Original Article

Stratification in lymph node cytology using the novel Sydney classification system: A cross sectional study

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ABSTRACT

Objective: The primary objective of this study is to assess the diagnostic performance of Lymph Node Fine-Needle Aspiration Cytology (LN-FNAC) using the Sydney System in a clinical setting, specifically focusing on patients with suspected lymphoma.

Material and Methods: This study employs a mixed-methods approach, combining both retrospective and prospective analyses. This study was conducted in Combined Military Hospital (CMH), Peshawar, Pakistan. The duration of study was from January 2021 to December 2022. Ethical approval was obtained from the Institutional Ethical Review Board Committee prior to the commencement of the study. LN-FNAC Cases meeting inclusion criteria were identified and corresponding histopathology specimens were included whenever available. Sydney System of lymph node classification was applied to categorize FNAC results in real-time. Histopathology served as the gold standard for diagnosis. Standard statistical tests were applied to calculate diagnostic parameters, including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of LN-FNAC. Risk of malignancy (ROM) for each Sydney System diagnostic category was also computed.

Results: Most prevalent category according to Sydney classification was Benign, L2 (39.6%). The sensitivity, specificity, positive predictive value and negative predictive value was 98.2%, 84.3%, 93.2% and 95.6% respectively. The ROM was highest for malignant category (98%) and lowest for benign category (4.5%). Discrepancies between FNAC and histopathology were noted, particularly in Hodgkin lymphoma cases.

Conclusion: This study demonstrates the high diagnostic accuracy of Lymph Node Fine-Needle Aspiration Cytology (LN-FNAC) using the Sydney System, especially in the context of suspected lymphoma. The study contributes essential data to the ongoing validation of the Sydney System, emphasizing its role in standardized and effective diagnostic protocols for lymphoma management.

Keywords: Lymph node FNAC, Lymphoma, Risk of malignancy, Sydney system classification

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INTRODUCTION

Lymphadenopathy, characterized by lymph node enlargement, is a common presentation in medical practice. Traditionally, the diagnosis of lymphoma has involved surgical lymph node excision. However, recent years have seen a significant rise in the adoption of less invasive techniques, such as lymph node fine-needle aspiration cytology (LN-FNAC) and core biopsy, for evaluating lymphoma. Despite their growing use, concerns about the diagnostic accuracy of these methods compared to excisional biopsies persist, leading to varying preferences among practitioners [1-3].

Advancements in integrating flow cytometry and immunohistochemistry into LN-FNAC have improved diagnostic precision, resulting in wider acceptance of this technique. To further augment precision, a novel approach encompassing both core biopsy and fine-needle aspiration (FNA) has been advocated, particularly beneficial in cases with constrained tissue samples [4]. Despite these advancements, the lack of a standardized cytopathological diagnostic classification and

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reporting scheme has caused uncertainty in applying LN-FNAC diagnoses to patient management, potentially leading to suboptimal clinical decisions [5].

Addressing this need for a comprehensive and standardized approach, the 20th International Congress of Cytology introduced the Sydney System for reporting LN-FNAC results. This framework includes two diagnostic levels: a classification into five diagnostic categories (inadequate/insufficient, benign, atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance, suspicious, and malignant), and the utilization of ancillary studies for specific subtyping whenever feasible [5].

While these advancements are promising, additional validation of the Sydney System is imperative [6, 7]. To contribute to this validation effort, we conducted a combined retrospective and prospective analysis of the diagnostic performance of LN-FNAC in our institution, focusing on patients with suspected lymphoma. The primary aim of this study is to assess the applicability of the Sydney System to lymph node FNAC, evaluate its diagnostic accuracy, and determine the risk of malignancy associated with each diagnostic category.

The Sydney System's introduction has paved the way for a standardized approach to lymph node cytopathology reporting, offering a coherent diagnostic framework for better communication amongst laboratories and clinicians. However, the underutilization of the system and limited available data in the literature highlights the necessity for further evaluation and validation. Our study aims to bridge this gap by systematically assessing the diagnostic performance of LN-FNAC in our clinical setting using the Sydney System's categories.

The study's findings will contribute crucial insights into the applicability and reliability of the Sydney System in diagnosis of lymph node diseases. By assessing its diagnostic accuracy and evaluating the associated risk of malignancy, we aim to enhance the understanding of this classification system's applicability in guiding clinical management decisions for patients with suspected lymphoma. This research aligns with the global efforts to establish standardized and effective diagnostic protocols, ultimately improving patient care and refining lymphoma management strategies.

MATERIAL AND METHODS

This study was conducted at the Department of Pathology, Combined Military Hospital (CMH), Peshawar, Pakistan, a renowned tertiary care center catering to the population of Khyber Pakhtunkhwa. CMH Peshawar serves as a crucial referral hub for regions including Bannu, Mardan, Nowshera, Risalpur, Landikotal, and Kohat city. The study timeline spanned from January 2021 to December 2022. Ethical approval was acquired from the Institutional Ethical Review Board Committee prior to the commencement of the study. A non-probability consecutive sampling technique was employed to select patients for the study.

Cases involving patients of all ages and genders were considered, ensuring a diverse representation. Pertinent clinical and demographic data were extracted from test request forms to compile a comprehensive profile of each patient. This encompassed clinical workup, radiological investigations, detailed history of the present complaint, and local examination. All case of lymph node enlargement, irrespective of benign or malignant diagnosis were included. Patients with non-lymphoid aspirates, and those with bleeding disorders were excluded. Data bank of our laboratory was researched for lymph node FNAC cases from January 2021 to December 2021 that tailored to our inclusion criteria including percutaneous aspirations and ultrasound guided FNAC. Corresponding histopathology specimens were also searched using patients name, age, hospital MRN number and contact information. Prospective collection of lymph node FNAC cases was done from January 2022 to December 2022 with corresponding histopathology specimens, whenever possible.

FNAC procedure comprised of care for strict aseptic precautions, following written

consent and detailed discussions about the procedure with the patients. A 22-gauge needle was employed for superficial swellings. All deep and non-approachable lymph nodes were aspirated using ultrasound guidance. Aspirated smears were stained using Hemacolor, hematoxylin and eosin and Papanicolaou stains, enabling effective cytological evaluation. To ensure consistency, cytology slides were re-examined by two experienced histopathologists (having at least 5 years' experience in signing out cytopathology cases), using predefined cytological criteria. Blinding of cases was done with discussion related to discordant cases and a final diagnostic category was decided. The diagnostic categories of the Sydney Classification System were meticulously applied: L1 (Inadequate/Non-Diagnostic), L2 (Benign), L3 (Atypical cells of undetermined significance/Atypical lymphoid cells of uncertain significance), L4 (Suspicious), and L5 (Malignant). Histopathology reports for all included patients were gathered and cross-referenced to validate diagnoses whenever possible. Histopathology served as the gold standard for diagnosis.

Diagnostic parameters were calculated for analytical groups, including benign (L2) and malignant (L4, L5) cases. A two by two table was computed for both categories and the Sensitivity (SN), Specificity (SP), Positive predictive value (PPV), Negative predictive value (NPV) and Accuracy of LN-FNAC was calculated using the following formulas and 95% confidence interval, SN= TP/TP+FN, SP= TN/TN+FP, PPV= TP/TP+FP, NPV= TN/TN+FN. (TP-True positive), (FP-False positive), (TN-True negative) (FN-False negative). Additionally, the risk of malignancy (ROM) for each category was computed by dividing histologically verified malignant cases by the total number of patients with available histopathology in each category.

RESULTS

A total of consecutive 368 cases of LN-FNAC were included in this study from January 2021 to December 2022 with 174 males (47.3%) and 194 females (53.7%). The majority of patients fell within the age range of 20-30 years (44.8%), followed by 31-50 years (36.1%). A significant proportion of cases (64.1%) had no relevant medical history. The cervical group was the most common lymph node location (76.1%), with other locations including axillary (6.3%), submandibular (11.7%), inguinal (2.4%), and supraclavicular (3.5%) (Table-I).

Lymph node aspirates were categorized according to the Sydney System, which included five diagnostic levels. The majority of cases fell into the "Benign" category (39.6%), followed by "Suspicious" (20%) and "Malignant" (15.4%) categories. The "Atypical cells of undetermined significance/Atypical lymphoid cells of uncertain significance" and "Inadequate/Non-diagnostic" categories accounted for 9.7% and 14.9% of cases respectively. The "Suspicious" category was further subcategorized into "Suspicious for Hodgkin lymphoma, suspicious for non-Hodgkin lymphoma and metastasis" with a notable number of cases diagnosed as suspicious for Hodgkin lymphoma (11.6%). In the "Malignant" category, both Hodgkin lymphoma and non-Hodgkin lymphoma were identified, making up 7.3% and 4.6% of cases, respectively (Table-II). Table-III elucidates the correlation between the Sydney System Diagnostic Categories and Histological follow-up for the 368 cases. In the L1 category, 55 cases were diagnosed as inadequate or non-diagnostic samples. However, 10 cases were lost to follow-up, leaving 45 cases for analysis. Within this category, histopathological correlation revealed diagnoses of reactive lymphoid hyperplasia (RLH, n=33), Hodgkin lymphoma (HL, n=11), and metastasis (n=1).

The L2 category, denoting benign conditions, encompassed 146 cases diagnosed by FNAC. However, 102 cases were lost to follow-up. Histopathological correlation within this category revealed a diverse diagnoses, including RLH (n=15), dermatopathic lymphadenitis (n=1), Rosai Dorfman disease (n=7), infectious mononucleosis (n=1), T cell-rich B cell lymphoma (n=1), Chronic granulomatous inflammation (Tuberculosis- n=7 ,Fungal infection- n=3 ,Foreign body reaction-n=1, HL- n=1), and abscess (Acute on chronic non-specific inflammation- n=5, Inflamed

Epidermal inclusion cyst- n=1 and Cat scratch disease- n=1)

The L3 category, signifying atypical cells seen, included 36 cases diagnosed by FNAC. Five cases were lost to follow-up. Histopathological correlation within this category revealed diagnoses of toxoplasmosis (n=3), dermatopathic lymphadenitis (n=2), and HL (n=26). The L4 category, suspicious for malignancy, included 74 cases diagnosed by FNAC. Eight cases were lost to follow-up. Histopathological correlation within this category revealed diagnoses of NHL (Follicular lymphoma -n=6, Diffuse large B cell lymphoma - n=9, Small cell lymphoma -n=4), HL (n=33), RLH (n=6), Infectious mononucleosis (n=1) and Squamous cell carcinoma (n=7).

The L5 category, indicating malignancy, comprised 57 cases diagnosed by FNAC. Six cases were lost to follow-up. Histopathological correlation within this category revealed diagnoses of NHL (Diffuse Large B cell lymphoma– n=11, Small cell lymphoma– n=3, Follicular lymphoma– n=2), HL (n=24), RLH (n=1), Anaplastic thyroid carcinoma (n=2), Squamous cell carcinoma (n=5), Melanoma (n=2) and adenocarcinoma (n=1).

Standard statistical tests were applied and sensitivity, specificity, positive predictive value and negative predictive value of FNAC test was calculated using the 2 x 2 table (Table-IV) and keeping confidence interval at 95%. Histopathological diagnosis was considered as gold standard. Sensitivity of FNAC was 98.2% (94.39% to 99.89%), Specificity 84.3% (91.43% to 98.97%), positive predictive value 93.2% (89.44% to 96.28%) and negative predictive value 95.6% (92.60% to 99.71%).

Risk of Malignancy (ROM) was calculated for each Sydney system diagnostic category. For L1 (Inadequate/Nondiagnostic) category the calculated ROM was 26.7% and for L2 (Benign) ROM has lowest value of 4.5%. For category L3 (Atypical cells of undetermined significance/Atypical lymphoid cells of uncertain significance), the ROM was 83.9% and for L4 (Suspicious for lymphoproliferative disorder/ malignancy), ROM came out to be 89.4%. The ROM for the malignant category was the highest, 98%.

Table-I: Demographics (N=368 cases).

Sample characteristics		Frequency	%
Sex	Male	174	47.3%
	Female	194	53.7%
Age	0-20	57	15.4%
	20-30	165	44.8%
	31-50	113	36.1%
	51-70	33	8.9%
Medical History	Previous pathological diagnosis	132	35.9%
	No relevant history	236	64.1%
Location	Cervical group	280	76.1%
	Axillary	23	6.3%
	Submandibular	43	11.7%
	Inguinal	9	2.4%
	Supraclavicular	13	3.5%

Table-II: Sydney system diagnostic categories.

Diagnostic categories		Frequency	%
L1 Inadequate/ non-diagnostic		55	14.9%
L2 Benign		146	39.6%
L3 AUS/ ALUS	Atypical Lymphoid cells seen	15	4.0%
	Atypical cells seen	21	5.7%
	Total	36	9.7%
L4 Suspicious	NHL	22	6.0%
	HL	43	11.6%
	Metastases	9	2.4%
	Total	74	20%
L5 Malignant	NHL	17	4.6%
	HL	27	7.3%

Metastases	13	3.5%
Total	57	15.4%

Table-III: Correlation between Sydney system diagnostic categories and histology/ clinical follow-up.

Diagnostic categories		FNAC diagnosis	Lost to follow up	Histopathological Correlation
L1 (Inadequate/ non-diagnostic)	55	(n=55)	10	RLH (n = 33) HL (n=11) Metastasis (n=1)
L2 Benign	146	Reactive lymphoid hyperplasia (n=63)	38	Reactive lymphoid hyperplasia (n=15) Dermatopathic lymphadenitis (n=1) Rosai Dorfman disease (n=7) Infectious mononucleosis (n=1) T cell rich B cell lymphoma (n=1)
		Chronic granulomatous inflammation (n=64)	52	Tuberculosis (n=7) Fungal Infection (n=3) Foreign body reaction (n=1) Hodgkin lymphoma(n=1)
		Abscess (n=19)	12	Acute on chronic non-specific inflammation (n=5) Inflamed Epidermal inclusion cyst (n=1) Cat scratch disease (n=1)
L3 AUS/ALUS	36	Atypical cell seen (n=36)	5	Toxoplasmosis(n=3) Dermatopathic lymphadenitis (n=2) Hodgkin lymphoma(n=26)
L4 Suspicious	74	NHL (n=22)	3	Follicular lymphoma (n=6) Diffuse large B cell lymphoma(n=9) Small cell lymphoma(n=4)
		HL (n=43)	3	Reactive lymphoid hyperplasia (n=6) Infectious mononucleosis (n=1) Hodgkin lymphoma (n=33)
		Metastasis (n=9)	2	Squamous cell carcinoma(n=7)
L5 Malignant	57	NHL (n=17)	1	Diffuse large B cell lymphoma(n=11) Small cell lymphoma(n=3) Follicular lymphoma(n=2)
		HL (n=27)	2	Hodgkin lymphoma(n=24) Reactive lymphoid hyperplasia(n=1)
		Metastasis (n=13)	3	Anaplastic thyroid carcinoma(n=2) Squamous cell carcinoma(n=5) Melanoma (n=2) Adenocarcinoma (n=1)
Total	**368**	**237**	**131**	

Table-IV: A 2×2 table of sensitivity and specificity.

Cytology	Histopathology		Total
	Malignant	Benign	
Malignant	TP (109)	FP (8)	117
Benign	FN (2)	TN (42)	44
Total	111	50	161

Table-V: Stratification of ROM in the Sydney system diagnostic categories (N=237 cases).

Sydney System Diagnostic Category	Histological or Clinical Follow-Up	Confirmed by Histopathology		Risk of Malignancy (ROM)
		Benign Lesions	Malignant Lesions	
L1 Inadequate/ non-diagnostic	45	33	12	26.7%
L2 Benign	44	42	2	4.5%
L3 AUS/ALUS	31	5	26	83.9%
L4 Suspicious	66	7	59	89.4%
L5 Malignant	51	1	50	98.0%

DISCUSSION

Persistent lymphadenopathy, particularly prolonged enlargement of lymph nodes 1 cm, is a source of considerable apprehension for patients. FNAC is generally recognized as the accepted minimally invasive procedure for

assessing lymphadenopathy. The Sydney System, an innovative classification framework for LN-FNAC, seeks to standardize result reporting by employing five diagnostic categories. It also advocates for specific subtyping through ancillary studies, when necessary, thereby enriching the diagnostic approach to lymph node conditions.

A total of 368 cases of LN-FNAC were included in this study. Most of the patients were in age range 20-50 years, with cervical lymph node being the most common lymph node location. Similar findings were found in a study by Elena Vigliar *et al* [8]. Majority of the patients presenting to our unit (64.1%) did not have any prior medical history or relevant investigations done. This is a major source of difficulty in reaching a sound diagnosis in FNAC samples as serological and radiological evidences serve as important adjuncts in FNAC diagnosis [9]. Currently a number of authors are suggesting the usefulness of a combined approach including flow cytometry and immunohistochemistry with LN-FNAC [10].

Within our study, 55 cases were categorized under L1 (Inadequate/non-diagnostic). Limitations inherent in lymph node aspiration encompass sampling errors arising from deep-seated or diminutive lymph nodes, extensive necrosis or inflammation and nodal fibrosis. Moreover, inadequacies in the obtained specimens contribute to diagnostic complexities, primarily due to the loss of architectural or vascular patterns and the partial involvement of the lesion within the respective lymph node [11, 12].

Majority of our study cases were diagnosed as benign entities (39.6%), comprising diagnoses including reactive lymphoid hyperplasia, chronic granulomatous inflammation and abscess. Apart from persistently enlarged, painful lymph nodes or lymph nodes not regressing after treatment, most of lymph nodes after a benign LN-FNAC diagnosis are not excised. Prevalence of a high tuberculosis disease burden in Pakistan leads to commencement of anti-tubercular treatment after LN-FNAC diagnosis of chronic granulomatous inflammation, serological tests and gene expert test [13,14]. Two cases in benign category showed discrepancy with Histopathological correlation. One case being Hodgkin lymphoma (Figure-I, II) and other T cell rich/ B cell lymphoma (Figure-III, IV).

Suspicious category L4 showed discrepancy in a total of 7 cases diagnosed as “Suspicious for Hodgkin lymphoma”. Subsequent resection of lymph node showed reactive lymphoid hyperplasia (Figure V, VI) in 6 cases and one case diagnosed as Infectious mononucleosis (Figure-VII, VIII).

L5-Malignant category had one case showing conflicting diagnosis. A case cytologically diagnosed as “Lympho-proliferative disorder- Hodgkin lymphoma” (Figure-IX), on resection showed Reactive lymphoid hyperplasia (Figure-X). This case was immunohistochemically confirmed with CD 3 and CD 20 stains.

Figure-I

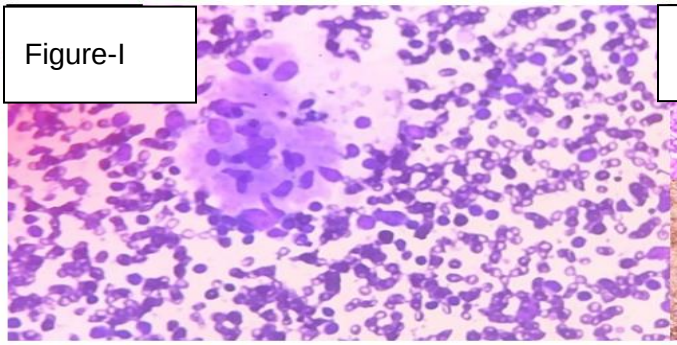

Figure-I: Case cytologically diagnosed as Chronic Granulomatous Inflammation (False negative).

Figure-II

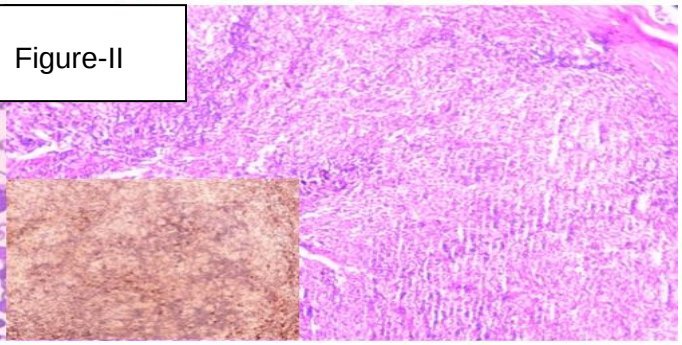

Figure-II: Same case histologically diagnosed as Hodgkin lymphoma. Inset shows CD 15 Positive RS cells.

Figure-III

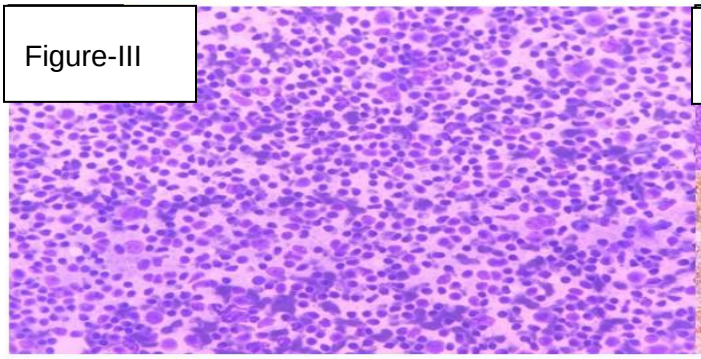

Figure-III: Case cytologically diagnosed as reactive lymphoid hyperplasia (False negative).

Figure-IV

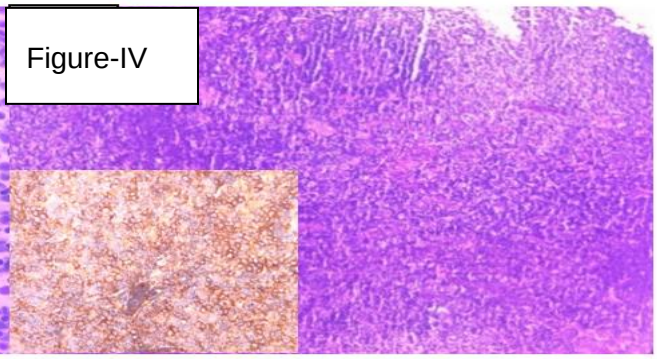

Figure-IV: Same case histologically diagnosed as T cell rich B cell lymphoma. Inset shows CD 3 positive T cells with scattered atypical B cells.

Figure-V

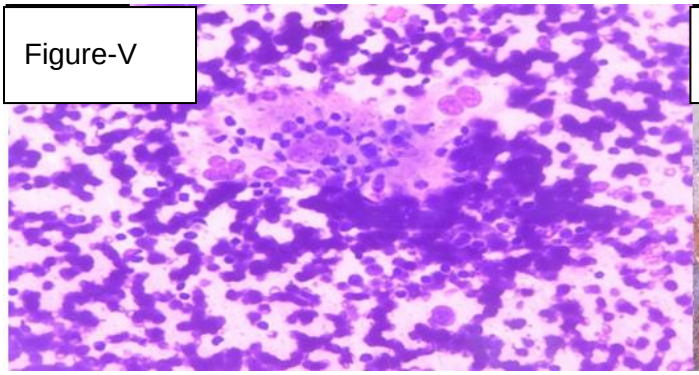

Figure-V: Case cytologically diagnosed as "Suspicious for lympho-proliferative disorder-Hodgkin lymphoma" (False positive).

Figure-VI

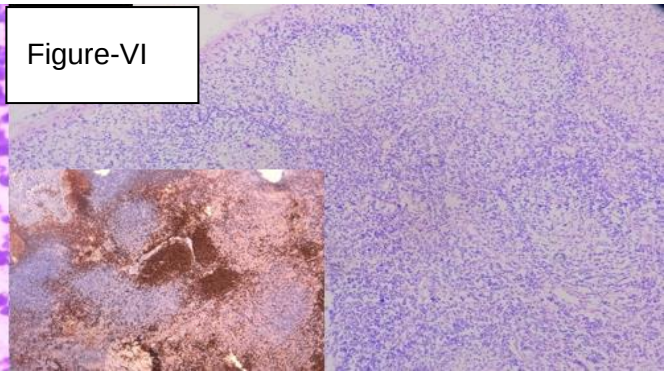

Figure-VI: Same case histologically diagnosed as Reactive lymphoid hyperplasia. Inset shows CD3 positive T cell zones.

Figure-VII

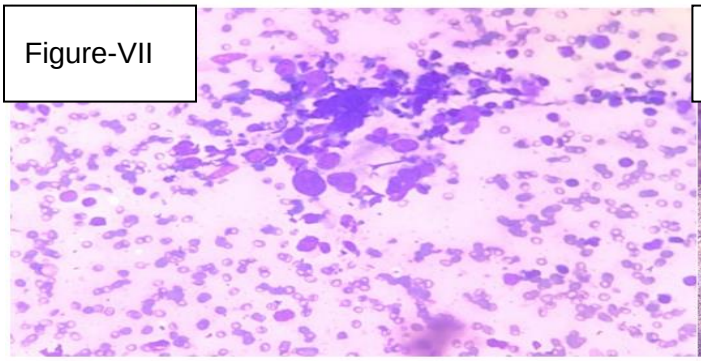

Figure-VII: Case cytologically diagnosed as "Suspicious for lympho-proliferative disorder-Hodgkin lymphoma" (False positive).

Figure-VIII

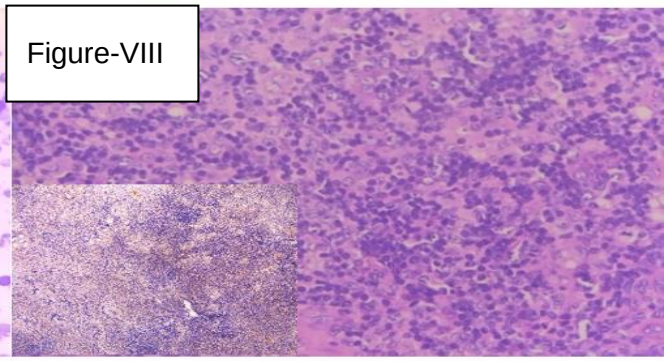

Figure-VIII: Same case histologically diagnosed as "Suggestive of Infectious mononucleosis". Numerous immunoblasts are seen. Inset shows CD30 negative cells.

Figure-IX

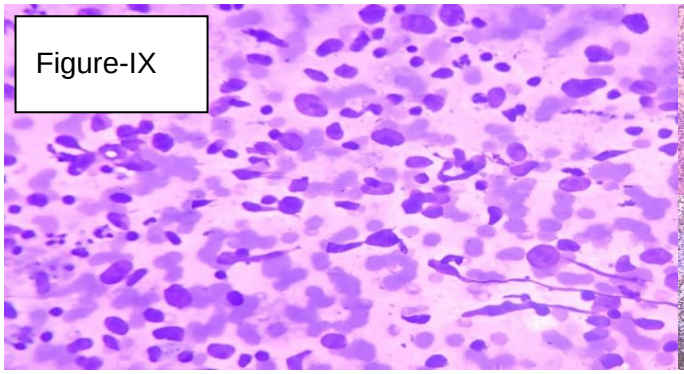

Figure-IX: Case cytologically diagnosed as "Lymphoproliferative disorder – Hodgkin lymphoma" (False positive).

Figure-X

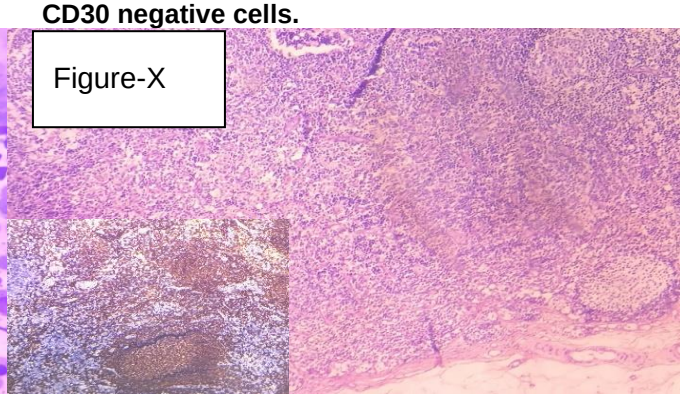

Figure-X: Same case histologically diagnosed as Reactive Lymphoid hyperplasia. Inset shows reactive pattern of staining (CD 20).

Majority of discrepant cases between cytology and histopathology were of Hodgkin lymphoma. Causes of misdiagnosis included sclerosis, a ` lymphoid cell population, vague collections of epithelioid cells and mononuclear RSLIKE cells. Indeed, reactive lymphoid hyperplasia and lymphomas with polymorphous population are difficult to diagnose on cytology alone. Many researchers suggest the use of additional diagnostic techniques (Immuno-cytochemistry and flow cytometry) with LN-FNAC for diagnosis of lymphoma on FNAC [15, 16].

According to our study, the sensitivity of FNAC was high (98.2 %), signifying that there were few false negative tests according to FNAC. However, specificity came out to be comparatively lower (84.3%), meaning a slightly greater number of false positive results. Our study showed a high positive and negative predictive value, 93.2 % and 95.6% respectively. A number of studies show similar findings [2,17-18]. In contrast, a study by Gupta *et al*. showed a lower sensitivity and higher specificity of 79.9% and 98.7% respectively [6]

The risk of malignancy (ROM) was lowest for L2 (Benign) category in our study with a value of 4.5%, similar to findings of a study by Torres Rivas *et al*. [19]. Conversely, studies by Saradva N *et al*. and Gupta *et al*. showed a higher ROM for L2 category of lymph node FNAC, according to Sydney classification. The ROM for L4 category was much lower in study by Saradva N *et al*. (50%) as compared to our study (89.4%). Comparable to our findings of high ROM in L4 and L5 categories are studies by Caputa A *et al*, Robert AS *et al* and few others [20-23].

CONCLUSION

The application of the Sydney System is advocated to achieve consistency and reproducibility in lymph node FNAC diagnoses, aiding in risk-stratification. The study's limitations include its partial retrospective nature, potential selection bias due to consecutive sampling, and the single-center setting, which may impact the generalizability of the findings. This study concludes that FNAC and adherence to the Sydney System, proves to be an accurate and a minimally invasive tool for evaluating lymphadenopathy

CONFLICT OF INTEREST

Authors declare no conflict of interest.

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHORS CONTRIBUTION

Hina Khan: Conceptualization, data curation, validation, methodology, revisions, accountable for all aspects of the work

Abdul Qadir: Methodology, supervision, accountable for all aspects of the work

Sadia Khan: Data analysis, revisions, accountable for all aspects of the work

Shehla Akbar: Data interpretations, revisions, accountable for all aspects of the work

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