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ORIGINAL RESEARCH

A Comprehensive Analysis of the Histopathological Spectrum of Lymphadenopathy: Insights from Northern India

Dr. Neha Ahuja[1], Dr. Monika Yadav[2], Dr. Parul Ahuja[3], Dr. Sangharsh Rao[4]

[1]Associate Professor, Department of Pathology, Rama Medical College, Hospital & Research Centre, Kanpur, U.P., India
[2]Post Graduate Students, Department of Pathology, Rama Medical College, Hospital & Research Centre, Kanpur, U.P., India
[3]Associate Professor, Department of Oral Maxillofacial Surgery, Dr. B.S. Kushwah Institute of Medical Sciences, Kanpur, U.P., India
[4]Assistant Professor, Department of Anatomy, Rama Medical College, Hospital & Research Centre, Kanpur, U.P., India

Corresponding Author
Dr. Neha Ahuja
Associate Professor, Department of Pathology, Rama Medical College, Hospital & Research Centre, Kanpur U.P., India

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ABSTRACT

Background: Lymphadenopathy constitutes a prevalent clinical issue, and biopsies conducted to ascertain the etiology of lymph node enlargement may reveal either neoplastic or non-neoplastic conditions. The former predominantly comprise lymphohematogenous malignancies and metastatic diseases, whereas the etiologies of non-neoplastic lymphadenopathy are diverse. The objective of this research was to ascertain the histopathological spectrum of Lymphadenectomies. **Materials and Methods:** This study adopted a descriptive cross-sectional design, reviewing 1000 cases of histologically diagnosed peripheral lymph node biopsies conducted within the Department of Pathology at the Rama Medical College, Hospital & Research Centre, Kanpur, U.P., during the period spanning from January 2022 to December 2024. Specimens obtained from surgical resection that included lymph node dissection were excluded from the study. **Results:** Neoplastic lesions were predominantly observed, accounting for 51.5% (515 instances) of the cases. Within this category, non-Hodgkin lymphoma constituted 31.1% (311 instances), Hodgkin lymphoma represented 10.8% (108 instances), and metastatic lesions comprised 9.6% (96 instances). The non-neoplastic lesions accounted for 48.5% of cases, comprising a total of 485 instances. Specifically, non-specific reactive lymphoid hyperplasia constituted 22.1% (221 cases), while other reactive or specific lymphoid hyperplasia represented 7.2% (72 cases). Furthermore, tuberculous lymphadenitis was observed in 18.4% (184 cases) of instances, and other granulomatous lesions were identified in 0.8% (8 cases). **Conclusions:** Lymph node biopsy is integral in determining the etiology of lymphadenopathy. Within the cohort of biopsied nodes, lymphomas constituted the most prevalent condition. This was followed, in descending order of frequency, by non-specific reactive hyperplasia, tuberculous lymphadenitis, and metastasis.

Key Words: Hodgkin lymphoma, lymphadenopathy, metastasis, reactive hyperplasia, tuberculous lymphadenitis.

INTRODUCTION

Lymphadenopathy represents a prevalent clinical issue, and biopsies are frequently performed to ascertain the etiology of nodal enlargement, which may be classified as either neoplastic or non-neoplastic. Neoplastic disorders primarily encompass lymphohematogenous malignancies and metastases. Conversely, the etiologies of non-neoplastic lymphadenopathy are more diverse, encompassing infections (bacterial, viral, fungal), adverse reactions to pharmaceuticals (including specific vaccines), lipid storage diseases, and an extensive range of miscellaneous non-neoplastic lymphoproliferative conditions, such as Castleman disease, Rosai-Dorfman disease, Kimura disease, Kikuchi-Fujimoto disease, and systemic lupus erythematosus (SLE). In

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clinical terms, lymphadenopathy can manifest as either peripheral or visceral. Peripheral lymphadenopathies are readily identified through routine physical examinations and frequently undergo biopsy due to their accessibility for lymphadenectomy, a minor surgical intervention. Conversely, the identification of visceral lymphadenopathy necessitates the employment of sophisticated imaging modalities or the undertaking of a laparotomy procedure. Within the context of peripheral lymph node biopsy, nodes located in the upper body regions (such as cervical, supraclavicular, and axillary) are more frequently selected for biopsy compared to those situated in the lower limbs (including popliteal, inguinal, or femoral). This preference is due to the higher likelihood of obtaining a definitive diagnosis from upper body nodes, whereas lower limb nodes often exhibit nonspecific reactive or chronic inflammatory and fibrotic alterations. Despite this, there is limited knowledge about the range of diseases affecting lymph nodes from this region. Consequently, this study was conducted with the objective of assessing the range of histopathological diagnoses associated with peripheral lymph node biopsies.

MATERIALS AND METHODS

This investigation was a descriptive cross-sectional study comprising 1000 cases of peripheral lymph node biopsies, which were diagnosed within the Department of Pathology at a prominent tertiary care teaching hospital, Rama Medical College, Hospital & Research Centre located in Kanpur, Uttar Pradesh, North India, spanning the period from January 2022 to December 2024. Cases were sourced from the departmental archives and subsequently subjected to a comprehensive review. For all patients, the biopsy was conducted as an outpatient procedure, resulting in minimal morbidity and no mortality. The clinical details were recorded from histopathology section, and all cases underwent examination following staining with hematoxylin and eosin (H&E). Specialized histological stains, such as Periodic Acid-Schiff, Gomori's Methenamine Silver and Ziehl-Neelsen were employed as necessary stains. Immunohistochemistry (IHC) was conducted utilizing pertinent antibodies in accordance with the histomorphological characteristics. The array of antibodies comprised cluster of differentiation (CD) markers including CD3, CD5, CD10, CD15, CD20, CD23, CD30, CD56, CD68, Epithelial Membrane Antigen, Leukocyte Common Antigen (LCA), cytokeratin, Bcl-2, Bcl-6, cyclin D1, lambda light chain, kappa light chain, Ki-67, smooth muscle actin, terminal deoxynucleotidyl transferase (TdT), desmin, vimentin, Human Melanoma Black (HMB)-45, chromogranin, synaptophysin, and S100. IHC was conducted utilizing the avidin-biotin peroxidase technique, with pre-treatment involving microwave heating. All cases of lymphoma were classified in accordance with the standard World Health Organization (WHO) classification of hemato-lymphoid malignancies, as established in 2008. The study did not include cases of En bloc lymph node dissection if there was established evidence of primary tumors or if such tumors were associated with primary manifestations elsewhere in the body.

RESULT

During the period under review, a total of 1000 lymph node biopsies were received, representing 1.6% of the entirety of surgical biopsy specimens. Among the observed cases, 61.3% (613 instances) were male, and 37.7% (377 instances) were female, resulting in a male-to-female ratio of 1.6:1. The age range for males was from 15 to 75 years, while for females it was from 15 to 85 years. The majority of cases were observed within the age group of 21 to 40 years, comprising 312 cases, which accounts for 31.2% of the total. Conversely, the fewest cases were recorded in the age group above 75 years, totaling 28 cases (2.8%). Among the total of 1000 lymph node biopsies examined, neoplastic lesions were predominately observed, constituting 51.5% (515 cases) of the sample as illustrated in Chart No.1. This category included non-Hodgkin lymphoma (NHL) at 31.1% (311 cases), Hodgkin lymphoma (HL) at 10.8% (108 cases), and metastatic lesions at 9.6% (96 cases) as illustrated in Chart No. 2. The non-neoplastic lesions constituted 48.5% (485 cases) of the total, encompassing 22.1% (221 cases) of non-specific reactive lymphoid hyperplasia, 18.4% (184 cases) of tuberculous lymphadenitis, 7.2% (72 cases) of other reactive or specific lymphoid hyperplasia, and 0.8% (8 cases) of other granulomatous lesions, as illustrated in Chart No. 3.

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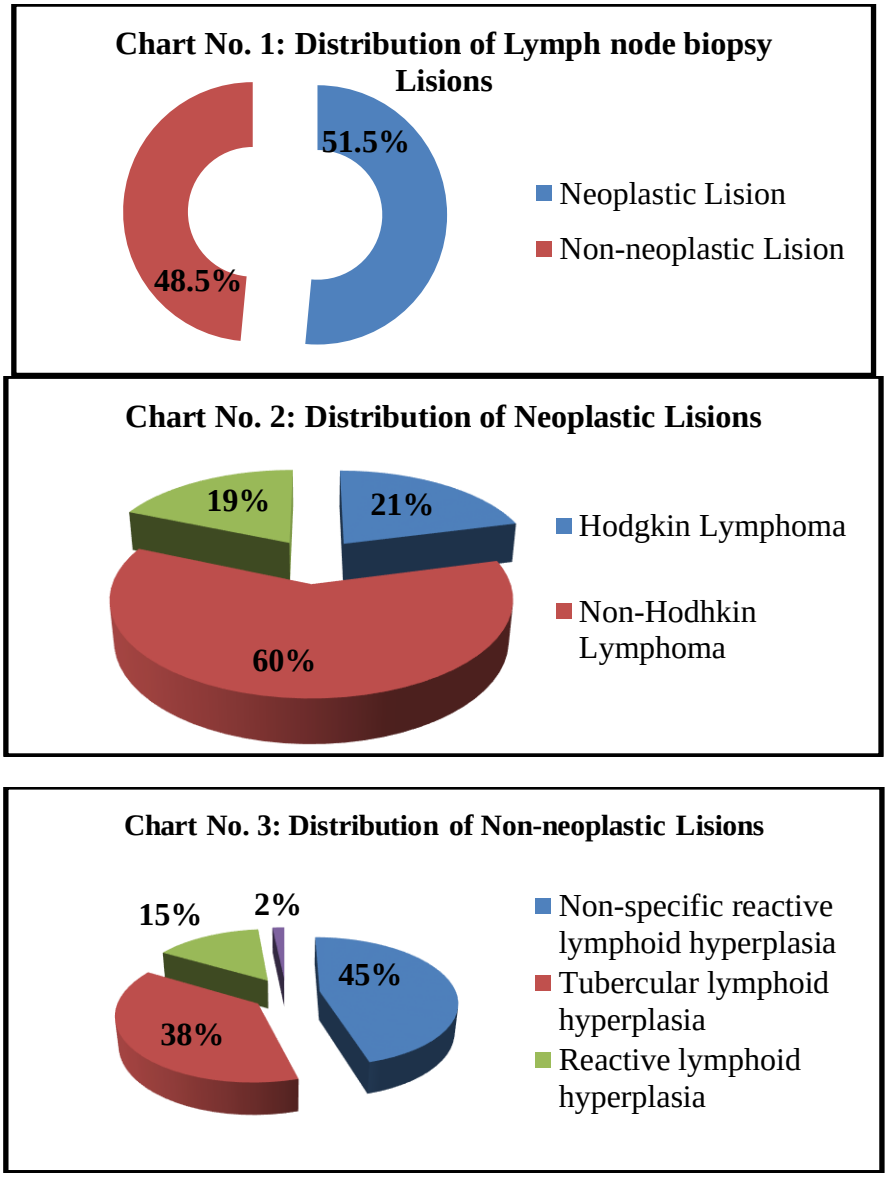

Within the category of non-neoplastic lesions (485 cases), reactive lesions were predominantly observed, constituting 65.2% (316 cases) of the total. A predominance of males was observed, with a male-to-female ratio of 1.7:1. The age group most commonly affected was 21 to 25 years. Within the category of non-specific reactive lymphoid hyperplasia, the majority, accounting for 43.7% (212 cases), was identified as follicular hyperplasia. Sinus histiocytosis constituted 7.2% (35 cases), and paracortical hyperplasia comprised 3.1% (15 cases) as illustrated in chart no. 4. The remaining 11.3% (54 cases) exhibited other specific patterns of lymphoid hyperplasia or lymphadenopathy, occurring in 5.3% (26 cases). These included cases of dermatopathic lymphadenopathy (6 cases or 1.2%), human immunodeficiency virus-associated lymphadenopathy (5 cases or 1.03%), Castleman disease (4 cases or 0.8%), infracted node (3 cases or 0.6%), Kikuchi Fujimoto disease (3 cases or 0.6%), hyalinized node (2 cases or 0.4%), systemic lupus erythematosus lymphadenopathy (1 case or 0.2%), Rosai Dorfman disease (1 cases or 0.2%), and Kimura disease (1 case or 0.2%),. Additionally, 28 cases (5.8%) were not specifically categorized or identified.

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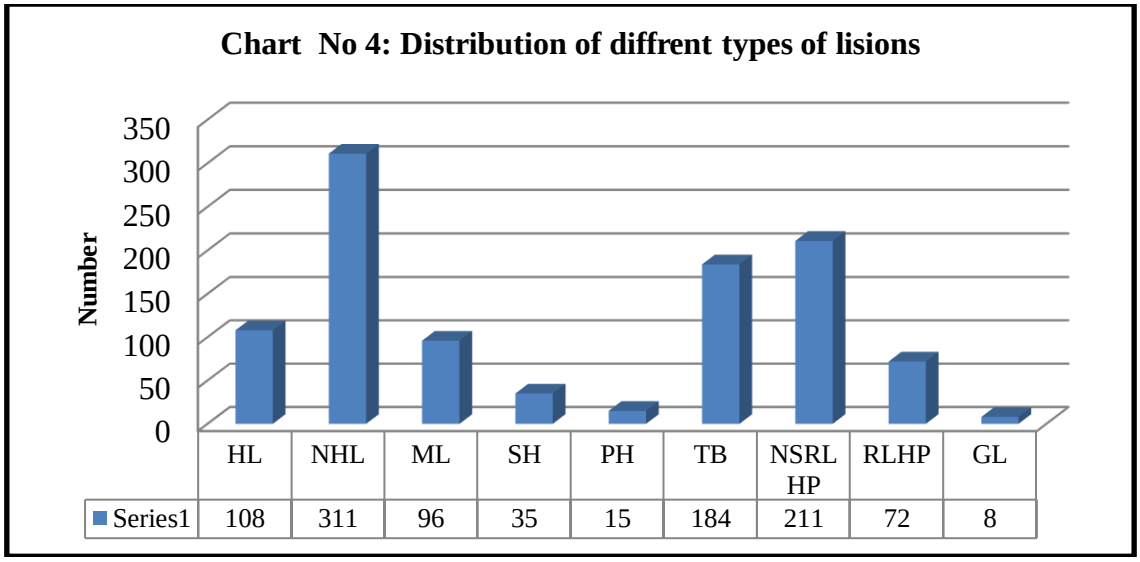

Tuberculous lymphadenitis constituted 38.3% (154 cases) of nonneoplastic lesions and was the second most frequently observed histologic pattern, primarily affecting young adult females, with 85.1% (131 cases) occurring prior to the age of 40 years, peaking between 21 and 30 years, exhibiting a slight female predominance (M:F = 0.84:1). Additional granulomatous lesions encompassed 8 cases of sarcoidosis, 5 cases of cat scratch disease, and 2 cases of toxoplasmosis.

There were 108 instances of HL, representing 10.8% of all lymph node biopsies and making up 26.4% of all lymphomas. The predominant age range was from 21 to 40 years with a higher prevalence in males (M:F = 2.6:1). Nodular sclerosis (NS) was the most frequently observed subtype of HL. A total of 311 cases of Non-Hodgkin Lymphoma (NHL) were recorded, representing 31.1% of all lymph node biopsies and comprising 69. 2% of all lymphoma diagnoses. Of these instances, 65.3% (203 cases) were observed after the age of 40, with the highest frequency occurring between the ages of 51 and 60, and a predominance of males over females (M:F = 2. 1:1). In a cohort of 311 cases of non-Hodgkin lymphoma (NHL), B-cell lymphoma accounted for 32.8%, equating to 102 cases, with diffuse large B-cell lymphoma (DLBCL) representing the most prevalent subtype at 20.6%, corresponding to 64 cases. Conversely, T-cell lymphoma constituted 29.9% of the cases, totaling 93 instances. Additional subtypes of B cell lymphomas identified in the study included follicular lymphoma (FL) at 4.2% (13 cases), mantle cell lymphoma (MCL) at 3.5% (11 cases), chronic lymphocytic lymphoma/small lymphocytic lymphoma (CLL/SLL) at 2.6% (8 cases), T-cell/histiocyte-rich large B-cell lymphoma at 1.9% (6 cases), marginal zone lymphoma (MZL) at 1.9% (6 cases), Burkitt lymphoma at 1.6% (5 cases), precursor B-lymphoblastic lymphoma at 0.6% (2 cases), and lymphoplasmacytic lymphoma (LPL) at 0.3% (1 case). The distribution of T-cell non-Hodgkin lymphomas (NHLs) encompassed 10.5% (29 cases) attributed to anaplastic large cell lymphoma (ALCL), 17.3% (46 cases) to peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), 1.85% (6 cases) to angioimmunoblastic T-cell lymphoma (AITL), 0. 9% (2 cases) to adult T-cell lymphoma/leukemia (ATLL), and 7.4% (10 cases) to precursor T-lymphoblastic lymphoma. The natural killer (NK)-T cell lymphoma and histiocytic/dendritic cell neoplasm accounted for 0.3% each, corresponding to two cases respectively. Twenty-six cases, accounting for 7.4% of the total, could not undergo further sub-classification. This limitation arose because the slides submitted for review from external sources lacked accompanying tissue blocks or due to immunohistochemistry (IHC) results that were inconclusive, potentially attributable to inadequate antigenic preservation. Among these, 12 cases were classified as high-grade, 4 cases as intermediate-grade, and 2 cases as low-grade non-Hodgkin lymphomas (NHLs). Metastatic cases comprised the remaining malignancies, accounting for 9.3% (93 cases) of the total lymph node biopsies. The predominant incidence of cases was observed within the age cohort of 41 to 70 years, accounting for 52 instances, which represents 55.9% of the total cases. The ratio of males to females was 1.7:1. In a study examining 93 instances of metastatic lymphadenopathy, it was found that 19.4% (18 cases) were classified as squamous cell carcinoma. Adenocarcinoma accounted for 31.2% (29 cases). Poorly differentiated carcinoma comprised 17.2% (16 cases), whereas undifferentiated carcinoma represented 12.9% (12 cases) of the total. Malignant melanoma, medullary thyroid carcinoma, seminoma, and small round cell tumor each constituted 3.2% (3 cases each). Rhabdomyosarcoma, anaplastic thyroid carcinoma, and small cell carcinoma each accounted for 8.6% (8 cases each), and neuroendocrine carcinoma and papillary thyroid carcinoma each constituted 7.5% (7 cases each) of the observed cases.

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DISCUSSION

The presence of palpable lymph nodes serves as a significant diagnostic indicator in determining the etiology of the underlying condition. While fine needle aspiration cytology is frequently employed to ascertain the etiological diagnosis, excisional biopsy of the lymph node continues to be regarded as the "gold standard" for diagnostic purposes. The findings of our study indicate a higher prevalence of the condition among male subjects. Furthermore, individuals diagnosed with benign etiology tended to be younger, whereas those with malignant etiology were generally of an older demographic. The current study demonstrated that lymphomas constituted the most prevalent cause of lymphadenopathy, neoplastic lesions were predominately observed, constituting 51.5% (515 cases) of the sample. This category included non-Hodgkin lymphoma (NHL) at 31.1% (311 cases), Hodgkin lymphoma (HL) at 10.8% (108 cases), and metastatic lesions at 9.6% (96 cases). The non-neoplastic lesions constituted 48.5% (485 cases) of the total, encompassing 22.1% (221 cases) of non-specific reactive lymphoid hyperplasia, 18.4% (184 cases) of tuberculous lymphadenitis, 7.2% (72 cases) of other reactive or specific lymphoid hyperplasia, and 0.8% (8 cases) of other granulomatous lesions In the Western hemisphere, the prevalence of Non-Hodgkin's Lymphoma (NHL) is documented to be three to four times higher compared to Hodgkin's Lymphoma (HL), with the incidence of NHL on the rise, whereas that of HL is declining[5-7]. The greater prevalence of NHL in Western countries compared to India may be partially attributed to racial and genetic factors, as comparative studies conducted in the United States have shown a higher incidence among Whites compared to Blacks. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) accounted for 2.6% of all lymphoma cases, representing 1.9% of all B-cell lymphoma cases. This proportion is comparable to, or lower than, the proportions observed in most developed nations and certain Asian countries. Nevertheless, this figure exceeds that observed in Hong Kong and Korea.[8-11] Our study exclusively considered CLL/SLL patients who underwent a lymph node biopsy as part of the diagnostic workup. Nodal marginal zone lymphoma (MZL) accounted for 2.6% of all cases of non-Hodgkin lymphoma (NHL), representing 2.1% of all B-cell lymphoma cases. Follicular lymphoma constituted 6.8% of all cases of non-Hodgkin's lymphoma, accounting for 8.6% of all B-cell lymphomas. This reinforces the previously reported low incidence of follicular lymphoma (FL) in developing nations and Asia.[11-14] The epidemiological determinants, whether genetic or environmental, that contribute to this reduced incidence of FL have yet to be clarified. Mantle cell lymphoma (MCL), which constitutes merely 3.5% of non-Hodgkin lymphoma (NHL) cases and 7.4% of all B-cell lymphomas is less prevalent in comparison to incidence rates observed in the most developed nations. The proportion is more closely aligned with the previously reported 3% from Hong Kong.[8] Diffuse large B-cell lymphoma (DLBCL), comprising 29. 3% (constituting 54.3% of all B-cell lymphomas), represents the largest subset of non-Hodgkin lymphomas (NHLs) observed in India. In a study conducted by Naresh et al.[15], diffuse large B-cell lymphoma (DLBCL) accounted for 34% of all non-Hodgkin lymphomas (NHL). Neoplasms of T-cells and NK cells constituted 38.3% of the total incidence of non-Hodgkin lymphoma (NHL). Reports emanating from Hong Kong and Shanghai indicate that T/NK-cell lymphomas collectively account for 25% and 28% of all non-Hodgkin lymphomas (NHLs), respectively.[16,17] The predominant subtypes of mature T-cell lymphomas identified include peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), which accounts for 17.3% of all NHLs (constituting 45.2% of all T-cell lymphomas), anaplastic large cell lymphoma (ALCL) comprising 10.5% of all NHLs (representing 27.4% of all T-cell lymphomas), angioimmunoblastic T-cell lymphoma (AITL) accounting for 1.8% of all NHLs (constituting 4.8% of all T-cell lymphomas), and adult T-cell lymphoma/leukemia comprising 0.9% of all NHLs (accounting for 2.4% of all T-cell lymphomas). In the context of precursor neoplasms, specifically B and T lymphoblastic lymphomas, which constituted 9.9% of all non-Hodgkin lymphomas (NHLs), it was observed that T-cell lymphoblastic lymphoma, representing 7. 4% of all NHL cases (and 19.4% of all T-cell lymphomas), appeared to occur with greater frequency compared to previous studies where the reported incidence was less than 3% [9,10,18]. Additionally, its prevalence was greater than that of B lymphoblastic lymphoma. According to the report by Advani et al.[19], lymphoblastic lymphoma, regardless of immunophenotype, accounted for 7.5% of all non-Hodgkin lymphomas (NHLs). The determinants potentially contributing to the heightened incidence of T-cell lymphoblastic lymphoma remain unidentified. Within the cohort of Hodgkin lymphoma (HL) cases, the nodular sclerosis subtype was the most prevalent, accounting for 39.2% of the instances. In the United States and Europe, classical Hodgkin lymphoma constitutes 70% of cases. However, the incidence rate exhibits significant variation across different geographical regions, with individuals possessing high socioeconomic status facing the highest risk. Numerous authors have identified tuberculosis as the primary causative factor for lymph node enlargement among adults in tropical regions.[20,21] Within the scope of our research, tuberculous lymphadenitis emerged as the third most prevalent cause of lymphadenopathy, accounting for 18% of total cases. In Western countries, the incidence of infectious diseases such as tuberculosis has significantly decreased, rendering them rare occurrences. Consequently, neoplastic conditions, particularly

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lymphoma, have emerged as the primary etiological factors for lymph node enlargement.[22,23] In our study, non-specific reactive hyperplasia was identified as the second most prevalent pattern, accounting for 21.6% of the cases. In the United States, non-specific reactive hyperplasia represents a prevalent etiological factor for lymphadenopathy, accounting for approximately 50% of all instances.[24,25] The relatively low incidence of tuberculosis and the earlier detection of malignancies prior to the development of nodal metastases likely contribute to the prominence of reactive hyperplasia within Western countries. The remaining nodal malignancies were identified as metastases, accounting for 8.5% of all lymph node biopsies. Among these, metastatic adenocarcinoma was identified as the most prevalent condition. In the United States, metastases account for 29% of cases of peripheral lymph node enlargement, with reactive hyperplasia being the most prevalent cause.[24,25]

CONCLUSION

A lymph node biopsy is integral in determining the etiology of lymphadenopathy. In our study, the most prevalent cause of biopsied lymphadenopathy was a diagnosis of lymphoma, with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). The prevalence of T/NK cell lymphomas is noted to be higher in comparison to those reported in other studies. Within the spectrum of non-Hodgkin lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL) was the most prevalent subtype, whereas among Hodgkin lymphoma (HL) cases, nodular sclerosis (NS) emerged as the predominant form. Among the non-neoplastic etiologies, reactive hyperplasia was the most prevalent, succeeded by tuberculous lymphadenitis.

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