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Original Research Article

Morphological Spectrum of Lymph Node Lesions: A Histopathological Analysis at a Tertiary Care Center

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Abstract

Background: Lymphadenopathy is a normal clinical finding that can be caused by reactive hyperplasia, tuberculosis, metastatic malignancy or lymphoma. Materials and methods: This study of a tertiary care center is a retrospective histopathological examination of the morphological spectrum of lymph node lesions.

Method: A total of 365 excised lymph node biopsies during the three-year period were analysed for the age, sex, site of biopsy, clinical indication, and final histopathological diagnosis. When necessary, special stains and immunohistochemistry were carried out.

Results: 238 cases of non-neoplastic lesion and 127 cases of neoplastic lesion were found (65.2 and 34.8 respectively). Commonest diagnosis was reactive lymphoid hyperplasia (116/365, 31.8%) followed by tuberculous lymphadenitis (82/365, 22.5%). Of the neoplastic lesions, there were 62 cases of metastatic carcinoma (17.0%), 43 cases of non-Hodgkin lymphoma (11.8%) and 18 cases of Hodgkin lymphoma (4.9%). The most common involvement of the lymph nodes was cervical (57.8 %), then axillary (16.4 %) and inguinal (11.8 %). Metastatic carcinoma was a more frequent condition in older adults, especially those over 50 years old ($p<0.001$), while tuberculous lymphadenitis was more common in younger adults. Immunohistochemistry proved to be crucial for subtyping lymphomas and to determine primary sites in some metastatic tumours.

Conclusion: It is concluded that lymph node biopsy is still a useful tool in the diagnosis of differentiating a reactive, infective and malignant cause of lymphadenopathy.

Keywords: Lymph Node, Lymphadenopathy, Reactive Hyperplasia, Tuberculous Lymphadenitis, Lymphoma, Metastatic Carcinoma.

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Introduction

Lymphadenopathy is a very common finding in practice and can be a normal immune response, an infection, an autoimmune disorder, metastatic tumour or a primary lymphoid malignancy [1]. Fine needle aspiration is helpful for initial evaluation, however, when architecture is necessary for diagnosis, such as suspected lymphoma and granulomatous disease, excision biopsy is important [2]. To examine the architecture, follicular pattern, sinus changes, granulomas and necrosis, and to look for metastatic deposits and cytological atypia, in histopathological examination of lymph nodes. The differential diagnosis can be wide, and in the diagnosis of lymphoid neoplasms, according to the current WHO classification, immunohistochemistry can be necessary [3,4]. Granulomatous lymphadenitis is a frequent cause of lymph node enlargement in areas with a high incidence of tuberculosis, and metastatic carcinoma is the most frequent cause in older patients [5]. Local histopathological audits support the understanding of the most common reasons for lymphadenopathy and support appropriate biopsy decisions. The objective of the present study was to study the morphological spectrum of lymph node lesion in tertiary care center and its correlation with age, sex and site.

Materials and Methods

The current study is a retrospective observational study that involved all excised lymph node biopsies that arrived in the Department of Pathology. Biopsies of inadequate quality, repeated biopsies from the same patient and autolyzed tissues and

cytology-only cases were excluded. Information about the clinical features: age, sex, location of lymph nodes, duration of the swelling, presence of systemic symptoms and known malignancy was obtained from requisition forms and records. All specimens were fixed in 10% neutral buffered formalin, grossed, paying special attention to size, cut surface, necrosis and matting and processed routinely. Histological sections of hematoxylin and eosin- were studied. When necessary, Ziehl-Neelsen stain, periodic acid-Schiff stain, Gomori methenamine silver stain and immunohistochemistry were performed.

The lymphoid neoplasms were classified on the basis of morphology and immunophenotype. Diagnoses were compiled into categories of reactive/non-specific, granulomatous, suppurative, metastatic carcinoma, Hodgkin's, non-Hodgkin's and other rare lesions. The data was analyzed by SPSS version 26. Frequencies and percentages were computed. The associations between diagnostic category and age group as well as site were evaluated using chi-square test with $p<0.05$ considered as statistically significant.

Results

A total of 365 lymph node biopsies were evaluated. The age ranged from 2 to 82 years, with a mean age of 34.2 +/- 18.6 years. There was a slight male predominance. Cervical lymph nodes were the most common site, followed by axillary and inguinal nodes. Non-neoplastic lesions were more common than neoplastic lesions. Reactive lymphoid hyperplasia was the commonest diagnosis overall. Tuberculous lymphadenitis was the second most frequent lesion and commonly showed epithelioid granulomas with caseous necrosis. Acid-fast bacilli were demonstrated in 21 cases. Metastatic carcinoma formed the largest neoplastic category and was commonest in patients above 50 years. Squamous cell carcinoma deposits predominated in cervical nodes, while adenocarcinoma deposits were frequent in supraclavicular and abdominal nodes. Non-Hodgkin lymphoma was more common than Hodgkin lymphoma. Immunohistochemistry enabled separation of diffuse large B-cell lymphoma, follicular lymphoma, and small lymphocytic lymphoma and T-cell lymphoma patterns.

Table 1: Age and site distribution of lymph node biopsies

Variable	Category	Number (%)
Age group	<=15 years	42 (11.5)
Age group	16-30 years	118 (32.3)
Age group	31-50 years	105 (28.8)
Age group	>50 years	100 (27.4)
Site	Cervical	211 (57.8)
Site	Axillary	60 (16.4)
Site	Inguinal	43 (11.8)
Site	Supraclavicular	28 (7.7)
Site	Abdominal/mediastinal	23 (6.3)

Total biopsies = 365.

Table 2: Histopathological spectrum of lymph node lesions

Diagnosis	Number	Percentage
Reactive lymphoid hyperplasia	116	31.8
Tuberculous lymphadenitis	82	22.5
Other granulomatous lymphadenitis	18	4.9
Suppurative/necrotizing lymphadenitis	22	6.0
Metastatic carcinoma	62	17.0
Non-Hodgkin lymphoma	43	11.8
Hodgkin lymphoma	18	4.9
Other rare lesions	4	1.1

Tuberculous lymphadenitis was diagnosed on morphology with supportive special stain or clinicopathological correlation.

Table 3: Diagnostic category by age group

Diagnosis group	<=30 years	31-50 years	>50 years	p-value
Reactive/non-specific	82	38	18	<0.001
Tuberculous/granulomatous	58	30	12	0.002
Metastatic carcinoma	4	15	43	<0.001
Non-Hodgkin lymphoma	10	15	18	0.08
Hodgkin lymphoma	6	8	4	0.31

Values are number of cases in each age category.

Discussion

The aim of this study was to assess the prevalence of non-neoplastic and neoplastic lesions in excised lymph nodes, and to determine the most common non-neoplastic and neoplastic lesions that were diagnosed. Non-neoplastic lesions were more prevalent than neoplastic lesions, and the most common non-neoplastic and neoplastic lesions diagnosed were reactive hyperplasia and tuberculous lymphadenitis, respectively. The same trends were seen on lymph node series in several histopathology-based tertiary centers [6].

Reactive lymphoid hyperplasia was most common in children and young adults. Follicular hyperplasia, paracortical hyperplasia and sinus histiocytosis were the patterns seen morphologically. Preserved architecture, polymorphous nature of the cell population, and the lack of destructive atypical infiltrates are helpful in distinguishing reactive lesions from lymphoma [7].

The second most frequent diagnosis was tuberculous lymphadenitis which was often associated with cervical nodes only. Granulomas were caseating and this suggested tuberculosis, however when special stains were undertaken only some were positive, highlighting the importance of clinicopathological correlation and/or microbiological confirmation where possible [8]. In endemic areas, tuberculous infection and lymphoma can present similar constitutional symptoms with similar nodal enlargement, so it is necessary to make the diagnosis through tissue diagnosis [9].

Neoplastic lesions were most common in the form of metastatic carcinoma and it was highly associated with older age. Squamous cell carcinoma metastasis to the cervical nodes occurred frequently and were associated with head and neck primary tumors, but in the case of adenocarcinoma, correlation with imaging and immunohistochemistry was necessary [10].

This cohort of patients had a higher number of non-Hodgkin lymphoma than Hodgkin lymphoma. In order to be classified correctly, it is necessary to combine the morphology, immunophenotype and genetic characteristics [11,12]. Limitations of this study include the retrospective design and the limited immunohistochemical data in older cases, as well as the absence of molecular data. However, it does validate the diagnostic importance of excisional biopsy in lymphadenopathy and gives helpful local epidemiological data [13-15].

The age distribution of this study proved to be a valuable diagnostic pattern; a high proportion of patients with reactive and tuberculous lesions were found in younger patients, while there was a marked rise in metastatic carcinoma after 50 years. The use of this age association should be used to direct clinical suspicion, but it does not replace biopsy; lymphoma and tuberculosis can present at any age [1,2].

The most frequent site of biopsy was the cervical nodes. This is due to its accessibility and the frequency of upper aerodigestive infections, metastasis of tuberculosis and head-neck malignancy. Hence, cervical lymphadenopathy should be carefully evaluated clinically, examining the oral cavity, pharyngeal, thyroid and pulmonary systems [5,8].

Follicular, paracortical and sinus histiocytic patterns were included in reactive lymphoid hyperplasia. These patterns can sometimes be clues to underlying immune stimulation, a viral infection, dermatopathic reaction or drainage from inflammatory sites. The preservation of the nodular architecture and the presence of a polymorphous cellular composition were important features which favoured benign reactive process [7].

Tuberculous lymphadenitis still continues to be a significant category of diagnosis in this context. The classical caseating granulomas were easily spotted and acid-fast bacilli could not be found in all cases. This limitation is well recognised, as the bacillary load can be low in the node and culture or molecular testing may be required if the morphology suggests the presence of a bacterial node but stain results are negative [8].

The other group was small, but included suppurative and necrotizing lymphadenitis, which have important differential diagnosis such as bacterial infection, Kikuchi disease, cat scratch disease and necrotizing granulomatous infection. For no misclassification to occur with the diagnosis of tuberculosis or lymphoma, clinicopathological correlation and selective special stains must be performed.

The most common neoplastic group was metastatic carcinoma. Squamous cell carcinoma that has spread to cervical nodes should be presumed as an origin in the upper aerodigestive tract until otherwise proven; adenocarcinoma deposits can require the use of immunohistochemistry to rule out a primary in breast, lung, gastrointestinal tract, thyroid or gynecological organs. This is a good example of how a stepwise IHC can be useful in practice [10].

Excision biopsy remains an advantage over cytology, in particular for lymphoma, where all of these: architecture, growth pattern and immunophenotype are required. Antibody panel direction and decreased diagnostic delay can be achieved by diffuse effacement, follicular colonization, nodularity, sclerosis and sinusoidal patterns [3,4].

Many tertiary care biopsy series have also shown that non-Hodgkin's lymphoma (NHL) is more common than Hodgkin's lymphoma (HL). It is clinically important as the two major types of DLBCL, follicular and SLL, and the T-cell lymphomas have significantly different therapeutic strategies and prognosis [11-13].

The study is limited in that it is retrospective and molecular characterization was not complete. Despite this, it shows that lymph node biopsy is still a high yield procedure when used in combination with clinical/radiological and laboratory parameters. Adopting a uniform reporting system of the lymph nodes could facilitate communication with physicians and oncologists [14,15].

Some clinical duration of lymphadenopathy was reported but the lymphadenopathy which persisted, increased in size or was generalized was more likely to be excised biopsy. This selection is meant to give the reader an understanding of the reasons why the number of neoplastic lesions in biopsy series tends to be higher than the number in unselected outpatient lymph node enlargement.

The gross examination of lymph nodes was helpful. Tuberculous, cheesy necrosis were matted nodes, firm gray-white were regarded as a diagnosis of possible lymphoma or metastatic carcinoma, and cystic or keratinous deposits as a diagnosis of metastatic squamous cell carcinoma. Yet gross appearance was always discounted as a diagnostic technique prior to microscopy. The major problem in reactive nodes was partial involvement by the lymphoma. Follicular hyperplasia can also resemble follicular lymphoma and paracortical expansion can be confused with T-cell lymphoma. When the morphology is ambiguous, immunohistochemistry of the following antigens is helpful: CD20, CD3, BCL2, BCL6, CD10 and Ki-67 [3,11].

For Hodgkin's lymphoma, Reed-Sternberg cells and context of the inflammation was required for diagnosis and the cells were then confirmed immunochemically. The key to differentiating classical Hodgkin lymphoma (cHL) from anaplastic large cell lymphoma (ALCL), metastatic carcinoma and EBV-associated reactive lesions is the different treatment, as there is a significant difference in treatment [13].

The lymph node may be the first tissue diagnosis of an occult primary tumor in the case of metastatic carcinoma. Indiscriminate staining of a limited antibody panel, depending on site, morphology and clinical findings, is better. This will help save tissue and ensure better interpretation. The study calls for the preservation of the role of excisional biopsy in spite of the progress of imaging and cytology. Fine needle aspiration is a useful technique for the diagnosis of many metastatic and granulomatous lesions, but architectural evaluation is necessary for the classification of lymphoma and to differentiate between reactive and neoplastic processes in a reactive versus neoplastic differentiation [2,4].

Site-specific interpretation was of special value in metastatic disease. The presence of supraclavicular adenocarcinoma led to the consideration of thoracic and abdominal primaries, while the presence of axillary metastasis in women necessitated careful exclusion of breast carcinoma. These clinicopathological considerations are used to choose the most useful immunohistochemical markers [10].

There is a need for future studies to integrate histology with microbiology, the flow cytometric and molecular tests. Stain-negative granuloma can be confirmed by mycobacterial culture or nucleic acid amplification and flow cytometry and clonality testing provide support in difficult cases of lymphoma. Accurate diagnosis is likely to be improved by integrated diagnostics in addition to morphology [4,8].

Timely use of ancillary tests in equivocal morphology and adequate grossing and preservation of nodal architecture are also all necessary for the QA in lymph node histopathology. Small biopsies and disorganized or disseminated nodal tissue can make the sinus pattern difficult to recognize and may make diagnosis of capsular invasion or focal granulomas impossible and repeat biopsy should be performed when clinical suspicion is still high even with an inconclusive report [3,4].

Conclusion

The most common histopathological patterns of lymph node lesions were reactive lymphoid hyperplasia and tuberculous lymphadenitis and the most common neoplastic lesional was metastatic carcinoma. While useful clinical clues were provided by age and site, definitive diagnosis was still essential to the diagnosis by using excision biopsy with special stains and immunohistochemistry.

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