases).

As the cytological picture of group 1 and 2 patients is regarded as diagnostic of tuberculosis, ZN staining for demonstration of AFB was done mainly for group 3 and 4 patients. AFB was demonstrated in 21.6% of group 3 cases. As per the protocol of our study, Group 4 cases were classified as tubercular only when they demonstrated AFB positivity.

#### 4. DISCUSSION

Human body is kept safe from invading microorganisms and rogue circulating neoplastic cells with the help of approximately 600 lymph nodes - tiny sentinel of our fragile health. On provocation, lymph nodes flare up and enlarge, ready to devour the hostile elements. At the same time, swollen lymph nodes act as a warning sign to the patient and his physician. However, bloated lymph nodes - which may represent minor irritants like reactive lymphadenitis or devastating illnesses like metastatic deposits - do not reveal their secrets easily. A clinician confronting lymphadenopathy

has to wade through myriad of differential diagnostic possibilities to seek a definitive diagnosis. The problem becomes all the more confounding when lymphadenopathy is deep seated, as the lesion is not easily accessible for microscopic evaluation. To add to this puzzle, are problems of medical resource deficiencies in developing countries, culturally inherent dislike of many patients to go under the knife and often the poor economic status of a patient that precludes use of more advanced diagnostic facilities. In this baffling scenario, FNAC seems to have emerged as a handy contrivance for the beleaguered patient and his physician.

In India, for a variety of reasons, TB has been an endemic disorder since a long time. Poverty, malnutrition, high illiteracy rate, lack of universal health care, overcrowding and insanitary living conditions - factors considered to be great allies of this once dreaded disease - are encountered frequently and to varying extent in different parts of this country. Every year 9.4 million new cases of TB are seen world over. India accounts for about 20% of these cases. This translates to 1.98 million new cases of TB every year in India. In HIV negative individuals, extrapulmonary TB (EPTB) constitutes 20% of all cases of TB and nodal TB constitutes 35% of all cases of EPTB. Extrapolation of this data indicates that about 0.12 million new cases of lymph node TB occur every year in India [3].

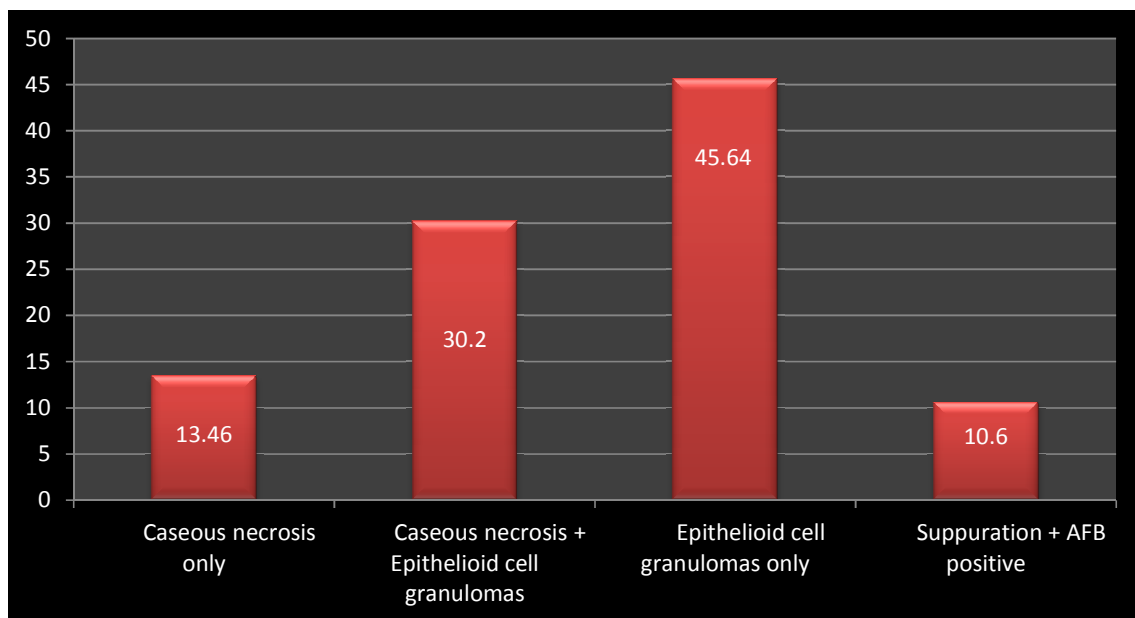


Fig. 5. Cytomorphological features seen in tubercular lymphadenitis

Central Uttar Pradesh is home to many of the factors that promote TB. Being a contagious disease, to eradicate tuberculosis, it is important that the disease be detected at its earliest stage. Whether FNAC can play a role in realization of these efforts, is investigated in our study. As detailed later, it is essential that the implicated strain of mycobacteria in TB LAN should also be identified - as it influences treatment. Fine needle aspiration can contribute in these efforts.

We have also studied the pattern of cytomorphological changes seen in TB LAN and compared our findings with workers from other parts of India. Utilizing already known facts about temporal evolution of tubercular lymphadenitis, an attempt has been made to see whether FNAC can help in detecting the disease at an earlier stage of its evolution.

In our study, lymph nodes of head and neck were the commonest group to be involved by a disease process (88.16% of cases). Other series from India also indicate that cervical lymph nodes are involved most frequently. Incidence of cervical lymph node involvement, as reported by some other workers ranges from 73- 83% [4-7]. The obvious reason for greater involvement of cervical group of lymph nodes is their close proximity to anatomical passages of the body that are constantly exposed to environmental infectious agents. They also drain lymphatics from a large part of the body, hence the increased likelihood of acting as a repository for metastatic deposits.

The commonest diagnosis in our series was non-specific reactive lymphadenitis (45.5% of all cases) followed by tubercular lymphadenitis (32.2% of all cases). Our results are in concordance with those of Qadri et al. [5], Ahmad et al. [7], and Hirachand et al. [8] but differ from the findings of Khajuria et al. [4], Chand P et al. [9] and Paliwal N et al. [10], who reported higher incidence of TB LAN compared to reactive LAN.

Criteria for diagnosis of TB LAN have been mentioned above. Cases showing only epithelioid cell granulomas, without AFB positivity, were also categorized as tuberculosis. Although many diseases can show granuloma formation, in our country tuberculosis is the predominant cause [11,12]. Also such patients – many of them cannot afford more expensive investigations - are often given a short therapeutic trial of anti-tubercular drugs. After the trial period, non-responders are investigated further [11,12]. Some studies from India have demonstrated that patients of granulomatous lymphadenitis, who were negative for tubercle bacilli on culture, responded to anti-tubercular treatment and showed clinical improvement [13].

In our series, cervical group of lymph nodes are involved most frequently by TB LAN (88.16% of cases). Similar data is reported in some other series also, viz. Chand P - 70% [9], Giri S - 51.89% [14], Gupta R - 70% [15], Rana - 83.6% [16].

In our series, TB LAN was seen most frequently in the third decade of life (35.5% of all cases)

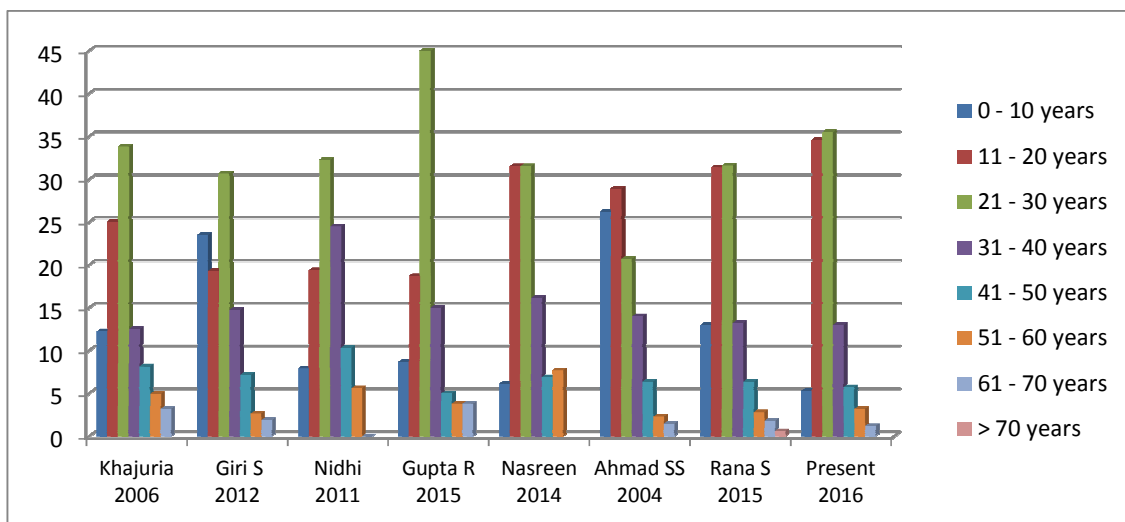


Fig. 6. Comparison of age distribution of TB LAN in different series

closely followed by second decade of life (34.6% of cases). Thus majority of cases of TB LAN (70.1% of all cases) are seen in between 11 to 30 years of age. Comparison of age distribution of TB LAN patients in our series with some other recent series from different parts of India is shown in Fig. 6. It is observed that in our series, TB LAN was more or less equally distributed in second and third decades of life. This is similar to findings of Ahmad et al. [7], Rana et al. [16] and Nasreen et al. [17], but at variance to those of Paliwal [10], Giri [14] and Gupta [15] who found higher incidence of TB LAN in third decade of life. In our series, the reason for high incidence of TB at an earlier age can possibly be attributed to high population, overcrowding, low literacy rates and low nutritional and immune status of patients in this part of the country. This needs to be verified further by carrying out more extensive epidemiological studies.

Cytomorphological patterns of TB LAN seen in our series were shown in Fig. 5. Other authors have also described similar cytomorphological features in TB LAN with or without minor variations [9,10,14,16,18,19,20]. Comparison of cytomorphological features of TB LAN in our series with some other recent studies from different parts of India is depicted in Fig. 7. It is seen that in our series a larger percentage of cases had presence of only epithelioid cell granulomas (45.64% of all cases). This can be explained when we consider the dynamics of evolution of histopathological changes in

tuberculosis. During initial phases, tubercle bacilli multiply within macrophages that accumulate in lymph nodes. Also, epithelioid cell granuloma formation begins. At this stage, little cell death occurs. After two to four weeks, macrophages develop the ability to destroy the bacilli. At the same time, macrophages and other cells are also destroyed by the by-products of type 4 hypersensitivity reaction which leads to caseation necrosis [21]. Hence, presence of epithelioid cell granulomas and absence of caseous necrosis indicates an early stage in evolution of TB. As nearly half of the patients in our series are showing epithelioid cells/ epithelioid granulomas only, it indicates that patients have been detected at an early stage of evolution of this disease. Many of the other studies referred to earlier were carried out at secondary or tertiary care centres. As the patient usually presents to these medical facilities at a more advanced stage of their disease, it may explain the variation in the pattern of cytomorphological profile seen in those series.

AFB positivity rate is low in our study possibly due to similar reasons. At least  $10^3$  to  $10^5$  bacilli/ml of sample should be present for a positive ZN stain [10]. Earlier stages of TB LAN are known to have low AFB load. Higher percentage of lymphocytes, epithelioid cells and giant cells limit proliferation of *M. tuberculosis*. Conversely, caseous necrosis is associated with proliferation of tubercle bacilli and high AFB load [18].

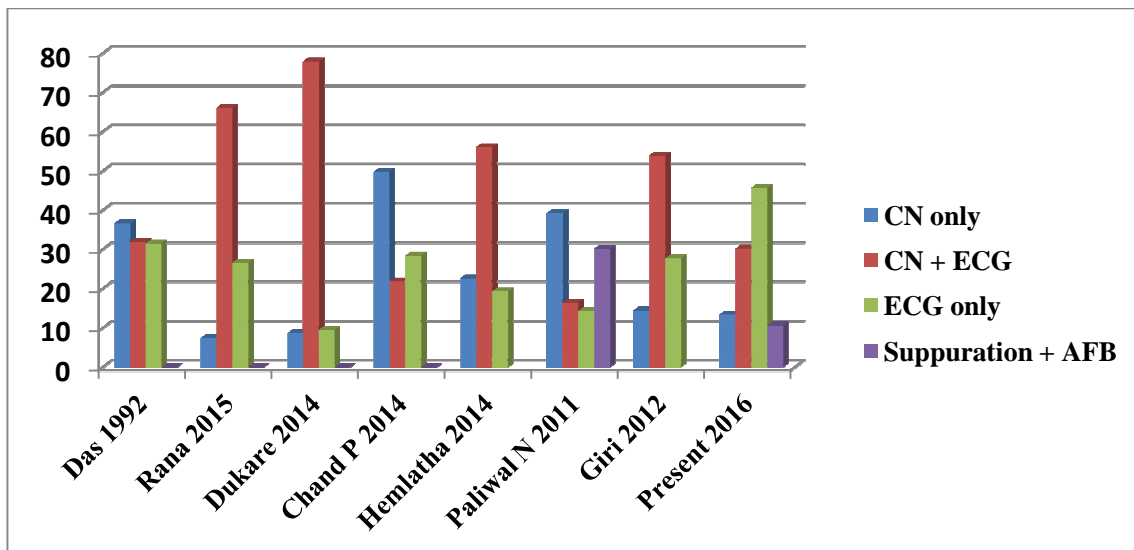


Fig. 7. Comparison of cytomorphological features of TB LAN in different series

Nodal tuberculosis is common not only amongst residents of the Indian subcontinent, but also in immigrants from this region to more advanced economies [22]. Important factors suggested for this predisposition are cultural practices like - close communal living and the habit of spitting in open (thus favouring oropharyngeal exposure), genetically determined tropism of mycobacterium towards lymph nodes of this population group and possibly BCG vaccination. Genetic differences in the virulence of organ tropism of different strains of *M. tuberculosis* have been demonstrated in other geographic locales [22]. Whether the same phenomenon exists in India needs to be investigated.

Tubercular cervical lymphadenitis (TBCLN) can be produced by *M. tuberculosis* (MTB) or by non-tubercular mycobacteria (NTM). MTB cervical lymphadenitis can be a local manifestation of a more widespread systemic disease or it can be due to reactivation of organisms spread earlier from lungs through lympho-hematogenous route [3]. In contrast, NTM cervical lymphadenitis is purely a local disorder caused by bacteria gaining direct access into lymph nodes through oropharyngeal mucosa, salivary glands, tonsils and gingiva [3]. In recent times, with emergence of drug resistant strains of mycobacteria, treatment of TB has become more complicated. Moreover, management of nodal tuberculosis differs from pulmonary TB [23]. As many cases of NTM TB are resistant to routine anti-tubercular treatment, surgical removal of lymph nodes has been proposed as a first line treatment in NTM adenitis and as a last resort management in systemic disease caused by drug resistant MTB [23].

Since a case of TBCLN may represent either 'NTM adenitis' or 'reactivated MTB adenitis' with quiescent primary disease', it is imperative that the two entities are distinguished at the very first instance - because the treatment differs. This practice is not being followed routinely in our country. Current recommendation for diagnosis of NTM infection states that the specimen should be obtained directly from the diseased organ [24]. Hence it is our view that FNA can be utilized for providing samples for diagnosis and sensitivity assays directly from the affected lymph nodes with minimal invasion and discomfort to the patient.

A word of caution, especially relevant for physicians working in a primary care setting is that a patient with FNAC diagnosis of reactive lymphadenitis should be kept on follow-up when

clinically warranted. TB LAN evolves through five stages. During the first stage, lymph nodes show non-specific features of reactive hyperplasia [3] and the diagnosis of TB can be missed sometimes [14]. Studies show that cases that were initially diagnosed on histological biopsy as reactive lymphadenitis went on to develop tuberculosis after six months of follow up [25].

## 5. CONCLUSION

FNAC can serve as a primary investigative modality for early diagnosis and management of TB LAN in resource poor settings in our country. It helps in early diagnosis and management of patients of tubercular lymphadenitis. About 32% of all cases of lymphadenopathy are due to tuberculosis. 70% cases of TB LAN are seen between 10-30 years of age and it also occurs at an earlier age in this part of the country. In about 90% cases TB LAN tends to involve lymph nodes of the head and neck region. Utility of FNAC in management of TB LAN is also discussed.

## CONSENT

The study is a retrospective analysis of a laboratory investigative procedure. No personal data of any patient is being presented. An informed consent of all patients was obtained prior to performing the investigative procedure.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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