Original Article

Categorization of Lymph Node Aspirates Using the Proposed Sydney System and Its Correlation with Histopathology to Assess Its Diagnostic Accuracy- A Two-Year Retrospective Study in A Tertiary Care Hospital

Veerpal Kaur[1], Preeti Joseph John[2], Sukhjinder Kaur[3]

[1]Assistant Professor, Department of Pathology, Adesh Medical College and Hospital, Mohri, Shahabad, Haryana, India [2]Associate Professor, Department of Pathology, Adesh Medical College and Hospital, Mohri, Shahabad, Haryana, India, [3]Assistant Professor, Department of Pathology, ESIC Medical College and Hospital, Bharat Nagar, Ludhiana, Punjab, India

Abstract

Background: Fine Needle Aspiration Cytology (FNAC) is one of the main methods used in the diagnosis of lymphadenopathy. The Sydney system was brought about in 2020 to improve not only the diagnostic accuracy but also interclinical communication in evaluating lymph-node cytopathology in terms of performance, classification, and reporting. The purpose of this study was to evaluate the risk of malignancy (ROM) and diagnostic performance of each Sydney system group. **Aim:** The research team did this work to investigate the diagnostic efficiency and the risk of malignancy (ROM) of each diagnostic category in the Sydney system. **Material and Methods:** This two-year retrospective study included lymphadenopathy patients who had FNAC and had histopathology available. The Sydney System was used to reclassify the diagnoses, and diagnostic accuracy along with ROM was correlated. The calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy was done using SPSS version 27. **Results:** 290 cases with histopathological correlation were included in total. Out of them, females (n=151, 52%) predominated the cases. The cervical lymph nodes were the most common site of the involvement (n=256, 88.2%). Statistical analysis demonstrated a sensitivity of 75.2%, specificity of 97.0%, positive predictive value of 91.4%, negative predictive value of 90.4%, and an overall diagnostic accuracy of 90.7%. **Conclusion:** The implementation of the Sydney system can result not only in agreement and repeatability of cytologic diagnosis but also in risk assessment on cytology.

Keywords: FNAC, lymph node, Sydney system, Risk of malignancy.

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Introduction

Lymph node fine needle aspiration cytology (FNAC) is a quick, affordable, and minimally invasive technique that also facilitates auxiliary methods including immunocytochemistry, flow cytometry, and cell block production.[1,2] Cytology specimens yield intact, well-preserved cells with superior DNA and RNA quality compared to formalin-fixed, paraffin-embedded tissues.[3]

Histopathological evaluation of a tissue biopsy is still the gold standard for diagnosing lymphadenopathy. When surgery isn't feasible due to age or illness, FNAC offers a minimally invasive diagnostic alternative, aiding in treatment planning.[4,5] FNAC of accessible lymph nodes in the neck, axilla, and groin can be performed even in the resource-limited settings.[5]

Considering a large number of benign and malignant conditions presenting as lymphadenopathy; the clinical history, physical examination, and radiological features are to be correlated and communicated well to the clinicians through the use of a standardized categorization.[6]

Nevertheless, the traditional method of reporting lymph node smears is devoid of uniform diagnostic classification, widely recognized nomenclature for reporting results, and classification of risk of malignancy and subsequent treatment.[7] For consistent and standardized reporting, and to enhance communication with clinicians, "The Sydney system" for classification and diagnosis of lymph node cytopathology was proposed in 2020 by the International Academy of Cytology (IAC) at Sydney 20th IAC Congress.[1]

Hence, the purpose of the current study is to assess the Sydney System's suitability for lymph node FNAC and its correlation with histopathology to assess its diagnostic accuracy.

Materials and Methods

The research took place at Adesh Medical College and Hospital's pathology department in Haryana. It was a hospital-based, retrospective study that examined data from January 1, 2023, to December 31, 2024, a span of two years. The study only

Address for correspondence: Dr. Sukhjinder Kaur, Assistant Professor, Department of Pathology, ESIC Medical College and Hospital, Bharat Nagar, Ludhiana, Punjab, India.
E-mail: sukhi.tt@gmail.com

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considered the records of patients who had undergone lymph node FNAC and subsequently had a biopsy for histopathological confirmation. An ethics approval was secured from the Institutional Research Committee (IRC) and Institutional Ethical Committee (IEC) of Adesh Medical College (No. AMCH/IRC/25/03).

Inclusion Criteria:

All patients from various departments presenting with lymph node swellings, who underwent FNAC procedure (Direct as well as guided) and subsequent excision of the swellings.

Exclusion Criteria:

1. Those patients whose histopathological diagnosis were not available, were not included in the research.
2. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy were not calculated for FNAC samples that fell into the non-diagnostic group (L1).

Two pathologists reviewed the original diagnoses. There was an endeavour to align the FNAC diagnosis with the Sydney system of lymph node cytology reporting and classification. This system comprises categories L1: inadequate or non-diagnostic; L2: benign; L3: atypical cells of undetermined significance or atypical lymphoid cells (AUS/ALUS); L4: suspicious; and L5: malignant. The correlation between FNAC diagnoses and histopathologic diagnoses was used to calculate the ROM and diagnostic accuracy. SPSS Version 27 was used to calculate the lymph node FNAC's sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. For calculation of above-mentioned parameters, the criteria followed are:

- True positive- L5, L4, and L3 [any histologically confirmed malignant lesion with a malignant (L5), suspicious (L4) or atypical (L3) cytological diagnosis].
- True negative- L2 [any histologically confirmed benign lesion with a benign (L2) diagnosis].
- False positive - any histologically benign lesion with an L5, L4, or L3 cytological diagnosis.
- False negative - any histologically malignant lesion with an L2 cytological diagnosis.

The ROM was calculated by dividing the number of malignant cases with histological confirmation by the total number of patients in each diagnostic group.

Results

During the study period, 385 patients underwent FNAC. However, this two-year retrospective study included total 290 patients whose histopathology was available. The minimum age of presentation was 3 years and maximum being 85 years. 139 males (47.9%) and 151(52.1%) females underwent the procedure during these two years. The age range of 41 to 60 years old accounted for the greatest number of patients who were seen. Most of the patients had cervical lymphadenopathy (88.2%), however, mediastinal, inguinal, intra-parotid, axillary and post-auricular swellings were also seen.

Table 1: The Sydney System of Classification's lymph node FNAC case distribution

Category	No. of cases (%)
Non-Diagnostic (L1)	13(4.5)
Benign (L2)	207(71.3)
Atypia of Undetermined Significance (L3)	20 (6.9)
Suspicious of Malignancy (L4)	15(5.1)
Malignant (L5)	35 (12.1)
Total	290

By applying Sydney system of classification, the cytological diagnosis was grouped into five categories; non-diagnostic (L1) -13 cases (4.48%), Benign (L2) - 207(71.37%), Atypia of Undetermined Significance (L3) - 20 cases (6.89%), Suspicious of malignancy (L4) - 15cases (5.17%) and Malignant (L5) - 35 cases (12.06%) [Table 1].

Representative depiction of lymph node cytology according to the Sydney system category: Fig.1a- 1e (L1 and L2 categories) & 2a- 2f (L3-L5 categories).

Table 2: Correlation between the final diagnosis in each category and the Sydney System diagnostic category's histology and range of motion

Category	No. of cases diagnosed on Cytopathology	Cases confirmed by Histopathology		ROM (%)
		Benign	Malignant	
Non-Diagnostic (L1)	13	*n*= 5 • Tubercular lymphadenitis- 2 • Reactive lymphadenitis-3	*n*= 8 • Metastatic carcinoma-5 • Non-Hodgkin lymphoma-3	61.50
Benign (L2)	207	*n*=194 • Tubercular lymphadenitis-91 • Reactive lymphadenitis-95 • Suppurative lymphadenitis-7 • Sinus histiocytosis-1	*n*=13 • Metastatic carcinoma-8 • Non-Hodgkin lymphoma-5	16

Atypia of Undetermined Significance (L3)	20	*n*= 5 • Reactive lymphadenitis-5	*n*=15 • Hodgkin lymphoma-7 • Non-Hodgkin lymphoma – 5 • Metastatic carcinoma-3	75
Suspicious of Malignancy (L4)	15	*n*= 1 • Reactive lymphadenitis-1	*n*= 14 • Hodgkin lymphoma-09 • Non-Hodgkin lymphoma-05	93.3
Malignant (L5)	35	*n*=0	35	100
Total	290	186	104	

Histopathological correlation: [Table 2] illustrates the relationship between the classification of cytological smears and the final diagnosis based on HPE and ROM. The ROM was determined for every diagnostic group.

ROM was highest in categories L4 (93.3%) and L5 (100%), and lowest was seen in category L2 (6.3%). Categories L1 (61.5%) and L3 (75%) showed intermediate values.

Table 3: Sensitivity, specificity, PPV, NPV, and diagnostic accuracy are calculated (taking cases in L3, L4, and L5 as true positives)

Indicators	Percentage
Sensitivity = TP/(TP+FN)	75.2%
Specificity= TN/ (TN+FP)	97.0%
PPV = TP/(TP+FP)	91.4%
NPV = TN/ (TN+FN)	90.4%
Diagnostic accuracy = (TP+TN)/ (TP+TN+FP+FN)	90.7%

Sensitivity was 75.2%, specificity was 97.0%, PPV was 91.4%, and NPV was 90.4% when suspicious (L4), malignant (L5), and atypical lymphoid cells of undetermined/uncertain significance (L3) were deemed positive. 90.7% of the diagnoses were correct highlighting the reliability of the proposed system in distinguishing malignant from non-malignant lymph node lesions [Table 3].

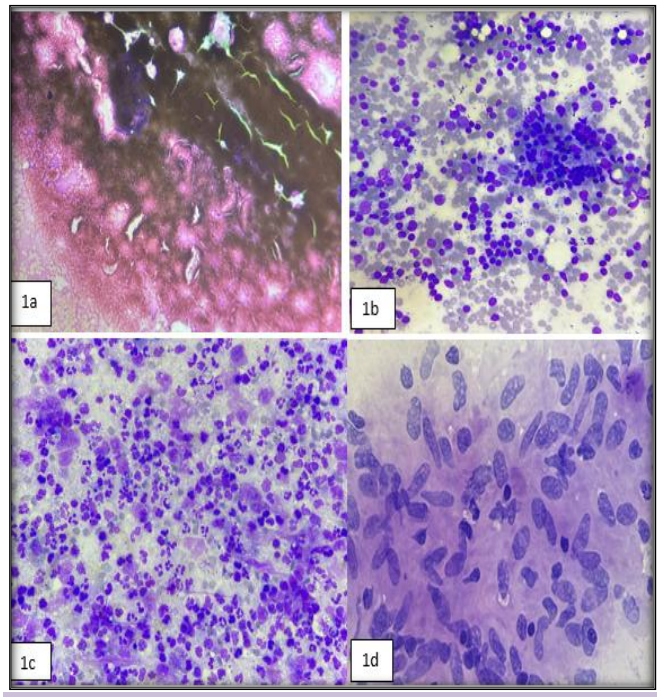
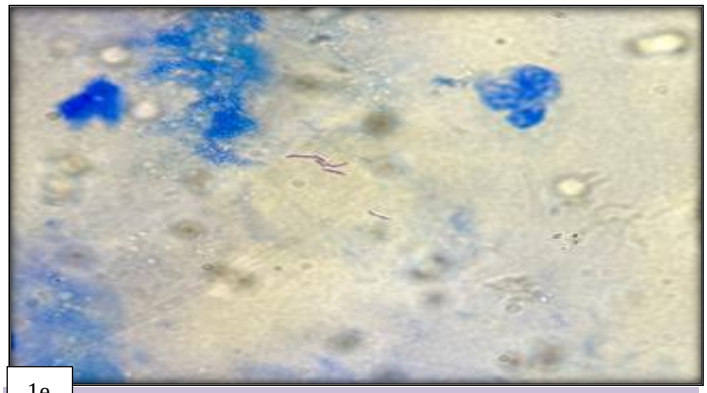


Figure 1: 1a- Blood only (L1: Non -diagnostic), H&E stain 40x. & 1b- Reactive lymphadenitis (L2: Benign), MGG stain 40x, 1c- Suppurative lymphadenitis (L2: Benign), MGG stain 40x, 1d- Granulomatous lymphadenitis (L2: Benign), MGG stain 40x



1e: AFB bacilli, ZN stain 100x

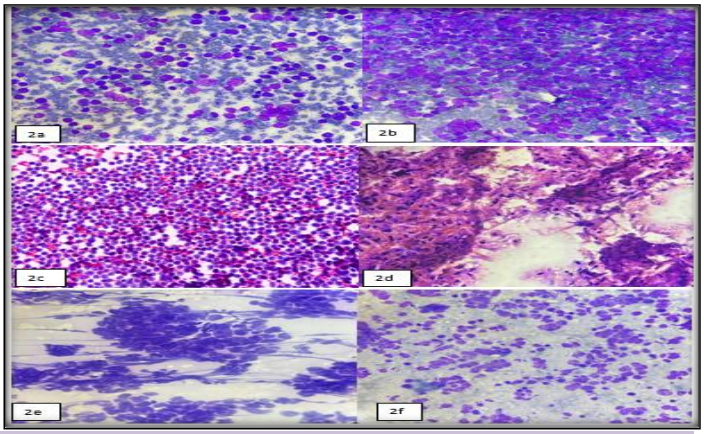


Figure 2: 2a- Large cells scattered among the lymphocytes (L3: AUS), MGG 40x, 2b- Suspicious of Non-Hodgkin lymphoma (L4: Suspicious for malignancy), MGG 40x, 2c- Non-Hodgkin lymphoma (L5: Malignant), MGG 40x, 2d- Metastatic squamous cell carcinoma (L5: Malignant), H&E 40x, 2e-f- Metastatic small cell carcinoma (L5: Malignant), MGG 40x.

Discussion

Standardized reporting ensures uniform use of terms and fosters clearer, more consistent communication with the clinician. The proposed Sydney system for lymph node cytopathology performance, diagnosis, and classification has effectively addressed this issue. The key features of the proposed classification include Rapid on-site evaluation (ROSE), guidance on additional investigations, management advice for each category, and ROM calculation for cytological diagnoses.[1]

Lymphadenopathy (LAP) signals various pathologies including infectious, inflammatory, autoimmune and malignancy. The size, consistency of abnormally enlarged lymph nodes and imaging findings can provide telltale signs of underlying pathologies. FNAC can be performed directly or under Ultrasound/CT guidance in case the lesion is non-palpable or located in close proximity to the blood vessels. LN-FNAC can prove to be an excellent tool when biopsy is not possible in some circumstances, in staging, follow up and even response to treatment, in known cases of malignancy. In clinical trials and research also, the potential candidates with easily accessible LNs diagnosed with metastatic disease, can safely and repeatedly undergo FNAC.[8]

In the present study, n =13 (4.4%) cases were categorized as L1(inadequate/non-diagnostic). This category comprises smears with insufficient cellularity, those showing only blood or necrosis, air-drying artifacts, or degenerated cells unsuitable for morphological assessment. On comparison, the malignant cases outnumbered the benign ones on histopathology. Interestingly, the risk of malignancy (ROM) of L1 category was remarkably high (61.5%). The reason for high malignant probability could be (a) shortcomings in aspiration technique, which often depends on the cytopathologist's level of expertise (b) Sometimes the cystic lymph nodes in malignancy give inadequate material on FNAC (c) lymph nodes are deeply seated or inaccessible (d) fibrotic lymph nodes yield scant aspirates. Das et al,[9] and Caputo A et al,[10] also reported high ROM in the L1 category, 60% and 66.7% respectively. However, according to Gupta et al,[11] 289 (4.1%) of the 6983-lymph node FNAs were classified as non-diagnostic/inadequate (L1). The ROM was 27.5% for L1 category, which was much less than the present study. They recommended repeat aspiration of all L1 aspirates from clinically significant LNs by an experienced cytopathologist, preferably with ROSE, to rule out malignancy and reduce inadequacy and false negatives.

The L2 category comprises maximum number of cases i.e. 207 (71.3%) and ROM was 6.3% This was less than that discovered by Caputo et al,[10] (9.38%) and Gupta et al,[11] (11.5%) whereas Vigliar et al,[6] and Das et al,[9] reported lowest ROM (1.92%) and (4.3%) respectively. Five cases of non-Hodgkin lymphoma and eight cases of metastatic carcinoma comprised the 13 malignant cases that fell into this group. On reviewing these smears, with knowledge of the histopathologic diagnoses, we could acknowledge sampling as well as interpretation errors. In their respective investigations, Gupta et al. and Vigliar et al,[6,11] encountered a similar issue whereby metastatic carcinoma's partial involvement of the lymph nodes failed to produce representative malignant cells on cytologic analysis. The interpretation errors were mainly caused by the smaller size of atypical lymphoid cells, which resembles centrocytes on FNAC, or the presence of a mixed population of lymphoid cells in a partially involved lymph node, or the background showing florid reactive lymphoid cells.

The L3 category is most challenging category to diagnose. According to the Sydney system criteria, this category includes: cases with heterogeneous lymphoid population suggest a reactive process but a follicular lymphoma cannot be excluded/or excess of large cells/ or immature small lymphoid cells/or atypical non lymphoid cells present.[12] The ROM for the L3 group was 73.3%, which is intermediate. In this study, five L3 cases later confirmed benign on histology, were diagnosed as reactive lymphadenitis. The misinterpretation could be because of the growth of interfollicular area, putting them in this group by causing FNAC smears to have big cells with irregular nuclei, conspicuous nucleoli, and sparse cytoplasm. Vigliar et al,[6] and Das et al,[9] similarly noted that reactive lymph nodes brought on by viral infections and inter-follicular proliferation can have cytology problems.

The ROM for the L4 (malignant) and L5 (suspicious for malignancy) categories in this investigation was extremely high, i.e. 93.3% and 100%, respectively. The L5 category included Hodgkin lymphoma, Non-Hodgkin lymphoma, metastatic deposits and melanoma. Das et al,[9] reported ROM of 90.6% and 100%, Gupta et al,[11] reported 88% and 99.6%, while Baruah et al,[7] reported 87.5% and 95% for these categories. Vigliar et al,[6] found 100% ROM in both categories, likely due to widespread use of ancillary techniques and flow cytometry.

Table 4: Comparison of statistical outcomes of cytology using the Sydney system across other studies

	Present study	Das et al. (n=456)[9]	Sreelekshmi et al. (n=250)[12]	Gupta et al. (n= 6983)[11]	Vigliar et al. (n=300)[6]	Baruah et al. (n=220)[7]
Sensitivity	75.2%	82.8%	95.65%	79.87%	98.47%	80.36%
Specificity	97.0%	97.5%	96.29%	98.71%	95.33%	85.71%
Positive Predictive Value (PPV)	91.4%	95.3%	95.65%	98.40%	96.27%	70.31%
Negative Predictive Value (NPV)	94.0%	90.1%	96.29%	83.15%	98.08%	91.2%
Accuracy	90.7%	92%	96%	89.32%	97.06%	84.13%

A comparison of the statistical outcomes of the present study on lymph node cytology using the Sydney system with previously published studies is presented in [Table 4].

In our study, statistical analysis revealed a sensitivity of 75.2% which is at par with observations made by Gupta et al,[11] and Baruah et al.[7] The specificity was 97%, consistent with the

results reported by other authors.[6,9,11,12] Our study's PPV is marginally less than Gupta et al.'s. report,[11] likely due to variations in sample size and the use of ancillary techniques for histopathological confirmation. The diagnostic accuracy in our study is 90.7%, comparable to the findings of Das et al,[9] and Gupta P et al. [11] Despite these variations, the overall diagnostic performance across studies highlights the utility of the Sydney system in achieving reproducible and clinically meaningful cytological interpretations.

Limitations of our study:

1. Ancillary techniques such as Flow Cytometry, Immunohistochemistry, molecular diagnostics are not available in our resource limited setting.
2. Our study is a single center retrospective cross-sectional study and the sample size is small. Therefore, the findings may not be true reflection of the outcomes which could be generalized to whole population of the area.

Conclusion

The Sydney System for reporting and classification of lymph node cytopathology can aid in better communication between clinicians and pathologists. By maintaining the standardization of reports, adequate measures can be taken for patient management.

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Conflicts of interest

There are no conflicts of interest.

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