Histological Surprises in Benign Cytologies after Lymph Node Biopsy—Surgeon’s Knife Improving Patient Care

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Abstract Lymphadenopathy can be due to multitude of causes. Owing to the high prevalence of infectious diseases in India, and malignancy being a life threatening cause for lymphadenopathy; accurate diagnosis is important in preventing delay or misdiagnosis and in improving patient care, thereby increasing longevity with quality. Fine needle aspiration cytology (FNAC) is the first line investigation commonly done. Should the doctor be contented with the benign FNAC or is a lymph node biopsy needed in this age? The aims of this study are the following: (1) to study the spectral pattern of lymph node biopsies done in a surgical oncology unit of tertiary care centre, (2) to assess the yield of malignant cases from lymph node biopsy and (3) to compare the reliability of benign FNAC with lymph node biopsy. Cross-sectional study of 114 cases that underwent lymph node biopsy during the year 2014, at the Surgical Oncology Department of St. John’s Medical College Hospital, Bangalore. Lymph node biopsies were done in the outpatient department (OPD) under local anaesthesia or in the operation theatre under local anaesthesia/monitored anaesthesia care based on the clinical condition of the patient. Regional lymph node dissections, central node biopsy, patients with known case of malignancy were excluded. Specimen sent for histopathological study and immunohistochemistry (IHC) done when needed. 58.8% were males among study population, age ranging from 15 to 80 years, 57% cervical and 29.8% axillary lymph node

biopsies done. Sixty-seven percent (67%) of biopsies done in OPD. Thirty-three percent (33%) of biopsies in the operation theatre among which 60.5% under local anaesthesia only. 35.1% cases were reactive hyperplasia, 24.6% lymphomas with non-Hodgkin’s lymphoma being the commonest, 13.2% metastatic disease with adenocarcinoma being the commonest. 72.7% of the supraclavicular nodes were malignant. 47.4% of subjects had prior FNAC of the lymph node. Twenty-five percent (25%) of the reactive hyperplasia’s on FNAC ($p < 0.0001$), 33.3% of inadequate FNAC ($p = 0.003$) and 75% of atypical cells in FNAC turned to be malignant on lymph node biopsy with a discordance rate of 20.3%. Lymph node size didn’t correlate with neoplasm. In our study, benign cytologies were malignant on biopsy and statistically significant. Lymph node biopsies are reliable in detecting malignancy and subtyping of the disease. In the presence of strong clinical suspicion, lymph node biopsy is essential even when the FNAC is promisingly benign in a country with limited resources. Lymph node biopsy can be safely done in OPD under local anaesthesia at a lower cost, resulting in a reliable diagnosis thereby improving patient care.

Keywords Lymphadenopathy · Lymph node biopsy · Benign cytologies · Aspiration cytology

Introduction

Lymphadenopathy, a common outpatient clinical finding can be due to malignancy, infections, autoimmune, miscellaneous, iatrogenic causes [1]. Many times in clinical scenarios with no diagnosis possible, pathological analysis of lymph nodes gives a clue to the diagnosis. Malignant causes of the lymphadenopathy can be primary lymphoproliferative disorders or secondary metastatic diseases sometimes from an unknown

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primary neoplasm, thereby aiding in diagnosis of a hidden cancer. Lymph node analysis also helps in diagnosis of the infectious agents like *Mycobacterium tuberculosis* [2]. Fine needle aspiration cytology (FNAC) is commonly employed as it is easy, less expensive, less traumatic, absent scarring and increased patient compliance. Lymph node biopsy is considered complex than FNAC by patients and even clinicians owing to the need for anaesthesia, operating room, increased cost, hospitalisation and less patient compliance [3]. Lymph node biopsies are commonly done in the operation theatre. In countries with high prevalence of infectious diseases and economic constraints for further advanced investigations, it is a common tendency to be satisfied with a benign FNAC report. How much can a benign cytology report be relied upon? Can lymph node biopsy procedure and cost be simplified? Our aims are to study the histopathological spectral pattern of lymph node biopsies in a surgical oncology unit, to study the yield of malignant cases from lymph node biopsy and the reliability of fine needle aspiration cytology versus lymph node biopsy.

Materials and Methods

This is a descriptive cross-sectional study of all the cases that had undergone lymph node biopsy in the department of surgical oncology of a tertiary care teaching hospital from January 1st to December 31st 2014. Case records of these patients were reviewed. Patients with known malignant primaries, who underwent central lymph node biopsies, regional lymph node dissection were excluded. Some of the patient's had prior fine needle aspiration cytology of the lymph nodes. Patients underwent lymph node biopsy in outpatient clinic under local anaesthesia or in operating room under local anaesthesia with or without monitored anaesthesia care based on the clinical condition of the patient. Lymph nodes were sent for histopathological analysis. Immunohistochemistry was done based on histopathological morphology when necessary. Two-tailed Fisher's test done for testing statistical significant occurrence of malignancy between FNAC and biopsy. Crosstabulation done between FNAC and biopsy for sensitivity, specificity, positive predictive value, negative predictive value, concordance and discordance.

Results

One hundred fourteen (114) patients underwent lymph node biopsy, 67 (58.8%) cases were male and 47 cases (41.2%) were female. Forty-eight cases (42.1%) were between 21 and 40 years of age, 35 cases (30.7%) were between 51 and 70 years of age. Seventy-six cases (66.7%) underwent lymph node biopsy in outpatient department (OPD). Thirty-eight

cases (33.3%) underwent biopsy in the operation theatre (OT) among which 23 biopsies (60.5%) were done under local anaesthesia only; 15 cases (39.5%) under monitored anaesthesia care with sedation. The peripheral lymph nodes commonly biopsied were cervical: 65 cases (57%), axillary: 34 cases (29.8%), supraclavicular: 11 cases (9.6%) and inguinal: 4 cases (3.5%). Nodes commonly biopsied in the OPD were cervical 78.5% (51/65 cases) and in the OT was axillary 47.4% (18/34 cases). Lymph node histopathology was benign in 71 cases (62.3%) and neoplastic in 43 cases (37.7%). Reactive hyperplasia 35.1% (40/114) is the commonest histopathological diagnosis followed by lymphoma 24.6% (28/114), metastatic disease 13.2% (15/114). The spectrum of histopathological diagnosis is shown in Table 1.

Subtypes of lymphomas and metastatic diseases in the lymph nodes is shown in Table 1. Non-Hodgkin's lymphoma (NHL) (15/114 cases, 13.2%) was more common with diffuse B cell lymphoma being the commonest subtype, adenocarcinoma was the commonest metastatic disease. The spectrum of benign versus malignant histopathologies in different lymph nodes is shown in Fig. 1.

Lymphomas (20 cases, 17.5%) was commonest in cervical lymph nodes, metastasis was equally seen in cervical (8 cases, 7%) and supraclavicular lymph nodes (8 cases, 7%). Prevalence of malignancy was highest in the supraclavicular lymph node biopsies (8/11 cases, 72.7%) as seen in Fig. 2.

Beyond 50 years of age, the prevalence of malignant histopathology increases more than the benign conditions as shown in Fig. 2. Eighty percent of non-Hodgkin's lymphoma (12/15 cases), 66.7% of metastatic disease (10/15 cases), 61.5% of Hodgkin's lymphoma (8/13 cases) were seen in patients older than 50 years. 30.8% of Hodgkin's lymphoma (4/13 cases) was seen less than 40 years of age.

Out of 114 cases, the lymph nodes were in the size between 1 and 2 cm in 83 cases (72.8%), greater than 2 cm in 19 cases (16.6%) and subcentimetric in 12 cases (10.5%). Among 43 malignant cases, the lymph nodes were in size between 1 and 2 cm in 29 cases (67.4%), greater than 2 cm in 6 cases (14%) and subcentimetric in 8 cases (18.6%).

In our study, 54 cases (47.4%) had fine needle aspiration cytology (FNAC) of the lymph node done prior to the biopsy. In 24 cases of reactive hyperplasia in FNAC, tuberculosis was seen in 1 case (4.1%) and lymphomas in 6 cases (25%), $p < 0.0001$ as shown in Fig. 3. Among the 6 cases of FNAC that were haemorrhagic aspirate, 2 cases (33.3%) were malignant (1 adenocarcinoma, 1 lymphoma) $p = 0.003$. Among the 4 cases of FNAC showing atypical cells, 75% (3 cases) were malignant (2 lymphoma, one small cell carcinoma) $p = 0.22$. One case of lymphoproliferative disorder on FNAC was metastatic neuroendocrine carcinoma on biopsy. Sensitivity, specificity, positive predictive value, negative predictive value, concordance and discordance, between FNAC and biopsy are shown in Table 2.

Table 1. The spectrum of histopathological diagnosisHistopathological spectrum of lymph node biopsies $n = 114$ (%)

Non-neoplastic causes 71 (62.3)

Reactive hyperplasia	40 (35.1)
Granulomatous lymphadenitis	13 (11.4)
Tuberculosis	10 (8.8)
Kikuchis disease	4 (3.5)
Dermatopathic lymphadenitis	4 (3.5)
HIV adenitis	1 (0.9)
Amyloidosis	1 (0.9)

Neoplastic causes 43 (37.7)

Lymphoma 28 (24.6)

Hodgkin's lymphoma	13 (11.4)
Non-Hodgkin's lymphoma	15 (13.2)

Subtypes of Non-Hodgkin's lymphoma

Diffuse B cell lymphoma	6
Mantle cell lymphoma	3
T cell lymphoma	3
Follicular cell lymphoma	2
Lymphocytic lymphoma	1

Metastatic disease 15 (13.2)

Adenocarcinoma	4
Squamous cell carcinoma	3
Lung carcinoma	3
Neuroendocrine carcinoma	1
Prostate Adenocarcinoma	1
Ovarian carcinoma	1
Poorly differentiated carcinoma	1
Megakaryoblastic leukaemia	1

Percentages given in the parenthesis
 n number of cases

Discussion

One hundred fourteen patients have undergone lymph node biopsy in our surgical oncology department. The number of lymph node biopsies was highest among the younger age group followed by elderly. The most common peripheral lymph node biopsied in our study was cervical lymph nodes followed by axillary nodes as seen in other studies [4, 5]. Presence of enormous amount of lymph nodes in the cervical region makes this site common for lymphadenopathy and subsequent biopsy. Cervical lymphadenopathy is sometimes the first manifestation of underlying carcinoma with corresponding primary in the ENT in 80% and in the aerodigestive

tract in 10% [6]. In our study, cervical lymph node biopsies were commonly done in the OPD owing to the superficial location of the nodes with easy accessibility, less bleeding, feasible under local anaesthesia in outpatient clinic setting.

In the OT, axillary lymph node biopsy was more commonly done, probably owing to their deep location, presence of fatty tissue in the axilla, increased local anaesthetic requirement, prolonged dissection time in the axillary region compared to cervical region makes it sometimes difficult for an OPD procedure if the patient's condition and cooperation is doubtful, thereby necessitating monitored anaesthesia care with little sedation in the OT. In our series, 60.5% of lymph node biopsies done in the OT did not require sedation or

Fig. 1. Spectrum of histopathological benign versus neoplastic diagnosis in various lymph nodes. Total number of cases 114, number of cases in individual group given in the parenthesis

Fig. 2. Age-wise spectrum of histopathological diagnosis in lymph node biopsies

anaesthesia; they were managed under local anaesthesia only. The advantages of doing a lymph node biopsy under local anaesthesia are lower costs compared to general anaesthesia with requirement of operating room [7], absence of general anaesthesia and intubation side effects, rapid recovery time, no need for hospital stay, patients under local anaesthesia can be safely repositioned as per surgeon's requirement, also there is no significant difference in the yield of lymph nodes or wound infection and seroma formation between procedure done under general anaesthesia or local anaesthesia [7, 8].

Biopsy of the entire lymph node is advised rather than wedge resection as lymph node capsular breach can lead to extranodal tumour growth [6]. Majority of the lymph node biopsies in our study was non-neoplastic with reactive hyperplasia being the commonest as found in other studies [9]. Reactive hyperplasia occurs due to various antigenic stimuli to the lymph node causing hyperplasia in any age group, raising the suspicion of malignancy in doubtful clinical cases.

Inguinal lymph nodes have the lowest and supraclavicular lymph nodes have the highest yield of malignancy as seen in other studies [10]. Lymphomas were most commonly seen in cervical lymph nodes. Some studies suggest that incidence of malignancy increases in lymph nodes as their size increases [10, 11], but in our study there was no significant association between size of the lymph node and neoplasia, hence a small

lymph node cannot be ignored always. Non-Hodgkin's lymphoma (NHL) was the commonest cause of neoplastic lymphadenopathy, with diffuse large B cell lymphoma being the commonest subtype [12] while in most of other studies, Hodgkin's lymphoma was the commonest lymphoma and diffuse large B cell was the commonest NHL [13, 14]. Above 50 years of age, NHL followed by metastatic disease and Hodgkin's lymphoma were the commonest causes of lymphadenopathy. The prevalence of NHL increases as the age of the patient increases [12]. The incidence of NHL is increasing in Indian registries; the reason for this increase is still unclear whether it is real or due to improved diagnosis, increasing AIDS prevalence, change in classification [15, 12].

In tropical countries, tuberculosis remains the common cause of benign lymphadenopathy [16, 17]. But in our study, granulomatous inflammation and acid-fast bacilli proven tuberculosis are fourth and fifth common causes of lymphadenopathy owing to the referral pattern, since ours is an oncology centre. In primary care setting, the prevalence of malignancy among lymph node enlargement is low as 1–2% [18], but in the referral centre setting as ours, the prevalence of malignancy increases among the lymph node biopsies [19], and it reaches 30–40% when the clinical suspicion of malignancy is high [20]. Despite the low prevalence of malignancy in primary care setting, it is the main concern for the clinician

Fig. 3. Malignant histopathology in benign reactive hyperplasia FNAC's and hemorrhagic FNAC's. Twenty-five percent of reactive hyperplasia cytologies were malignant on histopathology ($p < 0.0001$) and 33.3% of haemorrhagic cytologies were malignant on histopathology ($p = 0.003$)

Table 2. Crosstabulation between FNAC and biopsy

Crosstabulation FNAC vs biopsy		Histopathological examination		Total <i>n</i> (%)
		Malignancy <i>n</i> (%)	Benign <i>n</i> (%)	
FNAC	Malignancy	14 (56%)	0 (0%)	14 (25.9%)
	Benign	11 (44%)	29 (100%)	40 (74.1%)
Total <i>n</i> (%)		25 (100%)	29 (100%)	54 (100%)
Sensitivity			56.00%	
Specificity			100%	
Positive predictive value			100%	
Negative predictive value			72.50%	
Concordant (agreement)			79.63%	
Discordant (disagreement)			20.37%	

and patient. Therefore, lymph node enlargement cannot be ignored more so in the presence of known risk factors for malignancy. Beyond 50 years of age, the incidence of neoplastic conditions increases more than benign conditions with lymphoma being the highest in our study, the reason being all cases with known primary malignancy were excluded from our study; therefore, the real burden of metastatic disease is not reflected in this study.

One fourth of reactive hyperplasia in FNAC was actually lymphomas on lymph node biopsy. There were no false positive cases of malignancy on FNAC [21] but there was discordance in one case where lymphoproliferative picture on FNAC turned out to be metastatic neuroendocrine cancer on histopathology. Our study reported a low sensitivity for FNAC with discordance rate of 20.3% between FNAC and biopsy. Studies have shown 91% sensitivity for FNAC's in diagnosing lymphomas [22] and greater precision for diagnosing metastatic disease than lymphomas in FNAC [23, 24]. Studies have reported discordance between FNAC and biopsy in differentiating between lymphomas and metastatic disease [25, 26]. False negative cases in FNAC are commonly seen in low grade lymphomas [27]. Many times malignancies can be associated with granulomatous pictures, and malignant cells mimicking epithelioid histiocytes pose diagnostic challenge in FNAC, and thereby warranting lymph node biopsy [28]. One study has suggested overall diagnostic accuracy of 82.2% and overall discordance rate of 17.8% for malignancy, 85% diagnostic accuracy of reactive lymphoid hyperplasia, diagnostic accuracy of 100% for metastatic cases in FNAC of the lymph nodes [29]. Inadequacy of FNAC can be due to inadequate sampling, fibrosis, sampling from the reactive areas, lack of cellular architecture in the aspirates [26]. FNAC with immunohistochemistry also has been found to have discordance due to inadequate sampling and false positive cases [30]. There are studies which are for and against FNAC; in our study, there is discordance between benign FNAC and their corresponding lymph node biopsy which showed good statistical significance. Hence, FNAC should be supplemented with lymph

node biopsy which is a simple and low cost procedure as seen in our experience, in suspected cases for malignancy. A benign FNAC would mislead the actual diagnosis and cause delay in the diagnosis, treatment, progression of disease and increasing the economic burden. These deficiencies in FNAC necessitate lymph node biopsy even in twenty-first century stressing the importance of surgeon's knife in improving patient's care.

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