Histopathological spectrum of non- neoplastic and neoplastic lesions of lymph nodes: A retrospective and prospective study

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Abstract

Introduction: Lymphadenopathy is a clinical manifestation of regional or systemic diseases and signifies as an excellent clue to the important hidden disease. Lymph node biopsies are usually done to know the etiology of lymphadenopathy, which may be neoplastic and non-neoplastic. The neoplastic disorders are mainly lymphohematogenous malignancies and metastases while the causes of non-neoplastic lymphadenopathy are more varied such as infections (bacterial, viral, fungal), drug reactions

Material and Methods: This was retrospective and prospective study in a tertiary care hospital where lymph node biopsies of 100 patients were analysed. For retrospective study, the archived slides and blocks were retrieved for duration of 5 years from September 2011 to August 2015. For prospective study lymph node biopsy specimens of all indoor and outdoor patients received in Department of pathology from September 2015 to August 2017 were included.

Results: Age of patients, ranged from 1 years to 74 years with maximum number of patients in the third decade, followed by second and fourth decade of life, with a male to female ratio of 1.08:1. Of 100 lymph node biopsies analysed, 85 patients had non- neoplastic pathology while 15 patients had neoplastic lesions.

Conclusion: In our study non – neoplastic causes vastly out numbered neoplastic pathologies. Among non-neoplastic, the most frequent cause of lymphadenopathy was reactive hyperplasia. Neoplasic causes included lymphoma and metastatic malignancies. Lymph node biopsy plays an important role in establishing the cause of lymphadenopathy.

Keywords: Lymphadenopathy, Biopsy, Lymphomas, Granulomatous lymphadenitis.

Introduction

Lymphadenopathy is a clinical manifestation of regional or systemic diseases and signifies as an excellent clue to the important hidden disease.[1] It is one of the prevalent and important clinical presentation of outdoor patients, attending the clinics in most of the biopsies are usually done to know the etiology of lymphadenopathy, which may be neoplastic and non-neoplastic. The neoplastic disorders are mainly lymphohematogenous malignancies and metastases while the causes of non-neoplastic lymphadenopathy are more varied such as infections (bacterial, viral, fungal), drug reactions.

Clinically, lymphadenopathy may be visceral or peripheral. Peripheral lymphadenopathy are usually biopsied as they are readily accessible, on the other hand visceral lymphadenopathy demands major surgical processes or advanced imagining techniques for detection.

Once received in pathology department, a detailed examination of lymph node specimen is carried out routinely including accurate gross and microscopic examination since they may reflect pathological process in organs and tissues they drain.[2] Intrathoracic lymph nodes are biopsied on account of lesions in lungs and submandibular lymph nodes for pathology in oral cavity. Mesenteric lymph nodes are biopsied to exclude any intra abdominal visceral lesions. The most proximal draining peripheral node or nodes (auricular, axillary, inguinal and popliteal) should be examined in cutaneous disorders.[3] This study was carried out analyse histopathological spectrum of various neoplastic and non-neoplastic lesions of lymph nodes

Material and Methods

This was a retrospective and prospective study carried out in a large tertiary care hospital in northern India. For prospective study lymph node biopsy specimens of all indoor and outdoor patient received in Department of pathology from September 2015 to August 2017. The retrospective study was carried out on lymph node biopsies retrieved from the the department archieves received for duration of 5 years from September 2011 to August 2015. A total of 100 cases were taken for study including all age groups. Clinical information was obtained from the pathological requisition forms and clinical records of the patients. H and E stained sectof ion every case was reviewed.

Special stains including Ziehl Neelsen, periodic acid Schiff and Gomori's methenamine silver were used where indicated. Immunohistochemistry (IHC) was performed using relevant antibodies depending upon the histomorphological features for prospective study after assessing the gross features of the specimen sent to the department of pathology, the tissue was fixed in 10% formalin, dehydrated with ascending grades of alcohol, cleared in xylene and embedded in paraffin, and there after 3 to 5 micron thick paraffin sections were cut on a rotary microtome, dewaxed and stained with H and E, special stains and IHC.

Observations and Results

The present study was based on the histological examination of lymph node biopsy from 100 patients presenting with lymphadenopathy with study duration of 7 years.

The age of the patients varied from one year to 74 years. In this study, 52% patients were male and 48% were females. Maximum number of male patients were in the age group of 0-10 years and 31-40 years, whereas maximum number of female patients were in the age group of 21-30 years followed by the age group 11-20 years.

Table 1: Age sex wise distribution of patients

Age Group	Male	Female	Number of patients	%
0-10	10	03	13	13%
11-20	09	08	17	17%
21-30	07	22	29	29%
31-40	10	07	17	17%
41-50	04	04	08	08%
51-60	06	03	09	09%
61 and above	06	01	07	07%
Total	52	48	100	100%

Distribution of lesions

In this study of 100 patients, lesions of lymph nodes were mainly distributed as non-neoplastic and neoplastic. Out of 85 (85%) of patients with non-neoplastic diseases, 52 patients were diagnosed with reactive lymphadenitis, followed by granulomatous lymphadenitis in 33 patients.

Among neoplastic lesions, 13 (13%) patients were diagnosed with lymphoma. Nine (09%) patients had Non- Hodgkin Lymphoma and 04 (04%) were of Hodgkin lymphoma. Remaining 2 (2%) cases were of metastatic malignancy.

Table 2: Distribution of different typesof lesions of lymph nodes

S. No.	Etiology	No. of Patients	Percentage
1	**Non-neoplastic lesions** a) Reactive lymphadenitis b) Granulomatus lymphadenitis	 52 33	 52 % 33 %
2	**Neoplastic lesions** A) Hemato lymphoid malignancies a) Hodgkin lymphoma b) Non-Hodgkin lymphoma B) Metastatic malignancies	 04 09 02	 04% 09% 02%
	Total	100	100%

Clinical Presentation

Along with lymph node enlargement, fever was observed in 69 patients, 63 had weight loss and anorexia, 52 had cough, while 7 had night sweats. The duration of lymphadenopathy varied widely, but in general ranged from two weeks to six months in most of the patients.

Sites of lymphadenopathy

Cervical lymph nodes were the most frequently involved site in our study (56%). This was followed in decreasing order of frequency by mesenteric 23% and inguinal (08%), axillary (08%), supraclavicular (03%) and right iliac (01%) and pelvic node (01%).

Table 3: Sites of lymph node enlargement

Site	Number of patients	Percentage
Cervical	56	56%
Supraclavicular	03	03%
Axillary	08	08%
Mesenteric	23	23%
Pelvic	01	01%
Inguinal	08	08%
Right iliac node	01	01%

Reactive lymphoid hyperplasia

Reactive lymphoid hyperplasia was diagnosed in 52 patients (52%). The age of the patients in this group ranged from 4 years to 74 years with majority of the patients being in the first decade of life.

Out of 52 patients, maximum number of patients were males (57.70%) followed by females constituting 42.30% of cases. Cervical lymph nodes were the most commonly involved groups of lymph nodes, followed by mesenteric and inguinal group of lymph nodes.

Cervical lymph nodes were the site of lymphadenopathy in patients with Castleman`s disease and dermatopathic lymphadenitis.

Granulomatous lymphadenitis

A diagnosis of granulomatous lymphadenitis was made in 33 patients (33%). The age group of patients in this group varied from 9 years to 24 years. The maximum numbers of patients were in the 3rd decade of life. Half of the patients had a very low socioeconomic status. Out of the 33 patients, maximum number of patients were females (75.76%) followed by males (24.24%).

Clinical features

Other than lymph node swelling, 28 patients presented with moderate fever of at least a month duration, 14 showed weight loss while 12 showed anorexia. Past history of pulmonary tuberculosis could be elicited in eight patients.

Erythrocyte sedimentation rate(ESR) was raised in all 34 patients. Chest X-ray was done in 20 patients out of whom 13 patients showed evidence of either hilar lymph node enlargement or pulmonary pathology in the form of fibrocavitary lesion or consolidation.

Out of 33 patients, 12 patients were anemic. The differential count revealed lymphocytosis in 19 patients. The most frequently involved group of lymph nodes were the cervical nodes which was seen in 66.67% cases followed by axillary (12.12%), mesenteric (15.15%) and inguinal lymph nodes.

Acid fast bacilli (AFB) positivity on Ziehl-Neelsen staining

Ziehl-Neelsen (ZN) staining for tubercle bacilli was performed in all cases.The overall AFB positivity was 27.27% Patients were divided into Group 1, Group 2 Group 3, and group 4 according to the pattern observed.

Table 4: Distribution of granulomatous lesions of lymph node

Group	Pattern	Number	Total %
1	Nercotising granulomatous inflammation, AFB positive	5	15.15
2	Necrotising granulomatous inflammation, AFB negative	19	57.57
3	Non-Necrotising granulomatous inflammation, AFB positive	4	12.13
4	Non-Necrotising granulomatous inflammation,AFB negative	5	15.15

Lymphomas

Lymphomas were diagnosed in 13% (13) of the total cases in our study. Out of these cases, 69.23% (09) non-Hodgkin's lymphomas and 30.77% (04) cases of Hodgkin's lymphomas.

The age of the patients varied from 18 years to 65 years. Equal number of patients were in the sixth decade and fourth decade of life. Number of male patients were 08 (61.53%) whereas number of female patients were 05 (33.47%).

IHC was done for subtyping in these cases. Three cases were diagnosed as diffuse large B cell lymphoma.

Cases in which IHC was not done, were catagorised as high (4cases) and low grade (1 case) without any subtyping.

In Hodgkin lymphoma, 2 cases were diagnosed as mixed cellularity and two as nodular sclerosis subtypes of classical Hodgkin Lymphoma.

Table 5: Sites of Lymphoma Cases

Site	No of cases (% of cases)
Cervical	05 (38.46%)
Supraclavicular	01 (07.70%)
Axillary	02 (15.37%)
Mesenteric	01 (07.60%)
Inguinal	03 (23.17%)
Right iliac	01 (07.70%)
Total	13 (100%)

In lymphoma, most common site of lymphadenopathy was cervical lymph nodes, which was involved in 38.46% of cases, followed by inguinal lymph nodes in 23.17% of cases, axillary lymph node in 15.37% of cases and supraclavicular and right iliac in 07.70% of cases.

Lymph node metastasis

Two cases of metastatic malignancies were diagnosed. The age of the patients in this group was, one male aged 63 years and one female aged 60 years. Among metastatic carcinomas, both were adenocarcinoma. 1 case was from adenocarcinoma stomach and other from adenocarcinoma colon. Site of lymph node biopsy in these cases were cervical lymph nodes and mesenteric lymph nodes.

Demographic distribution

Out of 100 patients 23 (23%) were from urban and 77 (77%) from rural Population. Rural patients predominated in this study with the overall rural: urban ratio being 4:3.3.

Discussion

Lymphadenopathy is a symptom which frequently presents in primary care settings and affects patients of all ages. Enlargement of peripheral lymph nodes is a frequent clinical presentation of a various pathological conditions including systemic inflammatory conditions or hemato lymphoid malignancies and metastatic malignant process.

We evaluated the histological spectrum of 100 lymphadenopathy patients, who underwent excision biopsy and correlated with demographic and clinical details.

Neoplastic and non neoplastic distribution

In this study, 100 lymph node biopsies were analysed, out of which 85 % were non neoplastic, while 15% patients had neoplastic pathology. Similar findings were also observed by Damle RP et al,[4] Patel K et al[5] and Tiwari A et al.[6]

In a study by Patel K et al, out of total 266 cases, 166 cases were non neoplastic and 100 were neoplastic. Similarly in a study by Tiwari A et al , out of total 140 cases, 43 cases were neoplastic and remaining 97 cases were non neoplastic .In a study conducted by Damle RP et al non-neoplastic lesions were more common comprising 265 cases (80.06%) and neoplastic lesions were 66 cases (19.93%). In contract, study done by Olu-Eddo AN et al (2006)[7] revealed malignancy being the predominant lesion constituting 55% of cases.

Age and Sex Incidence

Out of total of 100 patients, 52 were males (52%) and 48 were females (48%) with a male to female ratio of 1.08:1. with slight preponderance of male patients. In a study by Roy A et al. (2013),[8] 63.2% were male patients and 36.8% were female (M:F ratio of 1.7:1) .

In the present study, age of the patients varied from 4 to 74 years with a mean age of 45 years. In a study by Damle RP et al. (2017), the age of patients varied from 3 to 85 years and in a study by Jamin P et al. (2014),[9] the age of patients varies from 1 month to 74 years.

Out of the 100 patients with, 23 were from urban area and 77 were from rural area. Rural patient predominated in the study, as study was carried out in a hospital, catering more to the rural population.

Sites of lymphadenopathy

In the present study, cervical lymph nodes were involved in 56 cases (56%), mesenteric in 23 cases (23%), inguinal in 08 cases (08%), axillary in 08 cases (8%), supraclavicular in 03 cases (03%), right iliac node in 01 case (01%) and 01 case (01%) of pelvic node. Similarly in a study by Patel K et al (2016)[5] cervical region was the commonest sites involved followed by mesenteric, axillary, inguinal and other regions. In a study by Jaimin P et al. (2014),[9] cervical group of lymph nodes constituted the most common nodal group. Similarly in a study by Vidiyadhar R et al. (2016),[10] cervical region was the commonest site involved.

Cervical lymph nodes are the sites of drainage for many primary faci of infections and malignancies. Reactive lymph node enlargement due to trivial conditions like poor oral and dental hygiene, upper respiratory tract infections including pharyngitis, laryngitis and tonsillitis commonly localizes to cervical lymph node. Tuberculosis is also a common infection that localizes frequently to the cervical lymph nodes. In older patients, various malignancies of the oropharynx, nasopharynx, larynx, esophagus and lung can lead to enlargement of cervical lymph nodes by metastasis.

Causes of lymph node enlargement

Reactive lymphadenitis was the commonest diagnosis in over half of our patients (52%), followed by granulomatous pathology in one- third of patients, (33%) while 15% patients had neoplastic etiology. Similar results were obtained by Dalmle R et al (2016),[4] 53.8% patients were diagnosed with reactive lymphadenitis and majority of cases were observed in 21-30 years age group.

Also in a study by Vachhani AB et al[11] reactive lymphadenitis predominated with 51% cases, followed by granulomatous pathology in 24% cases, while 25% patients had neoplastic etiology.

However in a study by Shrestha et al (2009),[12] the most common cause of lymphadenopathy was tubercular lymphadenitis (42 percent), followed by reactive lymphadenitis (23 percent), metastatic deposits (10 percent), non-specific lymphadenitis (3 percent), non-Hodgkin's lymphoma (2 percent), and lymphadenitis due to various other factors (7 percent). Kamat (2011)[13] analysed 244 lymph node biopsies in his study, granulomatous pathology was the commonest diagnosis in over half of patients (58.19 percent), followed by reactive lymphadenitis in one third of patients (30.73 percent), while 11% patients had neoplastic etiology .

In our study, tuberculosis was the second most common pattern constituting 33% of cases but several authors have reported tuberculosis as the predominant cause of lymph node enlargement.

Reactive lymphoid hyperplasia

Lymph nodes undergo reactive changes whenever they are challenged by microbiologic agents, cell debris, or foreign material introduced into the wounds or into the circulation. The histological picture of reactive lymph nodes may be quite variable depending on the degree of stimulation, the size and number of germinal centers and on whether the sample is taken mainly from a germinal center or from the interfollicular tissue. Biopsy from a node consist predominantly of large follicles with active germinal centers containing many small and large cleaved and non- cleaved cells.

Reactive hyperplasia was the most common diagnosis made in the present study. The most frequent site involved was cervical lymph nodes.

Dermatopathic Lymphadenopathy

In the presence of chronic skin disorders, lymph node enlargement is common. Histologically, there is follicular and paracortical hyperplasia and accumulation of phagocytized granules of melanin. Pigment from tattoos may mimic melanin accumulation. T In our study there was 1 case diagnosed as dermatopathic lymphadenitis out of total 100 cases. Similarly a low incidence was seen in a study by Vijyadhar R et al.[10]

Castleman disease

Castleman disease (CD) was first diagnosed in 1956 by Benjamin Castleman, who identified a group of patients with single hyperplasic mediastinal lymph nodes with small germinal center similar to Hassall's corpuscles of the thymus.

Castleman's disease (CD) is characterized by a benign proliferation of the lymphoid tissue that may be localized or unicentric Castleman's disease (UCD) and disseminated or multicentric Castleman's disease (MCD). Histologically, CD can be divided as hyaline-vascular (HV) type, plasma cell type, or a mixed type. Our case was hyaline vascular variant of CD.

In our study there was 1 case diagnosed as Castleman's disease, which is similar to a study conducted by Vidyadhara R et al. (2016)[10] Most common site involved was cervical, which is similar to a study conducted by Venkataramanan CG et al(2017).[14] All 10 cases were of hyaline vascular type in study conduted by Venkataramanan CG et al.(2011)[14] similar to our study with hyaline vascular type of castleman disease.

Granulomatous lymphadenitis

Although the morbidity and mortality from tuberculosis has steadily declined over the past decade, yet the disease continues to persist as a major public health problem. Tubercular lymphadenitis is one of the common manifestations of extra- pulmonary tuberculosis. It accounts for 30 % of all cases of extra-pulmonary disease and about 5% of all cases of tuberculosis.

The age group of the patients in our study varied from 1 year to 62 years. Hemaltha A et al (2014)[15] also reported a wide age spectrum among the patients with tuberculous lymphadenitis in her study.

Females vastly outnumbered males, which is comparable to a study by G Subha et al.[16]

Cervical lymph nodes were most commonly (44.44%) affected by tubercular pathology in our study, similar to study done by G Subha et al (2017) and Das et al (1990).[17]

Most cases of tubercular lymphadenitis in our study showed epithelioid cell granulomas along with caseous necrosis (72.72%), similar to a study done by Eshete A et al (2011).[18] Epithelioid granulomas without caseation necrosis was seen in 27.27% of the patients in our study. Das et al (1990), in his study, reported this type of pattern in 25.3% patients.

Although the presence of epithelioid granulomas along with caseous necrosis is the hallmark for the diagnosis of tuberculosis, in lesions that show only epithelioid granulomas, the diagnosis of tuberculosis should still be considered especially in countries with a high incidence of tuberculosis like India.

AFB Positivity

It is clear that for tubercle bacilli to be diagnosed microscopically, their number should be 10,000 to 1,00,000/ml of material. So absence of AFB in sections showing an otherwise histological picture suggestive of tuberculosis, should not weigh against the diagnosis and treatment of tuberculosis.

The sections containing epithelioid cell granulomas without necrosis revealed the least AFB positivity because the cell mediated immunity of the patient enable to mount a granulomatous response against the tubercle bacilli. In contrast the sections containing only necrotic material, show maximum AFB positivity because of a compromised immune condition of the patient and lack of a granulomatous response.

Although granulomas may also be seen in other conditions like mycoses, leprosy and sacroidosis, in India, however, the prevalence of tuberculosis being very high, finding epithelioid cell granulomas is highly indicative of tuberculosis unless it is proved otherwise.

Lymphomas

A well-processed hematoxylin and eosin (H&E) stained part of an excised lymph node is the mainstay of pathologic diagnosis in case of lymphoma usually, the

diagnosis of difficult lesions relies heavily on a careful evaluation of the underlying architecture. Lymphoma diagnoses are lesser about cytological detail and far more about altered architecture.

In the present study, lymphoma comprised of 13% cases. Non-Hodgkin's lymphoma was seen in 09 patients, while 04 had Hodgkin's lymphoma. In a study conducted by Sibanda EN et al [19], Kamat GC et al[13] and Tiwari M et al[20] number of cases of lymphoma reported, were comparable with our study.

Malignancies have been the predominant cause of lymphadenitis in developed countries than developing countries like India because of racial and genetic factors. In comparison to the study by Roy A et al (2013),[8] and Sinclaire S et al (1974)[21] lymphoma constituted 44.5%, and 63.29% which were very higher incidence than our present study, which can attributed to the fact that these were conducted in research centre.

Non hodgkin lymphoma

NHL comprises a large group of heterogenous neoplasm of lymphoid tissue. NHL have several types and far more common (62%) than HL. 90% are B cell type, with disseminated nodal spread. Extra nodal spread is quite common.

Hodgkin's Lymphoma (HL)

Hodgkin lymphoma is a malignant neoplasm of the lymphoid system, meeting the usual criteria for malignancies, including production of RS cells and potential to spread to many sites.

In Nodular Lymphocyte Predominance Hodgkin's Lymphoma, there is almost total obliteration of nodal architecture by a vaguely nodular process, an attenuated rim of residual node is compressed against the nodal capsule.

In Nodular Sclerosing form the classic histopathologic criteria are prominent nodularity, presence of lacunar RS cell variant and broad collagen bands.

In Mixed Cellularity, there is a diffuse obliteration of nodal architecture without capsular thickening or broad bands of parenchymal fibrosis. Classical RS cells are seen, in a background of lymphocytes, eosinophils, histiocytes, plasma cells or neutrophils.

In lymphocytic- rich Classical Hodgkin lymphoma, there is background rich in small lymphocytes along with the presence of RS cells.

In lymphocyte- depleted, histologic section show depletion of the reactive component of the neoplasm. There is predominance of RS cells compared with depletion of background lymphocytes.

In the present study, 4 cases of Hodgkin's lymphoma were diagnosed on biopsy. The age of the patients were varied 13 years to 65 years. The male patient were 08 (61.33%) and female patients were 05 (38.47%)

Our study shows more cases of Non Hodgkin lymphoma than Hodgkin lymphoma, which is similar to study conducted by Roy et al[8] and Jaimin P et al.[9]

Occasionally a false positive observation of Hodgkin's lymphoma may also be seen in some instances. These mainly include cases of peripheral T-cell lymphoma (PTCL), reactive hyperplasia caused by infectious mononucleosis and metastatic carcinoma.

Lymph node metastasis

Metastatic carcinoma, melanoma and sarcoma are easily recognized from histopathological evidence or suspected on clinical ground, but poorly differentiated neoplasm of this type may resemble malignant lymphoma. Cohesion of tumor cells, sinus involvement and clearly defined interface with normal lymphoid tissue are all strongly suggestive of carcinomas .IHC may be required for diagnosis. Metastatic carcinomas are CD45 negative and generally stain for cytokeratins.

Metastasis to lymph nodes was seen in 02 (02%) patients in the present study.

Metastatic carcinomas were adenocarcinoma in our study, which is similar to a study conducted by Vidyadhar R et al.[10] In our study, incidence of metastatic malignancies was low, which is similar to study conducted by Jaimin P et al (2014),[9] G Suba et al (2017)[16] and Tiwari A et al(2016).[20] Metastatic deposits were from adenocarcinoma stomach in one case and unknown primary in second case, in our study. This is comparable to study conducted by Vidyadhar R et al,[10] with 4 cases having metastatic deposits from stomach and 1 case with unknown primary. There is a wide variation in metastatic tumours affecting lymph nodes. The study of Khan AU (2011)[22] reports 32%, Shaikh et al (2010)[23] 27 % and Na DG (1997)[24] reported 43.8 % of metastatic tumors in lymph nodes.

Conclusion

Etiology of lymphadenopathy, can be divided into neoplastic and non – neoplastic causes. In our study non – neoplastic causes vastly out numbered neoplastic pathologies. Among non-neoplastic, the most frequent cause of lymphadenopathy was reactive hyperplasia. The most frequent cause of lymphadenopathy diagnosed was reactive hyperplasia which constituted about 52% of cases followed by granulomatous lymphadenitis in 33%, lymphomas in 13% and metastatic malignancies in 02% cases.

Patients aged 63 and 60 years were diagnosed with metastatic adenocarcinoma. One was from adenocarcinoma stomach and other one from unknown primary. Lymph node biopsy plays an important role in establishing the cause of lymphadenopathy.

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