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Pathology

CYTOLOGICAL EVALUATION OF LYMPH NODE ASPIRATES USING SYDNEY SYSTEM - A RETROSPECTIVE STUDY.

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ABSTRACT **Introduction:** Fine needle aspiration cytology is a simple, minimally invasive and routinely used diagnostic aid in the evaluation of lymph node pathologies. Previously no standardized reporting system was available for reporting lymph node cytology.In May 2019, a categorial system for classification and reporting of lymph node cytopathology was proposed at 20th International Congress of Cytology held in Sydney. **Aims And Objectives:** The present study aims to analyze and classify lymph node samples as per new proposed Sydney system and also to assess the risk of malignancy of each category by comparing with their corresponding histopathological diagnosis in available cases. **Materials And Methods:** This single institution retrospective study included lymph node FNAC cases over one year duration. FNAC smears of 337 lymph nodes were re-evaluated and categorized into 5 categories according to the new Sydney system for classification and reporting of lymph node FNAC. **Results:** A total of 337 lymph node aspirates were evaluated, with corresponding lymph node histopathology available in 142 cases (42.13%). The distribution of the 337 cytological diagnoses of lymphadenopathy, reclassified according to the Sydney system, was as follows: L1 - 84 cases (24.9%), L2 - 137 cases (40.6%), L3 - 18 cases (5.3%), L4 - 44 cases (13%), and L5 - 54 cases (16%). The risk of malignancy (ROM) for each category was found to be 37% for L1, 7.5% for L2, 54.5% for L3, 92% for L4, and 100% for L5. The benign category was the most common, with the most frequent diagnosis being nonspecific reactive hyperplasia. The most common malignant diagnosis was metastatic squamous cell carcinoma. **Conclusion:** The new Sydney reporting system introduces defined diagnostic categories that enhance uniformity and reproducibility of cytology reports, aiding in risk stratification and subsequent patient management.

KEYWORDS : Lymph node, FNAC, risk of malignancy, category, lymphadenitis

INTRODUCTION

Lymph nodes are widely distributed, easily accessible and integral components of the immune system, making their examination common in clinical practice for diagnostic purposes[1]. Fine Needle Aspiration Cytology (FNAC) is widely recognized as the initial method for evaluating lymphadenopathy of unknown cause.[2] Its minimal invasiveness, rapidity, cost-effectiveness, and capability to provide material for several ancillary techniques contribute to its wide applicability in the evaluation of lymphadenopathy[2,3]. The aspirated material can be used for ancillary studies such as flowcytometry, immunocytochemistry or immunohistochemistry on cell block preparations[4]. Lymph node cytological smears provide a highly reliable method for diagnosing metastatic malignancy.

Historically, there was no standardized reporting system or common terminology for lymph node cytology, unlike the systems available for cervical[5] and thyroid cytology[6]. At the 20th International Congress of Cytology held in Sydney in 2019, a panel of experienced cytopathologists from around the world proposed a standardized, category-based lymph node cytology reporting system. This system was endorsed by both the International Academy of Cytology (IAC) and the European Federation of Cytology Societies (EFCS)[7]. According to this system, cytologic aspirates from lymph nodes should be categorized into five categories based on specific cytologic features. The present study was aimed to evaluate and classify lymph node fine needle aspirates according to the new Sydney system and to assess the category wise Risk of malignancy (ROM) by comparing with their corresponding histopathological diagnosis in available cases.

MATERIAL & METHODS

The present study was a retrospective observational analysis of lymph node aspirates obtained during one year period from January 2023 till December 2023,in the department of Pathology of the tertiary care centre in January 2024.

FNAC smears of 337 lymph nodes were re-evaluated and categorized into 5 categories according to the new Sydney system for classification and reporting of lymph node FNAC.The essential features of the five basic categories are as follows[2,7]:

The diagnostic accuracy and ROM in each category was compared with their corresponding histopathological diagnosis.

Statistical Analysis

The ROM was calculated by dividing the number of cases confirmed malignant on histopathology by the total number of cases with available histopathology diagnosis in that category. Cases which were diagnosed malignant on cytology and histopathology were considered True Positive (TP). Cases diagnosed benign on cytology and histopathology was considered True Negative (TN). Cases which were malignant on cytology but were found benign on histopathology were False Positive (FP). Cases which were benign on cytology but found malignant on histopathology were considered FN cases. The sensitivity, specificity, PPV, NPV and diagnostic accuracy were also calculated. Using the formula diagnostic accuracy=(TP)+(TN) /(TP+TN+FP+FN), the accuracy of FNAC was found[8].

CATEGORY	DIAGNOSTIC CRITERIA
L1 - Inadequate/ Insufficient	Non-diagnostic due to scant cellularity, necrosis, or technical limitations
L2 - Benign	Includes suppurative, granulomatous, or specific infections in cases with a heterogeneous lymphoid population with small lymphocytes predominating.
L3 - Atypical Lymphoid (Cells) of Undetermined Significance/ Atypical (Cells) of Uncertain Significance (ALUS/AUS)	Cases with a heterogeneous lymphoid population suggest a reactive process, but a follicular lymphoma cannot be excluded; includes cases with an excess of large cells, immature small lymphoid cells, or atypical non-lymphoid cells. For these last cases, AUS should be used.
L4 - Suspicious	Small or medium-sized monomorphic atypical lymphoid cells suspicious for lymphoma, but the cytomorphology alone is not sufficient; includes cases where Reed-Sternberg like cells or atypical cells suspicious for metastasis are detected but are too scant to be diagnostic.
L5 - Malignant	Includes small to medium-sized cells of non-Hodgkin lymphoma (NHL) supported by flow cytometry or molecular studies, Hodgkin's lymphoma, and metastatic carcinoma or other malignancies.

RESULT

A total of 337 aspirates of lymphadenopathy were analysed. The age of patients varied from 3 years to 89 years with a mean age of 42 years in the study. There were 28 (8.3%) cytology aspirates in pediatric group and 72 (21.4%) in the age group above 60 years. Out of the 337 aspirates obtained, there were 158 (46.8%) males and 179 (53.11%) females, with an overall male to female ratio of 1:13. Most of the cases (309; 91.7%) presented with cervical lymphadenopathy followed by 13 (3.8%) cases of axillary lymphadenopathy, 9 (2.6%) cases of supraclavicular lymphadenopathy and 6(1.7%) cases of inguinal lymphadenopathy. Size of lymphadenopathy varied from 0.2 cm to 5 cm. Diagnostic categories per the Sydney system are shown in [Table/Fig-1].

Category	Total frequency (%) 337	Cytological Diagnosis	Frequency (%)
L1: Inadequate/Insufficient	84 (24.92%)	Scant cellularity Extensive necrosis Hemorrhage only	28 (8.3%) 22 (6.5%) 34 (10%)
L2 : Benign	137 (40.65%)	Reactive lymphoid hyperplasia Suppurative lymphadenitis Granulomatous lymphadenitis	82 (24.3%) 10 (2.9%) 45 (13.3%)
L3 : Atypical cells of undetermined significance/ Lymphoid cells of uncertain significance	18 (5.34%)	Atypical lymphoid cells. Atypical non lymphoid cells.	11 (3.2%) 07 (2.0%)
L4: Suspicious	44 (13.05%)	Suspicious of lymphoma Atypical cells suspicious of metastasis	09 (2.6%) 35 (10.38%)
L5: Malignant	54 (16.02%)	NHL HL Metastatic neoplasm	05 (1.48%) 02 (0.59%) 47 (13.94%)

Table 1: Category wise cytological diagnosis as per the proposed Sydney system

The study categorized 137 (40.6%) non-neoplastic lesions and 54 (16.02%) neoplastic lesions. Among the pediatric population, there were 28 (8.3%) cases, with the majority being non-neoplastic at 25 (8.3%) cases. There were 84 (24.92%) non-diagnostic aspirates in Category I/L1, including 34 (10%) cases of blood only, 22 (6.5%) cases of extensive necrosis, and 28 (8.3%) cases of scanty material, leading to a recommendation for repeat aspiration/biopsy. In Category II/L2, 137 (40.65%) cases included 82 (24.3%) cases of reactive hyperplasia, 45 (13.3%) cases of granulomatous lymphadenitis, and 10 (2.9%) cases of suppurative lymphadenitis. Epithelioid granulomas were present in all 45 (100%) cases of granulomatous lymphadenitis, with necrosis seen in 29 (64.4%) cases and Acid-Fast Bacilli (AFB) positivity in 8 (17.8%) cases.

Category III/L3 included 18 (5.34%) cytology diagnoses, where biopsy and immunohistochemistry (IHC) were recommended. Category IV/L3 consisted of 44 (13.05%) cases, with nine cases suspicious of lymphoproliferative lesions, advised for biopsy with ancillary studies recommended. Category V comprised 54 (16.02%) malignant lesions, including 47 (13.94%) metastatic malignancies and seven (10.29%) lymphomas. Metastatic malignancy at 47 (13.94%) cases, was the second most common cause of lymphadenopathy, following reactive lymphadenitis in this study. The breakdown of metastatic lymphadenopathy in 54 cases showed the highest incidence for squamous cell carcinoma, with 26 (42.60%) cases. Other metastatic tumors included poorly differentiated carcinoma, adenocarcinoma, small cell lung carcinoma, melanoma, small round cell neoplasm, and papillary thyroid carcinoma.

The corresponding lymph node histopathology diagnosis was available in 142 (42.13%) cases. Biopsy diagnosis of FNACs in categories I, II, III, IV, and V were available in 27, 40, 11, 26, and 38 cases, respectively. In Category I/L1, out of 84 cases of inadequate cytology, 27 were biopsied, revealing 10 cases of malignancy, 5 cases of granulomatous lymphadenitis and 12 cases of nonspecific reactive hyperplasia. In Category II/L2, among the 24 cytological smears of reactive lymphadenitis, 3 were diagnosed as malignant, while 21 were confirmed as reactive follicular hyperplasia on histopathology. Of the 5 smears of suppurative lymphadenitis, 3 were histologically confirmed, and 2 cases were identified as granulomatous lymphadenitis on biopsy. All 11 cytology diagnoses of granulomatous lymphadenitis were consistent with tuberculosis on histopathology.

In Category III/L3, out of 3 cases of atypical lymphoid cells, 2 were diagnosed as Non-Hodgkin's Lymphoma (NHL) and one as Hodgkin's Lymphoma. Additionally, 3 cases were diagnosed as metastatic carcinoma and 5 cases as reactive hyperplasia. In Category IV/L4, of the 26 cases biopsied, 6 cases were suspicious for lymphoma, with 4 confirmed as lymphoma, and 20 cases suspicious of metastatic carcinoma, all confirmed as metastatic carcinoma. The true and false positives and negatives in comparison to the gold standard are shown in [Table/Fig-2].

Histopathological diagnosis				
		Malignant	**Benign**	**Total**
Cytological diagnosis	Malignant	68 (TP)	07 (FN)	75
	Benign	13 (FP)	54 (TN)	67
	Total	81	61	142

Table 2 : True & false positive and negative value in comparison to gold standard.
TP: True positive, TN:True negative, FP: False positive, FN: False Negative

ROM in each category was calculated by dividing the number of cases with a confirmed malignant diagnosis by the total number of cases in each diagnostic category [Table/Fig-3].

Categorization of smears based on Sydney System	Cytology cases	No. of cases biopsied in each category	Malignant	Risk of Malignancy
L1: Inadequate/ Insufficient	84	27	10	37%
L2: Benign	137	40	3	7.5%
L3: Atypia of undetermined significance	18	11	6	54.5%
L4: Suspicious	44	26	24	92%
L5: Malignant	54	38	38	100%

Table 3 : Risk of malignancy (ROM) for each Sydney system category in the present study

The statistical values of FNAC diagnosis compared to gold standard are represented in [Tables/Fig-4].

Statistical analysis	Value
Sensitivity	83.9 %
Specificity	88.5 %
Positive predictive value	90.6 %
Negative predictive value	80.5 %
Diagnostic accuracy	85.9 %

Table 4: Statistical analysis of FNAC in comparison to histopathology diagnosis

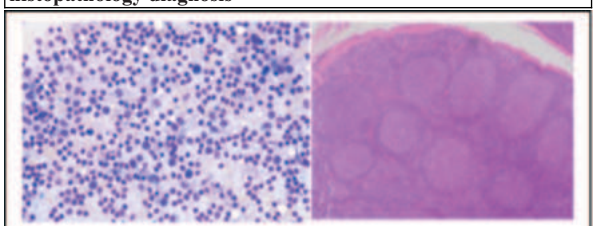

Fig. 1) Smears showing polymorphous lymphoid cells. category L2: Benign (MGG,10x) 2) Non specific reactive hyperplasia (H&E, 4X)

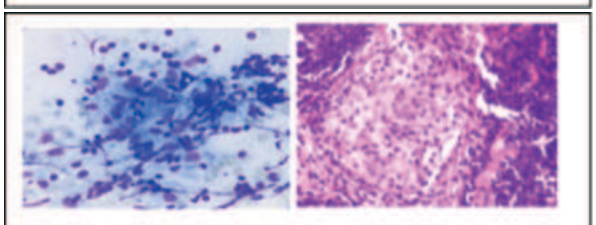

Fig.3) Cervical lymph node showing epitheloid cell granuloma, category L2 (MGG, 10X) 4) Granulomatous lymphadenitis (H&E, 10X)

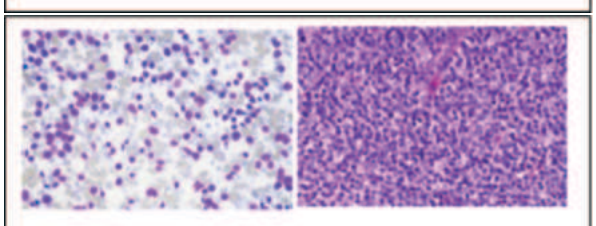

Fig. 5) NHL, category L5 (MGG, 10X), 6) Non hodgkin lymphoma, cervical lymph node (H&E, 10X)

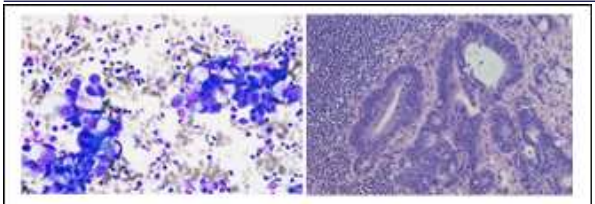

Fig.7) Adenocarcinoma metastasis L5 (MGG,10X) 8) Adenocarcinoma lymph node (H&E, 10X)

DISCUSSION

The application of standardized reporting systems in cytopathology has been shown to reduce intra-observer variability and enhance the communication of clinically relevant information consistently[8]. Additionally, it improves clinicians ability to interpret cytopathological reports concerning risk assessment[7]. The proposed reporting system in cytopathology is a recent development with limited publications available for comparison. This retrospective study includes cases of fine needle aspiration (FNA) of superficial lymphadenopathy over a period of one year, encompassing 337 cases, including both non-guided and ultrasound-guided (USG) FNA procedures.

In comparison, the retrospective study by Gupta P et al[9] included 6,983 cases, making our study smaller in terms of the number of cases. The retrospective studies by Rivas HE et al[10] and Vigliar E et al[11], also published in 2021, evaluated 363 and 300 cases respectively but included only USG-guided FNA of lymphadenopathy. In the current study, the age range of patients undergoing FNA was from 3 to 89 years, with a higher number of female patients. The cervical lymph nodes were the most common site evaluated, similar to the findings in the studies by Vigliar E et al[11], Sreelekshmi at al[8] and Gupta P et al[9].

In our study, Category L1 of insufficient aspirates was seen in 84 cases (24.9%), while Gupta P et al[9] reported 289 cases (4.1%), as they used the rapid on-site evaluation (ROSE) technique. The study by Rivas HE et al[10] had 13 aspirates (3.58%) in this category, likely due to the use of USG guidance for FNA. The L2 benign cytology category included the most cases (137, 40.65%) in our study, which was lower in comparison to the studies by Gupta P et al[9] and Saradva et al[12]. Eighteen (5.34%) cases were classified as atypical lymphoid cells of undetermined significance (ALUS, L3) in our study, while Gupta P et al[9] and Sreelekshmi et al[10] reported 0.5% and 1.6% of cases in this category, respectively.

The suspicious for malignancy category (L4) included 44 (13.1%) cases in the current study, which was higher than the studies by Gupta P et al[9] and Rivas HE et al[10]. The malignant cytology category (L5) included 54 cases (16%) in our study, similar to the study by Sardava et al[12] and much smaller number compared to the 41.76% and 46% reported by Gupta P et al[9] and Vigliar E et al[11], respectively. This discrepancy could be due to the larger number of cases in the Gupta P et al[9] study.

In this study, the risk of malignancy (ROM) was calculated for each diagnostic category in the Sydney system for lymph node cytopathology. The non-diagnostic category had a ROM of 37%, which was higher than Gupta et al[9] (27.5%) and lower than Vigliar et al[11] (50%) and Caputo et al[13] (66.7%). The higher ROM found by Vigliar et al[11] is attributed to the lower number of cases with histopathological follow-up data. The benign category (L2) had the lowest ROM at 7.5%, slightly higher than Vigliar et al[11] (1.92%) but comparable to Baruah et al[2] (5.3%).

The atypia of undetermined significance category (L3) was introduced to maintain high negative and positive predictive values in benign and malignant categories, respectively. The ROM for this category was 54.5%, comparable to 58.3% and 50% in studies by Vigliar et al[11] and Robert et al[14], respectively, but higher than Caputo et al[12] (28.6%). Most benign cases in this category were reactive lymphadenitis with interfollicular expansion, leading to large cells with irregular nuclei on cytological smears. This issue was similarly encountered by Vigliar et al[11] and Robert et al[14]. Other studies also faced similar challenges with cytology smears of reactive lymph nodes due to viral etiology and interfollicular expansion.

The suspicious for malignancy (L4) and malignant (L5) categories had high ROMs of 92% and 100%, respectively, comparable to Gupta et al[9] (88% and 99.6%) and Vigliar et al[11] (100% for both). False negatives can be further reduced by using ancillary techniques as suggested in the classification system proposal. The benign case in the L4 category was parafollicular hyperplasia with Reed-Sternberg-like cells, commonly mimicked by immunoblasts in cytology.

The most common cytological diagnosis in our study was non-specific reactive hyperplasia. The most common malignant lesion diagnosed on cytology was metastasis from epithelial malignancy. In the study by Gupta P et al[9], the most common cytological diagnosis was metastatic squamous cell carcinoma. In the present study, histopathological correlation was available in 142 (42.1%) cytologically evaluated cases. In comparison, 8.8% of cases had histopathological correlation in the study by Gupta P et al[9], while this number was 80.6% in the study by Vigliar E et al[11].

Our study found most cases in the benign category (40.7%) and only 16.1% in the malignant category, contrasting with the studies by Vigliar et al[11] and Gupta et al[9], due to the regional pattern of high tuberculosis prevalence and benign lymphadenopathies. The sensitivity, specificity, NPV, PPV, and accuracy were on par with other studies.

CONCLUSION

Fine Needle Aspiration Cytology (FNAC) is a minimally invasive, reliable, and accurate method for evaluating lymphadenopathy, boasting a diagnostic accuracy of 85.91%. The new Sydney reporting system introduces defined diagnostic categories that enhance the uniformity and reproducibility of cytology reports, aiding in risk stratification and subsequent patient management. This system confirms benignity in non-malignant lesions and alerts clinicians to follow up on atypical cases, thereby improving patient outcomes and ensuring appropriate follow-up care.

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