



Original Article

Categorization of lymph node aspirates based on 'The Sydney system for reporting lymph node cytology' – A four-year retrospective study

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ABSTRACT

Background: Lymph node aspirate cytopathology lacks a uniform reporting format due to the multitude of diseases it encompasses. To address this issue, The Sydney system was introduced to improve the reporting of lymph node cytopathology, with five diagnostic categories to standardize the reporting of lymph node fine needle aspirates. Our study aimed to assess the risk of malignancy associated with each diagnostic category of the Sydney system.

Materials and Methods: The present study is a retrospective cross-sectional analysis of lymph node aspirates obtained through fine-needle aspiration cytology over the past four years. The aspirates were categorized using The Sydney System into five groups from L1 to L5. To measure the risk of malignancy for each diagnostic category, the diagnoses were correlated with the corresponding histopathological diagnoses wherever available. The statistical tools used were sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and risk of malignancy.

Results: 238 cases of lymph nodes FNACs were recorded. These were grouped into five categories using the Sydney system L1(16), L2(148), L3(20), L4(18), and L5(36). Out of these 238 cases, histopathology correlation was available only for 60 cases, which included three cases in L1, 28 cases in L2, four cases in L3, nine cases in L4, and 16 cases in L5 categories, and the risk of malignancy were found to be 0%, 3.57%, 75%, 100%, and 100% for L1, L2, L3, L4, and L5 categories, respectively.

Conclusions: The findings of this study highlight the significant role of the Sydney system in enhancing the reliability of lymph node cytological diagnoses. The Sydney system helps pathologists to standardize reporting for better clinical and surgical management.

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INTRODUCTION

Fine needle aspiration cytology (FNAC) remains a key diagnostic tool in the evaluation of enlarged lymph nodes, as it provides material not only for cytomorphologic assessment but also for a range of ancillary investigations, including cell block immunocytochemistry and targeted next-generation sequencing.¹ Although FNAC is minimally invasive, rapid, and cost-effective, interpretation of lymph node cytology can be challenging due to overlapping morphologic features among reactive, infectious, and neoplastic lesions.² Moreover, the lack of a standardized reporting system has limited its widespread acceptance among clinicians.^{2,3} Histopathology, obtained through core biopsy or excision,

continues to be the gold standard, offering architectural detail and definitive diagnosis. However, it is more invasive and resource-intensive compared to FNAC. Several studies from different regions have highlighted both the utility and limitations of FNAC in lymph node pathology, underscoring the need for standardized diagnostic criteria.

To address this gap, the 20th International Congress of Cytology, held in Sydney in 2019, proposed a categorical framework for the performance, interpretation, and reporting of lymph node cytopathology. This standardized approach, known as the Sydney System, is grounded in extensive international research and expert consensus.^{4,5} Under this system, lymph node aspirates are stratified into five diagnostic categories, each with defined cytologic criteria and associated risk of malignancy. Subsequent studies applying the Sydney System have demonstrated its reproducibility and clinical utility in stratifying patients and guiding management. The present study aimed to evaluate the risk of malignancy associated with each diagnostic category of the Sydney System in our cohort, and to compare findings with those reported in earlier literature.

MATERIALS AND METHODS

The present study is a retrospective cross-sectional study conducted over a period of 4 years (January 2019 – May 2023) in the Department of Pathology, Pushpagiri Institute of Medical Sciences and Research Centre, and was approved by the Institutional Ethics Committee (reference no. PIMSRC/EI/388A/88/2023). The cytological slides were re-evaluated after implementing adequate blinding, whereby the reviewers had no access to the patients' prior diagnoses, or previous slide interpretations. This ensured an unbiased reassessment, and each slide was subsequently classified into one of the diagnostic categories defined by the Sydney System for reporting lymph node cytopathology. All cases of lymphadenopathy in which lymph node (LN) fine needle aspiration cytology (FNAC) was performed during the study period and had corresponding histopathological examination reports or clinical follow-up data available were included in the study. FNAC, a minimally invasive diagnostic procedure, involves using a fine needle to aspirate cellular material from an enlarged lymph node, which is then smeared on slides for microscopic evaluation. In this study, FNACs were performed either by residents from the Department of Pathology, consultant cytopathologists, or under ultrasonographic guidance by an interventional radiologist. The smears were stained with May-Grünwald Giemsa, Hematoxylin and Eosin, or Papanicolaou stains. Histopathology, considered the gold standard, was carried out on lymph node biopsy or excision specimens, where tissue sections were processed, stained, and examined microscopically to provide a definitive diagnosis.

Based on the morphology of the cells, the categories proposed in the Sydney system are: L1 for inadequate/nondiagnostic cases; L2 for benign; L3 for atypical cells of undetermined significance/ atypical lymphoid cells of uncertain significance (AUS/ALUS); L4 for suspicious for malignancy and L5 for malignant cases.⁴

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To assess the risk of malignancy in each category, histopathological diagnosis data were retrieved and correlated. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for differentiating benign and malignant lesions were calculated. The data analysis was done using Microsoft Excel software.

RESULTS

A total of 238 FNACs were performed for lymphadenopathy during the study period, of which 137 (58%) patients were female, and 101 (42%) patients were male. Most of the patients (46, 19%) were between 51- 60 years of age. 173 patients presented with cervical lymphadenopathy (72.7%) and 37 with axillary lymphadenopathy (15.5%).

238 cases were included in the study, out of which 16 (6.8%) were categorized as L1, inadequate/nondiagnostic; 148 (62.3%) as L2, benign; 20 (8.4%) as L3, atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance (AUS/ALUS); 18 (7.56%) as L4, suspicious and 36 (15.12%) as L5, malignant.

Histopathologic follow-up was available for 60 cases. This included three cases in L1, 28 cases in L2, four cases in L3, nine cases in L4, and 16 cases in L5. The risk of malignancy for these cases was assessed for each category (Table 1).

Table 1: Frequency distribution of various diagnostic categories as per The Sydney system, and their corresponding histopathological outcome, and risk of malignancies.

Category	Cytology	Histopathology		Risk of malignancy (ROM)
		Non-neoplastic	Malignant	
L 1	3	3	0	0%
L 2	28	27	1	3.57%
L 3	4	1	3	75%
L 4	9	0	9	100%
L 5	16	0	16	100%
Total	60	31	29	

The correlation between the categorized cytological smears and their final diagnosis based on histopathological examination and/or clinical follow-up data is shown in Table 2. Three cases (5%) were categorized in the L1 (inadequate) category, and all were non-neoplastic in the final histopathological diagnosis. A total of 28 cases (47%) were categorized under the L2 (benign) category, out of which 27 were non-neoplastic on histopathological follow-up, and one proved to be malignant, which was a case of metastasis from papillary thyroid carcinoma (false negative). The benign cases also included a case of Warthin tumor in the lymph node, which is a rare entity that arises from the entrapped salivary tissue within the lymph node during salivary gland development (fig.1). Other cases were those of tuberculous

lymphadenitis, sarcoidosis, toxoplasmosis, and cat scratch disease. Numerous trophozoites and microgranulomas were identified in the case of toxoplasma lymphadenitis (fig.2). Four cases (7%) were categorized under the L3 (atypia of undetermined significance) category, out of which three (75%) proved to be malignant. The cases that were placed under this category were those showing features of a reactive process where follicular lymphoma could be excluded, and cases with occasional atypical cells. Out of the three malignant cases, two were cases of lymphoproliferative neoplasms, and one was a case of metastatic deposit from nasopharyngeal carcinoma. The L4 (suspicious for

malignancy) category included cases that were suspicious for lymphoma/metastasis. Nine cases (15%) were placed into this category, all of which showed concordant results on histopathological follow-up. This included lymphoproliferative neoplasms as well as metastasis from primary carcinomas such as adenocarcinoma lung, squamous cell carcinoma, and papillary thyroid carcinoma. 16 cases (26%) were categorized under the L5 (malignant) category, all of which showed concordant results on histopathology. Four cases of lymphomas and 12 cases of metastasis were identified. The results of cytological and histopathological correlation are summarized in Table 2.

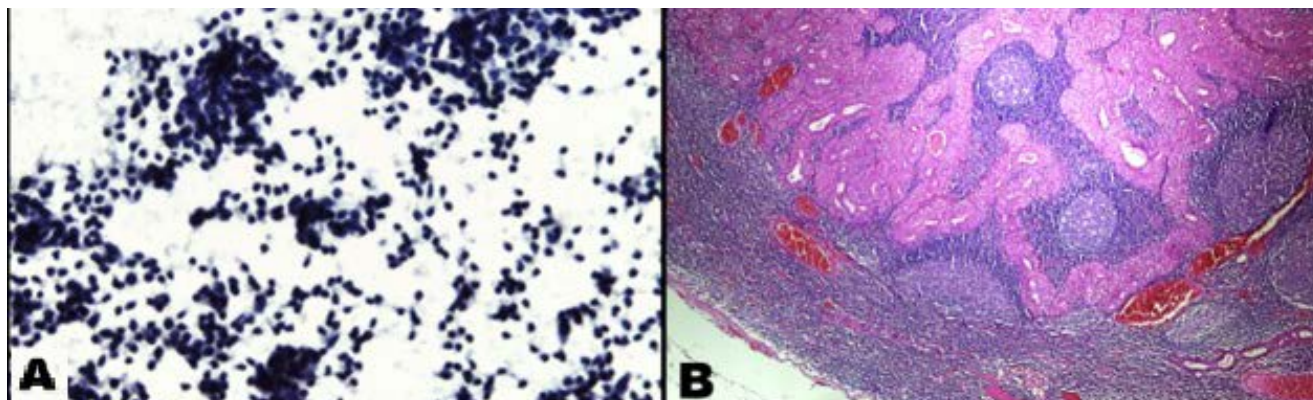


Figure 1: Category 2 - Benign: A. Fine Needle Aspiration Cytology smear showing mature and transforming lymphocytes suggestive of a reactive lymph node. [Papanicolaou; 10x]; B. Corresponding histopathology showing features of Warthin tumor. [HE stain, 10x]

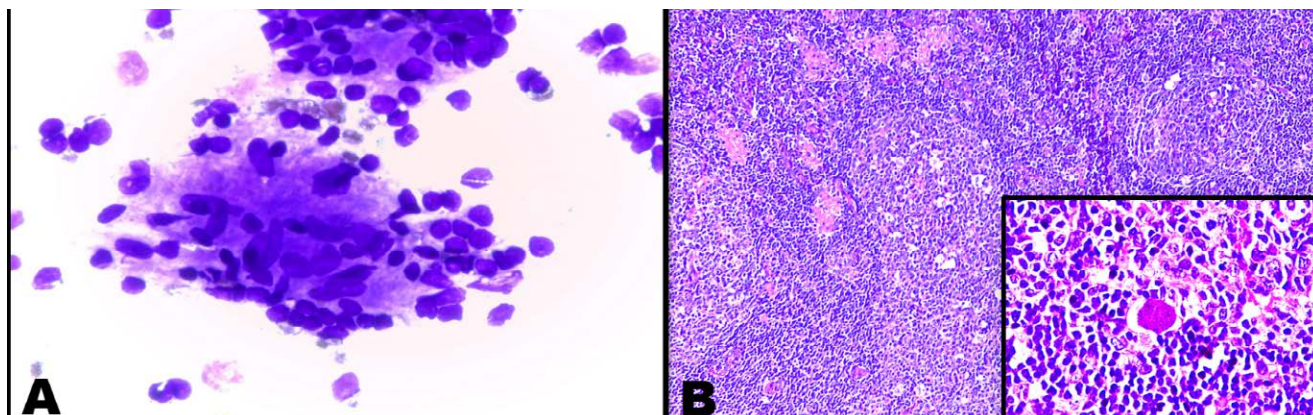


Figure 2: Category 2 - Benign. A. Fine needle aspiration cytology smears showing collection of epithelioid histiocytes forming granulomas [MGG; 400x]; B. Corresponding histopathology revealing microgranulomas. Inset: Macrophage with numerous trophozoites, suggestive of Toxoplasmosis. [HE stain; 40x]

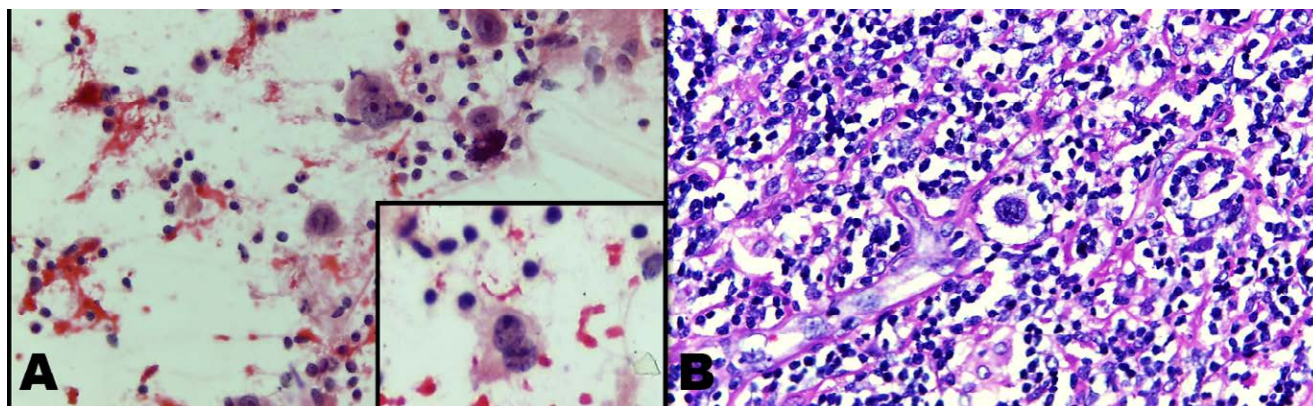


Figure 3: Category 4 - Suspicious for malignancy. A. Fine needle aspiration cytology smear showing Reed-Sternberg cells against a reactive lymphoid background. [Papanicolaou; 40x]; Inset shows Reed-Sternberg cells. B. Corresponding histopathology showing Hodgkin lymphoma with presence of Reed-Sternberg cells. [HE stain, 40x]

Table 2: List of cytologic diagnosis with corresponding histopathological diagnosis and risk of malignancy

Sydney category	Cytology	Histopathology	
		Non-neoplastic/ Benign	Malignant
L1 (n=3)	Non-diagnostic - 3	Tuberculous lymphadenitis - 2	
		Reactive lymph node- 1	
L2 (n=28)	Reactive lymphoid hyperplasia - 11	Reactive lymph node-7	
		Tuberculous lymphadenitis- 2	Metastasis from poorly differentiated carcinoma - 1
		Warthin tumor- 1	
	Granuloma / Suppurative granuloma- 14	Tuberculous lymphadenitis -10	
		Cat scratch disease - 1	
		Toxoplasmosis - 1	
L3 (n=4)	ALUS - (predominantly polymorphous with occ atypical cells)	Sarcoidosis- 2	
		Tuberculous lymphadenitis - 2	
L4 (n=9)	Suspicious for lymphoma/ metastasis -9	Cat scratch disease -1	
L5 (n=16)	Lymphoproliferative neoplasm - 4		Lymphoproliferative neoplasm - 2
			Metastasis from nasopharyngeal carcinoma - 1
			Hodgkin Lymphoma – 1
			Non-Hodgkin Lymphoma – 4
			Metastasis from adenocarcinoma lung - 1
	Metastasis - 12		Metastasis from Squamous cell carcinoma - 2
			Cystic metastasis from Papillary thyroid carcinoma- 1
			Hodgkin Lymphoma – 2
			Non-Hodgkin Lymphoma- 2
			Metastasis from Papillary carcinoma thyroid– 4
			Metastasis from Squamous cell carcinoma– 2
			Metastasis from Adenocarcinoma – 2
			Metastasis from Melanoma – 1
			Metastasis from ovarian carcinoma – 2
			Metastasis from Poorly differentiated carcinoma - 1

The L4 and L5 categories had the highest risk of malignancies of 100% while the L1 category had the lowest ROM of 0% (Table 1). The sensitivity, specificity, positive predictive

value, negative predictive value, and accuracy of FNA were calculated to be 96.6%, 96.4%, 96.6%, 96.4%, and 96.5%, respectively (Table 3).

Table 3: Comparative study between cytological diagnoses and their corresponding histopathological outcome

Cytological diagnosis	Histopathological diagnosis		Total
	Non- malignant	Malignant	
Non-malignant	30	1	31
Malignant	1	28	29
Total	31	29	60
Validity study			
Sensitivity	96.6%		
Specificity	96.4%		
Positive predictive value	96.6%		
Negative predictive value	96.4%		
Accuracy	96.5%		

DISCUSSION

The utilization of standardized reporting systems in cytopathology aids in conveying clinically pertinent information in a consistent and reproducible manner. It also helps decrease the inter-observer variability in reporting and helps to enhance the interpretation and risk assessment.⁶⁻⁸

In the present study, the risk of malignancy was calculated for each diagnostic category defined by the Sydney system of reporting lymph node cytopathology. The risk of malignancy in the non-diagnostic category was 0%, which is considerably lower than the rates reported in previous studies—66.7% by Caputo et al.¹¹ in a cohort of 1,458 lymph node aspirates, 50% by Vigliar et al.⁷ in 300 aspirates, and 27.5% by Gupta et al.¹⁰ in 6,983 aspirates. The use of rapid on-site evaluation (ROSE) and guided FNAC likely contributed to the reduced rate of false-negative results in this category in our study. Additionally, the smaller sample size compared with earlier studies may have further contributed to the lower observed risk of malignancy. Utilization of rapid on-site evaluation (ROSE) and the use of guided FNAC explains the lower rate of false negative results in this category in our study. The smaller sample size in our study, compared with previous reports, may also have contributed to the lower observed risk of malignancy.

The ROM for the benign category (L2) was 3.60%. This is comparable to that found by Vigliar et al.⁷ (1.92%) but lower than that found by Caputo et al.¹¹ (9.38%) and Gupta et al.¹⁰ (11.5%). The single false negative case in our study was that of metastatic deposit from papillary carcinoma thyroid. The histopathology slide showed partial involvement of the lymph node by the metastatic component, and this explains the lack of representation in the cytopathological slide. Similar cases were seen in other studies as well.^{7,12}

The L3, or atypia of undetermined significance category, was introduced to help maintain high negative predictive value in benign categories and high positive predictive values in malignant categories. In our study, the L3 category had a ROM of 75%. This was higher than that in the studies conducted by Caputo et al.¹¹ (28.6%), Vigliar et al.⁷ (58.3%), and Gupta et al.¹⁰ (66.7%). The single benign case in histopathological sections in this category was that of reactive lymphadenitis, which showed interfollicular expansion resulting in cytological smears with large cells having irregular nuclei, prominent nucleoli, and scant cytoplasm.

The L4 (suspicious for malignancy) and L5 (malignant) categories each had a very high ROM of 100%, which was comparable to that of Vigliar et al.⁷ (100%) for both categories. The ROM calculated for these categories by Gupta et al.¹⁰ was 88% and 99.6%, respectively.

The sensitivity, specificity, NPV, PPV, and accuracy calculated as per our study were 96.6%, 96.4%, 96.4%, 96.6%, and 96.5%. This was all found to be on par with

the studies conducted by Vigliar et al.,⁷ Gupta et al.,¹⁰ and Caputo et al.¹¹

The present study had limitations such as a small sample size, single-center study, and limited use of ancillary techniques.

CONCLUSIONS

The Sydney system for reporting and classifying lymph node cytology plays a crucial role in establishing consistency and reproducibility in cytopathological diagnoses. This approach facilitates a more accurate assessment of the risk of malignancy, contributing to enhanced uniformity in subsequent clinical management decisions. The findings of this study highlight the significant role of the Sydney system in enhancing the reliability of lymph node cytological diagnoses. While the Sydney system seems promising and robust for classification and reporting, it is prudent to conduct multicentric studies with larger sample sizes to thoroughly evaluate the reliability and validity of this system.

Conflicts of interest: None

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