Original Article

Cytological Evaluation of Enlarged Peripheral Lymph Nodes: An Institutional Experience from Kumaon Region of Uttarakhand

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Abstract

Introduction: Peripheral lymphadenopathy is a common clinical entity. It is significant as the underlying cause could range from a simple infection to a malignant lesion which could be either primary or metastatic. Fine needle aspiration cytology (FNAC) is the first line of investigation usually done to diagnose enlarged lymph nodes**. Materials and Methods:** This retroprospective study was done in the Department of Pathology, Government Medical College, Haldwani, from January 2008 to December 2018. Relevant details of the patients were taken from the records. The cytological diagnosis and site were noted and divided into major diagnostic categories with respect to age group, sex, and site. **Results:** A total of 16,985 cases were studied. About 42% showed reactive morphology, 31.77% were tubercular, 23.65% metastatic lesions, 2.49% were hematological malignancies, and only 0.08% were parasitic. The cervical lymph node was the most common site aspirated and it was also the most common site for metastasis (60.45%). Among the metastatic lesions, squamous cell carcinoma accounted for maximum cases (69.10%). **Conclusion:** FNAC is a simple procedure for investigating enlarged peripheral lymph nodes. The underlying cause may vary depending on the sociodemographic profile of the patients. It is a safe and effective procedure for giving a quick and reliable diagnosis in peripheral lymphadenopathy, thereby avoiding unnecessary excision biopsy.

Keywords: Fine needle aspiration cytology, lymphadenopathy, metastasis, tubercular lymphadenitis

Introduction

Lymph nodes are small reniform structures which are distributed throughout the body and are part of the lymphatic system. The lymphatic system is part of the immune system and helps in fighting off infections and keeps them from spreading. Enlarged peripheral lymph nodes, whether regional or systemic, is one of the most frequent presenting complaints of patients encountered by clinicians. It could be the manifestation of a wide variety of underlying diseases ranging from illnesses which could be self-limiting and treatable to being the sign of an underlying primary or metastatic malignancy. Clinical and pathological staging of cancer is dependent on the identification of lymph node metastasis. Cervical lymph nodes are most noticed by both the clinician as well as the patient. Depending on the geographical location, the etiology may vary. In tropical countries, like ours, the most common benign cause of lymphadenopathy could be infections. Among the infections, tuberculosis would be the largest contributor. The location of the enlarged lymph nodes and age group of the patient can help to narrow down the cause. In children, they are often enlarged when they first come in contact with new germs even if they do not have an infection. As they grow up, upper respiratory tract infections and infections in the oral cavity are among the most common causes for enlarged lymph nodes, especially in the head-and-neck region. In the elderly age group, however, malignancy should be ruled out first before considering any other cause.

Kun in 1847[1] was the pioneer of aspiration. Lymph nodes were aspirated much later by Grieg and Gray in 1904 for the first time in a patient of sleeping sickness.[2] Fine-needle aspiration cytology (FNAC) is one of the first investigative procedures of choice for evaluating lymphadenopathy. It is easy and cheap and can be carried out as an outpatient procedure. The results can be

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obtained faster than a biopsy, the procedure needs no anesthesia and neither does it leave any scar, unlike biopsies. Like any other technique, FNAC also suffers from certain limitations. Sampling errors due to improper technique and/or lack of experience, insufficient aspirated material due to the small size of the node, and inability to assess the architectural pattern of the lymph node in evaluating lymphomas are the major drawbacks of this technique. While interpreting the observed cytomorphology, we have to bear in mind that in FNAC, only a very small area is being sampled. Therefore, the diagnosis does carry the risk of both under as well as overdiagnosis of certain lesions and caution must be exercised to avoid this.

The present study was undertaken to study the spectrum of cytomorphological findings in patients with enlarged peripheral lymph nodes and assess the diagnostic utility of FNAC.

Materials and Methods

This retrospective study was carried out in the Department of Pathology, Government Medical College, Haldwani, Nainital District of Uttarakhand, India. A total of 16,985 aspirations of peripheral lymphadenopathy were retrieved over a period of 11 years from January 2008 to December 2018. FNAC was performed using a 23-gauge needle. An average of two passes and a minimum of four slides had been made for each case. Slides were stained with papnicolaou, hematoxylin and eosin, and May–Grunwald–Giemsa stain. The cytological diagnosis was noted and divided into major groups including reactive, tubercular, metastatic, hematological, and parasitic lesions, and analyzed. Relevant data including age, sex, and site were retrieved from records. The site of peripheral lymphadenopathy was noted and divided into major sites including cervical, axillary, supraclavicular, and inguinal. Patients with metastatic lymphadenopathy were divided into various age group and common age groups were analyzed. The cytological diagnosis of metastatic lesions was divided into major groups of metastatic squamous cell carcinoma, metastatic adenocarcinoma, and metastatic poorly differentiated carcinoma.

Results

A total of 16,985 aspirates were studied which were taken over a period of 11 years. Of these, 57% (n = 9674) were male and 43% were female (n = 7311) [Figure 1].

Maximum aspirates (73.85%) showed benign morphology (n = 12,545) and metastatic and hematological malignancies contributed to 26.14% (n = 4440) of the cases. Reactive lymphadenitis (42%, n = 7134) was the most common etiology reported, followed by tuberculosis (31.77%, n = 5397). Parasitic etiology was seen only in 0.082% of the cases. Metastasis was observed in 23.65% (n = 4017) and hematological malignancies were reported in only 2.49% (n = 423) of the patients [Table 1].

The cervical lymph nodes were aspirated in maximum patients accounting for 60.45% (n = 10,269) and the least (n = 643) aspirated were the inguinal lymph nodes (3.78%). Maximum cases of tubercular lymphadenitis (58.7%) and reactive lymphadenitis (57.8%) were also observed in the cervical lymph nodes [Table 2].

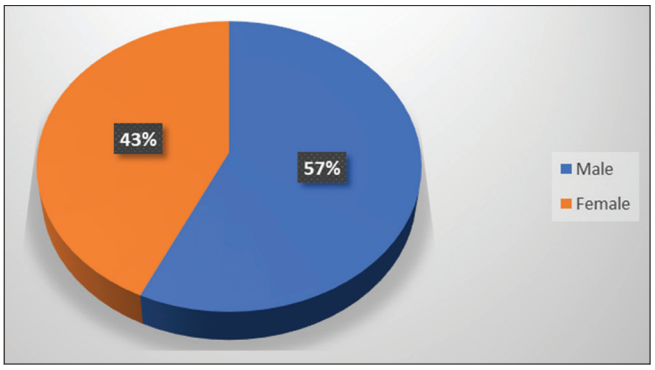

Figure 1: Showing the male and female distribution of patients

Metastatic lesions were seen predominantly in the cervical group of lymph nodes (69%), followed by the supraclavicular lymph nodes (26.7%) [Table 2]. Among the metastatic lesions, squamous cell carcinoma was seen in maximum number of patients [Table 3].

Reactive lymphadenitis and metastatic lesions were seen more in female patients, whereas tubercular lymphadenitis was observed more in the male gender [Table 4].

Unfortunately, the annual number of metastatic lesions showed an increasing trend in our institute [Figure 2].

Discussion

Peripheral lymphadenopathy is among one of the most common aspirations done in routine practice for all age groups. Owing to the ease, simplicity of the technique, and the fast results that it gives, it has now become the first investigation ordered to evaluate enlarged peripheral lymph nodes. In our country where infections, especially tuberculosis, are still rampant, it is imperative to give a quick diagnosis to the clinician so that the treatment can be initiated at the earliest.

The study population comprised more of males (57%) than females (43%). This is similar to the studies done by Giri and Singh,[3] Hirachand *et al*.,[4] and Patil *et al*.[5] However, Pavithra and Geetha[6] have shown a female preponderance in their study.

In the present study, 73.85% of aspirates showed features of benign pathology and only 26.14% of the cases showed hematological and metastatic malignancies. Ahmed *et al*. (86.4%),[7] Khan *et al*. (92%),[8] Fatima *et al*. (73.2%),[9] and Bapotara and Jhaveri (95%)[10] have also reported a predominance of benign aspirates in their studies. Lymph nodes being the drainage as well as limiting point for infections are frequently involved when the body faces any foreign organism. This explains the fact that a reactive, tubercular,

Table 1: Cases according to the diagnosis in relation to the age group

Age group (years)	Reactive, % (*n*)	Tubercular, % (*n*)	Metastasis, % (*n*)	Hematological malignancy, % (*n*)	Parasitic etiology, % (*n*)
0-10	12.7 (906)	3.2 (171)	0	0.55 (2)	14.3 (2)
11-20	15.7 (1123)	31.1 (1681)	0.09 (4)	16.1 (68)	7.1 (1)
21-30	20.4 (1458)	46.7 (2522)	1.04 (42)	11.1 (47)	7.1 (1)
31-40	26.4 (1881)	12.4 (671)	3.1 (125)	5.4 (23)	35.7 (5)
41-50	14 (998)	4.9 (264)	12.9 (520)	5.2 (22)	28.6 (4)
51-60	5.6 (402)	1.07 (58)	37.6 (1512)	39 (165)	7.1 (1)
61-70	3 (220)	0.5 (28)	40.1 (1613)	21.7 (92)	0
71-80	2 (140)	0.04 (2)	4.75 (189)	0.9 (4)	0
81-90	0.08 (6)	0	0.3 (12)	0	0
Total	7134	5397	4017	423	14

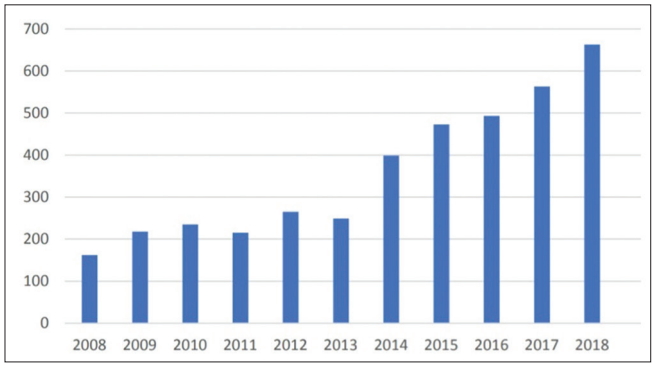

Figure 2: Showing the annual incidence of metastatic lesions in peripheral lymphadenopathy

and occasionally, a parasitic etiology is reported in maximum cases of enlarged peripheral lymph nodes.

The maximum number of patients (23.96%, *n* = 4070) in our study belonged to the age group of 21–30 years. Bapotara and Jhaveri[10] and Badge *et al*.[11] have also reported the same. A minimum number of patients (0.10%) were in the age group of 81–90 years.

Cervical lymph nodes were the most common group of lymph nodes involved (60.45%), followed by the axillary (20.01%). Similar findings were observed by Patil (69%),[5] Pavithra and Geetha (85.27%),[6] Chandanwale *et al*.[12] (96.72%), Kocchar *et al*. (80.2%),[13] and Mohanty and Wilkinson (66.48%).[14]

Reactive lymphadenitis was the most common pathology seen in our study accounting for 42% of cases. Our results were similar to the study conducted by Naiding *et al*.[15] (reactive: 42.25% and tubercular: 33.15%), Ahmed *et al*.[7] (reactive: 53.6% and tubercular: 32.8%)), Hirachand *et al*.[4] (reactive: 41.55% and tubercular 28%), Kocchar *et al*.[13] (reactive: 41.25% and tubercular: 35.7%), and Biradar and Masur[16] (reactive: 55.62% and tubercular: 23.75%). However, Khajuria *et al*.[17] (reactive: 37.2% and tubercular: 52.3%) and Fatima *et al*.[9] (reactive: 16.1% and tubercular: 52.7%) have reported tubercular lymphadenitis as the most common pathology. The difference in the relative frequency of pathologies among the different studies can be explained by the difference in the sociodemographic profile of the study population. A maximum number of patients showing reactive pathology (26.4%) were in the age group of 31–40 years in our study.

Tubercular lymphadenitis (61.96%) was the second common pathology seen with maximum cases in 21–30 years age group in our patients, which is similar to the studies by Duraiswami *et al*.,[18] Badge *et al*.[11] and Bapotara and Jhaveri,[10] and Paliwal *et al*.[19] Tuberculosis showed a male preponderance in our study in contrast to the study conducted by Duraiswami *et al*.,[18] Badge *et al*.,[11] and Bapotara and Jhaveri[10] but similar to Paliwal *et al*.[19] Clinically, the cervical region was the most commonly affected site by tubercular lymphadenitis. This is in concordance with studies of Bezabih *et al*.[20] and Paliwal *et al*.[19] Tubercular lymphadenitis remains the most common form of extrapulmonary tuberculosis. In a country like ours which comes in the endemic zone for tuberculosis, granulomatous lymphadenitis is also treated as tubercular unless proved otherwise. Referred to as "scrofula" in early literature, tubercular lymphadenopathy remains the most common cause of cervical lymph node enlargement in majority of the developing countries, especially in India. Diagnosing as well as treating tubercular lymphadenitis can get challenging due to certain reasons. Differentiating it from other causes of lymphadenopathy may be difficult, as common features of tubercular lymphadenitis like multiplicity, matting, and caseating necrosis are neither specific nor sensitive. A definitive diagnosis of tubercular lymphadenitis requires the demonstration of mycobacteria by Ziehl-Neelsen stain which may not be found in every case, which later proved to be of tubercular etiology. Furthermore, despite treatment, the lymphadenopathy often persisted or even increased.[21] The pathogenesis of tubercular lymphadenitis, especially cervical, remains obscure. Kent[22] blamed the lymphohematogenous spread of pulmonary tuberculosis to be responsible for cervical tubercular lymphadenitis. However, Powell[23] disagreed with this explanation and said that this entity was merely a hyperreaction of the lymph nodes against a previous pulmonary infection with tuberculosis. Another plausible explanation was given by Yew and Lee[24] They suggested that tubercle bacilli used the lymphatic route and since the supraclavicular and the

Table 2: Distribution of cases according to the cytomorphological diagnosis in relation to the site

Site	Reactive, % (*n*)	Tubercular, % (*n*)	Metastatic, % (*n*)	Hematological malignancies, % (*n*)	Parasitic etiology, % (*n*)	Total
Cervical	57.8 (4123)	58.7 (3168)	69 (2772)	46.8 (198)	57.1 (8)	10,269
Supraclavicular	11.2 (799)	14.4 (780)	26.7 (1074)	4.7 (20)	7.1 (1)	2674
Inguinal	5.4 (387)	1.7 (93)	2.2 (89)	17.2 (73)	7.1 (1)	643
Axillary	25.9 (1825)	25.1 (1356)	2 (82)	31.2 (132)	28.6 (4)	3399
Total	7134	5397	4017	423	14	

Table 3: Distribution of cases showing metastasis in relation to the morphology

Metastatic lesion	Number of cases	Percentage
Squamous cell carcinoma	2776	69.10%
Adenocarcinoma	187	4.65%
Poorly differentiated carcinoma	1054	26.24%

Table 4: Distribution of cases according to the cytomorphological diagnosis in relation to the gender

Diagnosis	Male, % (*n*)	Female, % (*n*)
Reactive	39.9 (3832)	44.8 (3302)
Tubercular	34.3 (3300)	28.4 (2097)
Metastatic	22.8 (2188)	24.8 (1829)
Hematological malignancies	3 (285)	1.8 (138)
Parasitic etiology	0.05 (5)	0.12 (9)
Total	9610	7375

cervical lymph nodes were in the lymphatic route draining the major portions of the lung, it is obvious that they get enlarged in pulmonary tuberculosis. This falls short of explaining the pathogenesis of cervical tubercular lymphadenitis in the absence of pulmonary tuberculosis. Golden and Vikram[25] proposed that tubercular lymphadenitis could be a consequence of direct exposure to the infection.

Metastatic lesions contributed to 23.65% of cases in our study. Bulk of the patients (40.1%, $n = 1613$) were in the age group of 61–70 years, followed by patients in the age group of 51–60 years contributing 37.6% of cases. The older age groups beyond 70 years and the younger age groups below 40 years showed lesser cases of metastatic lesions. The possible explanation of the elder patients showing lesser cases is that the life expectancy in our country is approximately 65 years for males and 68 years for females.[26] Except for certain malignancies which are prevalent in the pediatric age group, for many cancers, the incidence increases with advancing age. It is an established fact that there are certain cellular events that take place with aging like genomic instability, shortening of the telomere length, epigenetic alterations, mitochondrial dysfunction, reduced DNA repair activity, and stem cell exhaustion. Stem cells also undergo alterations with age. Adult tissue stem cells have been exposed to genotoxic stimuli for a longer period of time. Their DNA repair activity is therefore exhausted and/or markedly reduced over time. This makes them susceptible to genomic instability and therefore to the development of cancer.[27]

The annual number of cases increased progressively over the study period in our institute which is similar to the study by Khajuria *et al*.[17] The projected number of new cancer cases in India from 2011 to 2026 will increase from 0.589 million in 2011 to 0.934 million in 2026 in males and in females from 0.603 to 0.935 million. The main factors behind this dismal projection are the increasing population with enhanced survival, urbanization, and globalization.[28] The international agency for research on GLOBACAN project has predicted that the burden of cancer patients will be more than 1.7 million by 2035.[29]

Among the metastatic lesions, squamous cell carcinoma was the most common (69.10%) which correlates with the findings of the studies done by Patil *et al*. (75.7%)[5] and Pavitra *et al*. (56.25%).[6] The high incidence of squamous cell carcinoma can be due to the fact that tobacco chewing and smoking is very prevalent in this region which has a definite role to play in the etiopathogenesis of malignancies of the oral cavity, upper respiratory tract, and lung. Most of the carcinomas in the head-and-neck region are squamous cell carcinomas which carry a high rate of occult nodal metastasis. Carcinoma of the oral cavity, especially, has a predilection for early metastasis to the cervical lymph nodes. It therefore becomes the most important independent variable in determining the survival of patients in cancers of the head-and-neck region. Therefore, though the percentage of metastatic lesions (23.65%) seems to be numerically insignificant, the fact that lymph node metastasis forms an integral part of the clinical staging of malignant tumors (TNM Staging) which has a prognostic and therapeutic significance for the patient, it makes the cytomorphological diagnosis imperative for the patient.

Conclusion

FNAC of enlarged peripheral lymph nodes is a safe, cost-effective, simple investigation that gives quick results determining the nature of the pathology. It does not require any special preparation or surgical procedure and has a good patient compliance as no hospital admission is needed. It is a convenient and reliable alternative to open biopsy of the lymph node. It is reliable in diagnosing both nonneoplastic and neoplastic lesions of the lymph node. Enlarged peripheral

lymph nodes can be the first indication of malignancies where both the clinician and patient may be unaware of the occult primary and in malignancies of the lymph node. Our study highlighted the cytomorphological pattern of lymphadenopathy in the patients in our hospital. Although the most common diagnosis was reactive lymphadenitis, the burden of tubercular lymphadenitis is significant. This is unfortunate as the government has been running a national program for it. It clearly indicates that much work needs to be still done and possibly the current guidelines need to be reconsidered and revised regarding this disease.

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Conflicts of interest

There are no conflicts of interest.

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