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The Analytical Feasibility of Sydney System in Reporting Lymph Node Cytology in a Tertiary Care Hospital

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Abstract
Introduction: FNAC is the first diagnostic step in patients with lymphadenopathy because of its simplicity and minimal invasive nature which helps to confirm the clinical suspicion. A definite specific diagnosis may not be possible in few cases but a categorisation of the disease and differential diagnosis can help to suggest the most efficient further investigations, saving time and resources.
Aim: The aim of this study is to ascertain the system's applicability and precision in the diagnosis of lymph node cytology.
Methodology: This is a retrospective cross sectional study of lymph node cytology conducted from January 2023 to June 2023 and the results were reported using the Sydney System into 5 groups from L1 to L5. For accuracy, the cytological diagnoses were compared with corresponding histological diagnoses and also with specific clinical findings that warranted FNA. The statistical tools used were calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and risk of malignancy (ROM).
Results: 60 cases were evaluated by FNAC. Out of this 43 were benign cases which comprised of 16 cases of Reactive lymphadenitis, 22 cases of Granulomatous/Tuberculous lymphadenitis and 4 cases were of Acute suppurative lymphadenitis and 1 case of only Caseous necrosis. Out of 17 malignant cases, 1 case was of Non Hodgkins lymphoma, 2 cases were of Hodgkins lymphoma and 14 cases were of metastatic carcinoma.
Conclusion: The Sydney system was used for clinicopathological diagnosis of patients presenting with lymphadenopathy and was found to be a reliable tool for evaluation of risk of malignancy and its subsequent management of the patient.

Keyword: Fine needle cytology, Lymph node, Sydney system, risk of malignancy

I. INTRODUCTION

Fine needle aspiration dates back to 1950.Fine needle aspiration cytology(FNAC) is most common method for evaluation of lymphadenopathy In addition to cytological preparations, samples obtained through FNAC can also be utilized for microbiological and biochemical analyses, further enhancing its diagnostic utility. This comprehensive approach allows for a more accurate diagnosis and management of a wide range of medical conditions, making FNAC a valuable tool in clinical practice. FNAC serves as a valuable diagnostic tool in the management of patients with AIDS, other immunocompromised conditions, and post-transplantation settings. Its ability to provide rapid, minimally invasive diagnosis and monitoring contributes significantly to improving outcomes and quality of life for these individuals.[1].

A definite specific diagnosis may not be possible in a few cases but a categorisation of disease and differential diagnosis can help suggest the most efficient further investigations, saving time and resources. Applied in this manner, it has become just as dispensable as surgical histopathology.

Hence, a categorical system for performance, classification, and reporting of lymph node cytopathology was proposed at the 20th International Congress of Cytology in Sydney in the year 2020 and was called the Sydney system. It is based on years of experience of the contributing authors from all over the world and well documented international cytopathological studies It grants the categorisation of Lymph Node-Fine Needle Aspiration diagnoses, provides an operational blueprint, and has been validated by the International Academy of Cytology and the European Federation of Cytology Societies[2]

The main purpose of this system was to provide consensus guidelines and a framework to facilitate system based practice.

AIM:
To ascertain the system's applicability and precision in the interpretation and reporting of lymph node cytology and to provide a consensus guideline to facilitate systems-based practice.

II. METHODOLOGY:

This is a retrospective cross sectional study of lymph node cytology conducted from January 2023 to June 2023 and the results were reported using the Sydney System into 5 groups from L1 to L5[3] (Table 1).
For accuracy, the cytological diagnoses were compared with corresponding histological diagnoses and also with specific clinical findings that warranted FNA.

The statistical tools used were calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and risk of malignancy (ROM).

Table.1: Categories in Sydney system of reporting lymph node cytology

CATEGORY		FEATURES
L1	Inadequate/ Insufficient	• Scant cellularity • Extensive necrosis • Technical limitations that cannot be overcome
L2	Benign	• Suppurative and granulomatous inflammation • Reactive lymphoid population
L3	Atypical (Cells) Undetermined significance/ Atypical lymphoid (cells) of Uncertain significance (ALUS/AUS)	• Heterogeneous lymphoid population, features suggest a reactive process, follicular lymphoma cannot be excluded • Excess of large cells (centroblasts or immunoblasts) or immature small lymphoid cells
L4	Suspicious	• Suspicious of lymphoma, but the cytomorphology alone is not sufficient • Polymorphous lymphoid smears, few Hodgkin- or Reed-Sternberg-like cells are detected • Large cell or Burkitt lymphomas scantly cellular • Atypical cells suspicious for metastasis present, but are too scant to be diagnostic
L5	Malignant	• NHL; HL • Metastatic neoplasms

Inclusion criteria:
The study focused on individuals who had undergone FNAC for enlarged lymph nodes (lymphadenopathy) and who either had histopathological reports or clinical follow-up data.

Exclusion criteria:
Cases without corresponding histopathological correlation: Patients for whom there is no additional tissue analysis (histopathological examination) available were excluded. This step ensures that there is a way to verify or validate the FNAC results against more conclusive diagnostic methods.
Loss to follow-up cases: Patients for whom subsequent clinical follow-up data could not be obtained were excluded. This is to prevent bias caused by missing data and to ensure that the study is based on comprehensive information.
Inadequate or Non diagnostic FNAC Samples (L1): FNAC samples yielding inadequate or non-diagnostic material (labelled as L1) were excluded from certain calculations.

Study procedure
FNAC procedures were performed after obtaining informed consent from patients. Rapid Onsite Evaluation (ROSE) using toluidine blue stain was done for assessing specimen adequacy. An explanation of the procedure to the patient along with its possible risks and benefits was given and consent was taken. A 23G needle was used to conduct the procedure, and direct smears were prepared from the first pass. The superficial and palpable lymph node aspirations were taken blindly and for non-palpable and deep lymph nodes, image guidance was taken, mostly by ultrasonography guided FNA.

At least two air dried and three wet fixed smears were made and stained with Papanicolaou, Haematoxylin and Eosin (H&E) as well as May Grunwald Giemsa (MGG) stain. Additional smears were made in suspected cases of tuberculosis and stained with Ziehl Nelson stain. Subtyping was done using additional Immunohistochemical markers for suspected cases of lymphomas on histopathological samples. The smears were reported and classified into 5 different diagnostic categories based on the proposed Sydney system of reporting. (Table 1) A prior ethical clearance was taken from the Institutional Ethical Committee.

Statistical analysis:

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The statistical analysis was done with the help of software International Business Management (IBM) SPSS version 26.0. The sensitivity and specificity were calculated with the help of true positive (TP) and true negative(TN) results of FNA diagnosis, whereas positive predictive value and negative predictive value were derived from true malignant and false malignant results ratio with total malignant results.

Among the 36cytologically benign cases, 14 cases were proved to be histopathologically benign (TN). 1 case was diagnosed histopathologically as malignant, False Negative (FN). Among the 23 Cytologically malignant/suspicious cases, 16 cases were proved to be malignant histopathologically were True positive (TP), and 2 cases was diagnosed as benign, False Positive (FP) on cytology. The True and False Positives and Negatives in comparison to gold standard shown in Table 2. 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 3)

Table 2: The True and False Positives and negatives in comparison to gold standard

		Histopathology Diagnosis		
Cytology		Malignant	Benign	Total
	Malignant	16(TP)	2(FP)	18
	Benign	1 (FN)	14(TN)	15
Total		17	16	33
*L1-non diagnostic category (1 cases) excluded; TP: True positive; TN: True negative; FP: False positive; FN: False negative				

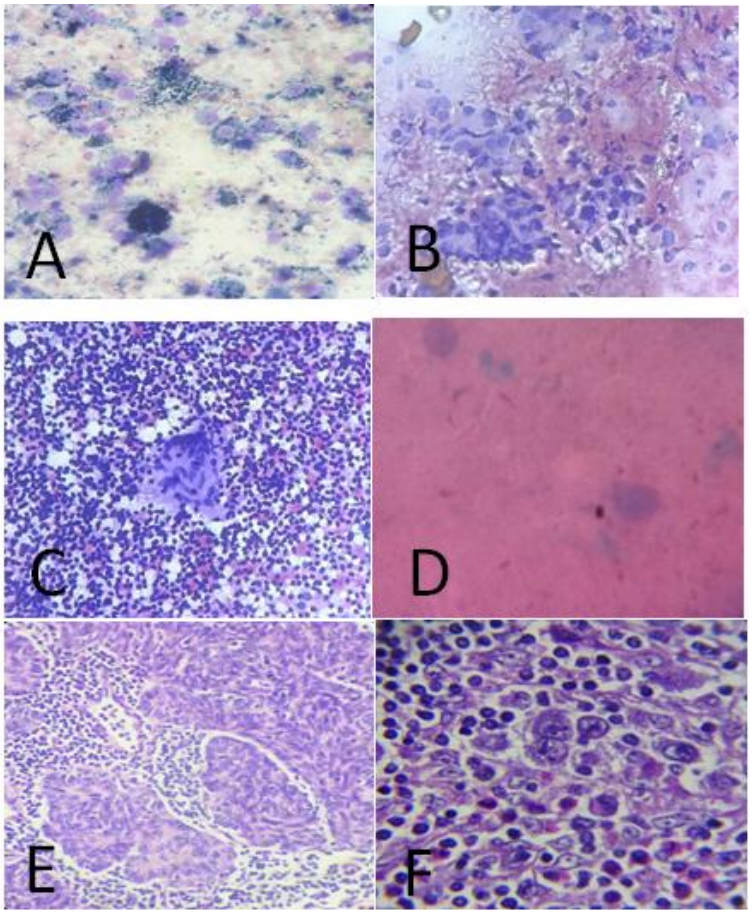

Figure 1: Photomicrographs of Lymph node aspiration cytology (A-D) & Biopsy-(E-F)(A) Malignant melanoma metastasis with pigment in cytoplasm of cells (MGG, 40X);(B) Metastatic squamous cell carcinoma (MGG ,40X); (C) Granulomatous lymphadenitis (MGG, 40X); (D) AFB bacilli (ZN stain 100X); (E); Squamous cell carcinoma of oral cavity (H&E 10X)(F) Hodgkin's Lymphoma showing RS cell(H&E 40X).

III. RESULTS

A total of 60 aspirates of lymphadenopathy were analysed. The corresponding lymph node histopathology diagnosis was available in 34 (56.6%) cases. The age of patients varied from 6 months to 65 years with a mean age of 30.64 years in the study.Out of the 60 aspirates obtained, there were 38 (63.33%) males and 22 (36.66%) females, with an overall male to female ratio of 1.72:1. Out of this60 cases, 43 were benign comprising of 16 cases of Reactive lymphadenitis, 22 cases of Granulomatous/Tuberculous lymphadenitis,4 cases of Acute suppurative lymphadenitis and 1 case of just Caseous necrosis. Out of 17 malignant cases, 1 case was of Non Hodgkins lymphoma, 2 cases were of Hodgkins lymphoma and 14 cases were of metastatic carcinoma. (Table 4)

Category L1-There was 1case with scanty material with what looked like necrosis. Cytologically it was diagnosed as Caseous necrosis. Repeat aspirate was suggested.

Category L2-Out of 36 cases in L2, there were 10 reactive lymphadenitis, granulomatous lymphadenitis in 22 and 4 suppurative lymphadenitis cases. Diagnosis of reactive background with histiocytes, to rule out toxoplasmosis by serology was given in 4 cases. Epithelioid granulomas were seen in all 10 cases of granulomatous lymphadenitis (Fig 1-C). Acid-Fast Bacilli (AFB) positivity was seen in 1 cases (Fig 1-D). AFB positivity was confirmed later with a sputum positive test.

Category L3-There were 8 cases in this category. Atypicalcells in a reactive background, large cells and immunoblasts were found. Biopsy and IHC were recommended.

Category L4-There were 8 cases. 7 were suspicious of metastasis, where granuloma, necrosis and atypical cells were found. One case was suspicious of lymphoproliferative lesion wherein biopsy was advised with recommendation for ancillary studies (Fig1-F).
Category L5-Included 7 malignant lesions, all were metastatic malignancy (Fig1-A,1-B, 1-E)

Table 3: Risk of Malignancy calculated for each category.

CATEGORY	ROM
L1	-
L2	2.7%
L3	12.5%
L4	100%
L5	100%

Table 4: Correlation of the cases categorized under each category with final diagnosis based on histopathological correlation and clinical follow up

CATEGORY	CYTOLOGICAL DIAGNOSIS	HISTOPATHOLOGICAL DIAGNOSIS
L1	• Caseous necrosis (n=1)	• Granulomatous lymphadenitis • N=1
L2	• Suppurative lymphadenitis (n=4) • Reactive lymphadenitis (n=10) • Granulomatous lymphadenitis (n=22)	• Reactive lymphadenitis (n=4) • Granulomatous lymphadenitis (n=10) • Hodgkins lymphoma (n=1)
L3	• Reactive lymphadenitis (n=6) • Atypical lymphocytes (n=2)	• Hodgkins lymphoma (n=1) • Reactive lymphadenitis (n=2)
L4	• Mets (n=7) • Non Hodgkin lymphoma (n=1)	• PTC (n=4) • SCC from the oral cavity(n=3) • Diffuse large B cell lymphoma (n=1)
L5	• Mets (n=7)	• IDC of breast (n=3) • Melanoma of foot (n=2) • Adenocarcinoma of lung (n=2)

Table 5: Comparison of statistical evaluation of Lymph node cytology using Sydney System with the gold standard in various studies [4,5,6,7]

Variables	Sreelakshmi et al, (2023) [4]	Gupta P et al.,(2021) [5]	Vigilar E et al.,(2021) [6]	Cupato A et al.,(2021) [7]	Present study (2024)
Sensitivity	95.23%	79.9%	98.4%	97.9%	94.1%

Specificity	94.11%	98.7%	95.3%	96.2%	87.5%
Positive predictive value	98.36%	98.4%	96.3%	99.5%	88.8
Negative predictive value	84.21%	83.1%	98.1%	86.3%	93.3

Table 6:Comparison of Risk of Malignancy (ROM) stratification with other study results [4,5,6,8]

Diagnostic category Sydney system	Sreelakhmi et al,(2023) [4]	Gupta P et al., (2021) [5]	Vigliar E et al., (2021) [6]	Joshee A and Joshee R (2021) [8]	Present study (2024)
L1	0%	27.5	50%	34.7	0%
L2	3%	11.5	1.92%	20	2.7%
L3	66.6%	66.7	58.3%	15	12.5%
L4	100%	88	100%	78.5	100%
L5	100%	99.6	100%	96.7	100%

IV. DISCUSSION:

Cytological evaluation of lymphadenopathies can be extremely challenging; nonetheless, a growing body of data show that the proper handling of diagnostic material to perform ancillary techniques, coupled with clinical data, ensures satisfactory diagnostic accuracy; indeed, as reported above, in the present study we demonstrate high diagnostic accuracy. However, the use of lymph node FNAC is still not uniformly accepted by clinicians, mainly as a consequence of a lack of guidelines and reporting system [6].

Comparison of statistical evaluation of Lymph node cytology using Sydney System with the gold standard in studies was done (Table 5), where sensitivity was in concordance with majority of studies [4,6,7] while Gupta et al [5] had lower sensitivity. The present study had lower specificity rate in comparison to other studies [4,5,6,7]. Vigilar et al [6] reported highest negative predictive value while it was lower in other studies including the present one. Positive predictive value in the present study was considerably lower than the others. [4,5,6,7]Comparison of ROM for Sydney system categories in other studies is shown in Table 6. Present study showed similar ROM as Sreelakshmi et all [4] for L1, L2, L4 and L5 while L3 results were similar to Joshee A and Joshee R et al [8].

The Sydney System is a comprehensive approach to categorizing lymph node fine-needle aspiration diagnoses, combining both broad diagnostic categories and more specific diagnostic entities using ancillary techniques.[9,10,11] In this system, the first level of diagnostic categorization (L1-L5) likely allows for a general classification of lesions based on their characteristics, which include categories such as inadequate (L1), benign (L2), and suspicious/malignant (L3-L5). This initial classification provides a broad understanding of the nature of the lesion. The second diagnostic level involves utilizing additional techniques, such as immunocytochemistry (ICC), fluorescent in situ hybridization (FISH), and cell block preparations, to further refine the diagnosis and identify specific diagnostic entities. These ancillary techniques can provide more precise information about the cellular and molecular characteristics of the sample, aiding in distinguishing between different types of malignancies or other pathologies.

By incorporating these two diagnostic levels and utilizing advanced techniques for more accurate characterization, this system seems to be designed to enhance the reliability and specificity of lymph node cytopathology diagnoses.[11]This could be particularly valuable for guiding patient management and treatment decisions.

In the present series, we showed the ability of the Sydney system to secernate lymph node pathology.

The proposed system for reporting LN-FNAC cytopathology has the following aims

Develop Consensus Guidelines and Framework:
Establish a set of agreed-upon guidelines and a framework to improve communication between various medical professionals involved in lymph node FNAC, including cytopathologists, hematopathologists, clinicians, and surgeons. This collaboration ensures a shared understanding and approach to diagnosis and management.[9,10]

Obtain Key Diagnostic Cytopathological Features:
Identify and establish the essential diagnostic features that are commonly observed in different categories of lymph node FNAC samples. Understanding these features enables accurate categorization and diagnosis of various types of lesions.

Make Recommendations on Standardized Diagnostic Reports:
Propose a standardized format for diagnostic reports to enhance communication between cytopathologists and clinicians. Clear, uniform reporting helps healthcare providers better understand the diagnosis, which in turn can lead to more effective patient management.[10]

Provide Management Recommendations Linked to Reporting Categories:
Offer management suggestions based on the reported diagnostic categories. Recommendations could encompass clinical and imaging follow-up, additional ancillary testing, and the consideration of potentially excising the lymph node if necessary.

Encourage Cyto-Histopathological Correlations, Cell Storage, and Research:
Promote the correlation between cytopathological findings and histopathological results for further validation. Encourage the storage of cellular material for future reference and research purposes, focusing on both neoplastic (cancerous) and non-neoplastic (non-cancerous) lymph node specimens.

Increase LN-FNAC Reliability and Clinician Awareness:
Improve the reliability of LN-FNAC results through standardized guidelines and practices. Also, enhance clinicians' awareness of the diagnostic potential outcomes.

V. LIMITATIONS:

Small sample size, less histopathological follow-up and lack of adequate ancillary techniques were the main limitations of this study.Also ancillary tests for the final diagnosis of lymphoid malignancy such as flow cytometry or molecular studies were not available.

VI. CONCLUSION

Lymph node fine needle aspiration cytology helps in the primary diagnosis of lymphadenopathy which is very useful for further management according to the lesions[12]. The recently proposed Sydney system of lymph node reporting system is a promising and important classification system that is useful in risk stratification as well as management and has high sensitivity and specificity. However, multicentric studies with a larger sample size along with advanced ancillary techniques are required for more accurate results.The Sydney reporting system provides a structured framework for reporting cytological and histological findings in lymph node lesions. It emphasizes on including essential clinical data, radiological findings, and site information. The core of the system involves categorizing findings into five basic diagnostic categories (L1-L5), along with additional details like microscopic descriptions, ancillary techniques used, and any secondary diagnoses provided.

However, the Sydney system remains underutilised and there is limited data in literature to date. Therefore, the present study was aimed to assimilate the diagnostic utility of Sydney reporting system in fine needle aspiration cytology for lymph node lesions

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