ORIGINAL RESEARCH PAPER

Pathology

APPLICATION OF THE PROPOSED SYDNEY SYSTEM IN REPORTING OF THE LYMPH NODE CYTO-PATHOLOGY – A RETROSPECTIVE STUDY

KEY WORDS: Sydney system, lymph node, fine needle aspiration, risk of malignancy.

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ABSTRACT

Introduction: Fine needle aspiration cytology (FNAC) is a widely accepted first line of investigation to diagnose the cause of lymphadenopathy. A standardized categorization and reporting system for lymph node cytology was proposed in 20th International Congress of Cytology at Sydney which consisted of 5 categories (L1, L2, L3, L4, L5) with management recommendations for each. Aims and Objective: To review the application of the Sydney system in achieving a uniform standardized approach for classifying and reporting lymph node cytology and to assess the risk of malignancy (ROM) for each category. **Materials and Methods**: A 2 year single institute retrospective study. Clinical details were collected from the patient records and cytology smears were reviewed by 2 cyto-pathologists as per the Sydney system. Histological correlation was done wherever possible. Statistical analysis was performed. **Results:** 437 cases were re-evaluated, with mean age of 39.66 years, slight male preponderance and cervical lymph node being the most common site. L2/Benign was the most common category with reactive lymphoid hyperplasia being the most common diagnosis and metastatic squamous cell carcinoma was the most common L5/malignant diagnosis. Histopathological correlation was available for 40 (9.1%) cases and the highest calculated risk of malignancy (ROM) was for L4 and L5 categories (100% each). The diagnostic accuracy of the proposed Sydney system in our study was 96.66%. **Conclusion:** The proposed Sydney system improves the diagnostic accuracy and standardizes the reporting of lymph node cyto-pathology. It improves the patient care by giving management recommendation to the clinicians.

INTRODUCTION:

Fine needle aspiration cytology (FNAC) is a first line of investigation that is accepted widely to diagnose the cause of lymphadenopathy in patients of all age groups. It has several advantages such as being cost effective, rapid and minimally invasive. It not only provides sufficient material for cyto-morphological study but also for other ancillary techniques like flow cytometry, immunocytochemistry and fluorescent in situ hybridization[1-5].

But often identifying the pathology producing lymphadenopathy can be challenging by FNAC due to overlapping features between pathologies and wide variety of benign and malignant conditions presenting as lymphadenopathy[3,4]. This added with lack of a standardized reporting system for clear communication between cyto-pathologists and clinicians that can give management advice was one of the drawbacks of lymph node FNAC until a few years ago[5,6].

To overcome the latter setback, a standardized categorization and reporting system for lymph node cytology was proposed in 20th International Congress of Cytology at Sydney by renowned cyto-pathologists from all over the world. There were five cytological categories based on various cytological features with management advice given for each category in this system[1,3,4,6]. The five categories of the Sydney system include L1 - inadequate/non-diagnostic, L2 - benign, L3 - atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance, L4 - suspicious for malignancy and L5 – malignant[6]. The literatures available so far state that the Sydney system is a uniform, reproducible reporting system and provides a simpler way of communication between the clinicians and the cyto-pathologists[1,4,6,12].

The aim of our study is to review the application of the Sydney system in achieving a uniform standardized approach for classifying and reporting lymph node cytology and to assess the risk of malignancy (ROM) by correlating with the corresponding histopathological diagnosis wherever possible.

DATA COLLECTION MATERIALS AND METHODS:

This was a retrospective study which included all the cases of lymph node fine needle aspiration cytology that were conducted in the Department of Pathology at Shivamogga Institute of Medical Sciences, Shimoga for 2 years from January 2021 to December 2022. The study was approved by the Institutional ethics committee. The clinical, demographic and radiological details were collected from the patient requisition form. The procedure was explained to the patients, written informed consents were obtained from them and the FNACs were performed under aseptic precautions using a 23 gauge needle. The aspirates that were stained using Geimsa and Hematoxylin-eosin stain were reviewed by two cyto-pathologists using cytological criteria defined by the proposed Sydney system for reporting lymph node cytology and categorized accordingly. Histopathological correlation was done by looking in the histopathology archive of the department, wherever the corresponding histopathology slides and forms were available. By dividing the number of histopathologically confirmed malignant cases from the total number of cases with a histopathological diagnosis in a category, the risk of malignancy (ROM) was calculated for that category. Since histopathology was considered as the gold standard test in our study, true positive (TP) were the cases

which were malignant both on cytology and histopathology, true negative (TN) were the cases which were benign both on cytology and histopathology, false positive (FP) were the cases which were diagnosed malignant on cytology but benign on histopathology, false negative (FN) were the cases made benign on cytology and malignant on histopathology. Using above parameters sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of the FNAC for lymph node were calculated.

RESULTS:

A total of 437 non guided fine needle aspirations were performed from lymph node during the duration of the study. The age ranged from 3months to 96 years, with most common age category 18 to 64 years and mean age group of 39.66 years. There were 226 (51.7%) male patients and 211 (48.3%) female patients with male to female gender ratio of 1.07:1. The most common lymph node groups aspirated were cervical nodes which were 386 (88%) cases followed by axillary 21 (5%), inguinal 18 (4.1%), pre-auricular 5 (1.1%), post-auricular 4 (1%), suboccipital 2 (0.5%) and femoral 1 (0.2%) lymph nodes.

There were 36 (8.23%) cases which were categorized under non-diagnostic/inadequate L1 category of Sydney system. 34 of them showed only hemorrhage and the rest 2 cases showed predominantly necrosis. The benign L2 category was the most common category in our study and consisted of 277 (63.4%) cases. In this the most common diagnosis was reactive lymphoid hyperplasia (Fig 1) in 150 (54.1%) cases. Other diagnoses in the category included granulomatous lymphadenitis (Fig 2), suppurative lymphadenitis, tubercular lymphadenitis, necrotizing lymphadenitis, chronic lymphadenitis and necrotizing granulomatous lymphadenitis. In cases of tubercular lymphadenitis ZN (Ziehl Neelsen) stain was performed to identify the acid fast bacilli (Fig 3).

There were 5 (1.1%) cases falling under L3 category of atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance (ALUS) in our study. The L4 suspicious for malignancy category had 9 (2.1%) cases with diagnosis of suspicious for metastasis. The L5 category of malignant cases was the second most common category in our study which had 110 (25.5%) cases out of which 64 (58.2%) were diagnosed as metastatic deposits, 43 (39%) cases were assigned malignancy not otherwise specified (NOS) category and 3 (2.7%) were diagnosed as Non Hodgkin lymphoma. Metastatic squamous cell carcinoma 45 (41%) cases was the most common malignant diagnosis (Fig 4). Other metastatic deposits included carcinoma breast, poorly differentiated carcinoma, adenocarcinoma, metastasis from papillary thyroid carcinoma (Fig 5) and metastasis from malignant germ cell tumor (Fig 6).

Table 1 depicts the Sydney system category wise cytological diagnoses of all the lymph node fine needle aspirate cases.

Table – 1 Category Wise Cytological Diagnoses

Category	Cytological diagnosis	No. of cases
L1- inadequate/non-diagnostic	Hemorrhage	34
	Necrosis	2
L2- benign	Reactive lymphoid hyperplasia	150
	Granulomatous lymphadenitis	59
	Suppurative lymphadenitis	21
	Tubercular lymphadenitis	19
	Necrotizing lymphadenitis	13
	Chronic lymphadenitis	8
	Necrotizing granulomatous lymphadenitis	7
L3- atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance	Atypical cells	5
L4- suspicious for malignancy	Suspicious for metastatic deposits	9
L5- malignant	Metastatic squamous cell carcinoma	45
	Metastatic breast carcinoma	8
	Metastatic adenocarcinoma	4
	Metastatic poorly differentiated carcinoma	5
	Metastatic papillary carcinoma thyroid	1
	Metastatic malignant germ cell tumor	1
	Non Hodgkin Lymphoma	3
	Not otherwise specified (NOS)	43

40 (9.15%) out of 437 cytology cases had histopathology slides and records available. 19 (47.5%) of these cases had benign and the rest 21 (52.5%) cases had malignant diagnoses. Granulomatous lymphadenitis 10 (25%) was the most common histopathological diagnosis. Metastasis from breast carcinoma 8 (20%) and squamous cell carcinoma 8 (20%) were the most common malignant histopathological diagnoses. Histopathological correlation was available for 6 (16.6%) out of 36 cases in L1 category and 3 of them were diagnosed malignant, and the ROM for this category was 50%. Out of 277 cases in L2 category 17 (6.13%) had histopathological correlation and 1 of it turned out to be malignant. ROM for category L2 was 5.90%. 2 (22.2%) of 9 cases from L4 category had histopathological correlation and both of them were confirmed to be malignant, hence the ROM of L4 category was 100%. 15 (13.6%) of 110 cases in L5 category had histopathological correlation and all 15 cases has confirmed malignant features. The ROM for this category was 100%. We did not find any histopathological correlation for category L3.

Based on the cytology and histopathological correlation, the sensitivity, specificity, PPV, NPV and diagnostic accuracy of our study was 92.85%, 100%, 100%, 94.11% and 96.66% respectively.

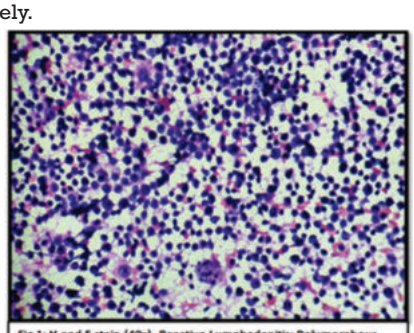

Fig 1: H and E stain (40x). Reactive Lymphadenitis: Polymorphous population of lymphocytes at varying stages of maturation with tingible body macrophages.

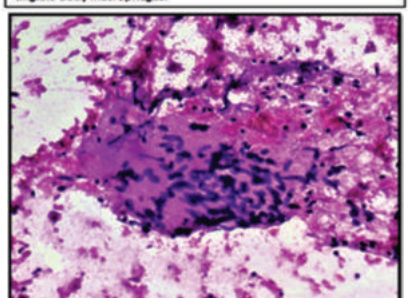

Fig 2: H and E stain (40x). Granulomatous Lymphadenitis: Smear shows granuloma with collection of epithelioid cell aggregates and lymphocytes.

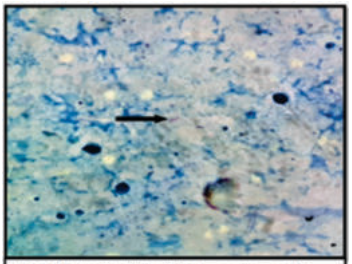

Fig 3: Ziehl Neelsen stain (100x) with black arrow showing acid fast mycobacterium tuberculosis.

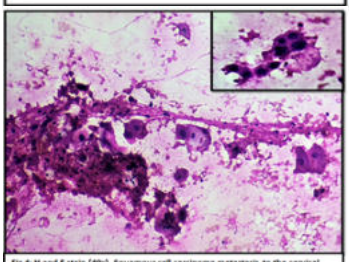

Fig 4: H and E stain (40x). Squamous cell carcinoma metastasis to the cervical lymph node. The outer picture shows scattered atypical squamous cells with pleomorphic nucleus and abundant cytoplasm arranged against a dirty background consisting of necrosis. The picture in picture shows a sheet of immature squamous cells with high N:C ratio and hyperchromatic nucleus.

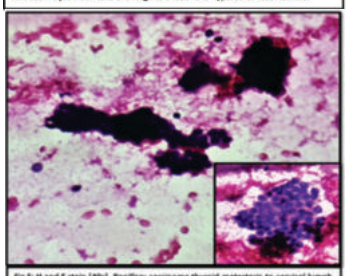

Fig 5: H and E stain (40x). Papillary carcinoma thyroid metastasis to cervical lymph node in a 60 year old male patient. Outside picture shows papillary architecture of thyroid follicular cells. Picture in picture shows longitudinal nuclear grooves in the thyroid follicular cells.

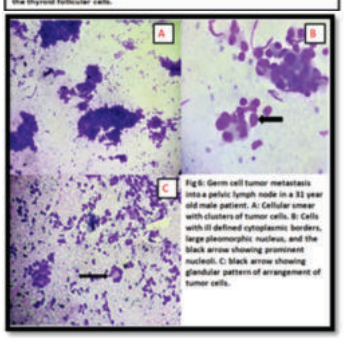

Fig 6: Germ cell tumor metastasis into a pelvic lymph node in a 31 year old male patient. A: Cellular smear with clusters of tumor cells. B: Cells with ill defined cytoplasmic borders, large pleomorphic nucleus, and the black arrow showing prominent nucleoli. C: black arrow showing glandular pattern of arrangement of tumor cells.

DISCUSSION:

Several infective, malignant and benign conditions present as lymphadenopathy in the outpatient department and FNA is a rapid efficient way to evaluate the cause[1-5]. There was no universally accepted system for lymph node cytology reporting until 2019, when the 20th International Cytology Congress was held and the committee of international cyto-pathologists came up with the proposed Sydney system for reporting lymph node cytology consisting of 5 categories[6]. This system not only provided the diagnostic criteria for each category but also gave management guidelines for each which were aimed at helping in better disease management[1-6].

Since this system was proposed recently, there were only few publications to compare our study with. This system of categorization was deemed easy to implement by the 2 cyto-pathologists who reviewed the cytology smears in our study. The retrospective study conducted by Gupta P et al also had a similar opinion with regards to this system[4]. Ours was a retrospective study which involved 437 lymph node non guided FNA cases over a period of 2 years. Our study had smaller number of cases as compared to the retrospective study by Gupta P et al with 6983 cases in 2 years and Shankar M et al with 1204 cases in 1 year[4,8].The fear associated with the spread of the Covid-19 pandemic might have been the reason behind limited hospital visit by non Covid-19 cases leading to decreased sample size in our study. Vigliar E et al and Rivas HE et al conducted retrospective studies with 300 and 363 cases respectively but considered only ultrasound guided FNA cases as opposed to our study[3,7].

In the present study the mean patient age was 39.66 years and the patient age ranged from 3 months to 96 years. The mean age was comparable to Gupta P et al (38.9 years)[4]. It was lower than the study by Vigliar E et al (54.6 years) and Rivas HE et al (54 years)[3,7]. Our study had male preponderance (M:F = 1.07:1) with most common site being cervical lymph node (88%) which was in concordance with the studies conducted by Joshee A et al, Gupta P et al and Shankar M et al[1,4,8].

Our study had 36 (8.23%) cases under L1 category. It was comparable to Joshee A et al 148 (10.5%) and Shankar M et al 127 (10.5%)[1,8]. Gupta P et al had a lower percentage of L1 category cases 289 (4.1%) due to the utilization of rapid on-site evaluation (ROSE) technique[4,9]. Vigliar E et al 20 (6.7%) and Rivas HE et al 13(3.58%) had smaller number of L1 category cases due to the performance of FNA under ultrasound guidance[3,7]. In the current study L2 category had 277 (63.4%) cases which was comparable with Joshee A et al (66.29%) and Shankar M et al (66.86%)[1,8].

L3 category had 5 (1.1%) cases in our study which was similar to Gupta P et al (0.5%) and Rivas HE et al (1.93%)[4,7]. Our study had 9 (2.1%) L4 category cases which was comparable with the results of Gupta P et al (1.4%) and Shankar M et al (1.4%)[1,8]. The last L5 category had 110 (25.2%) cases in the present study which was similar to Shankar M et al (20%) and much lesser compared to Gupta P et al (45.4%) and Vigliar E et al (46%)[3,4,8]. The reason for this discordance might be because, Vigliar E et al conducted their study in a referral hospital by including only ultrasound guided FNAs and Gupta P et al had a larger sample size[3,4].

Reactive lymphoid hyperplasia was the most common cytological diagnosis and metastatic squamous cell carcinoma was the most common malignant diagnosis in our study. This was comparable with Joshee A et al[1]. As the study was conducted in a referral hospital the Gupta P et al had metastatic squamous cell carcinoma as the most common diagnosis[4].

The present study had 40 (9.15%) cases with histopathological correlation which was in concordance with Gupta P et al (8.8%)[4]. The percentage was much lower compared to Joshee A et al (18.7%) and Shankar M et al (17.3%)[1,8]. The medical management of cytologically benign cases and the referral of cytologically malignant cases to higher center with ancillary techniques might be the reason for lower percentage of histopathological correlation in our study.

In our study out of 36 cases in L1 category histopathological correlation was available for 6 cases. 3 cases turned out to be malignant on histopathology which made the ROM for this category to be 50%. This was in concordance with the study conducted by Vigliar E et al (50%)[3]. The ROM of our study was much higher compared to Joshee A et al (34.7%) and Gupta P et al (27.5%)[1,4]. There were 34 cases with only hemorrhage in our study. This might be due to the lack of expertise in aspiration technique which depends on the experience of the cyto-pathologist. There were 2 cases with predominantly necrosis in our study. Due to high ROM for this category we recommended repeat FNA by experienced cyto-pathologist, image guided FNA, or excision biopsy in such cases, which were also the management recommendations for L1 category according to the Sydney system. Also application of rapid on-site evaluation (ROSE) helps in reducing false negative rates according to the proposed Sydney system[6].

In current study 17 cases in L2 category had histopathological correlation. 1 case of reactive lymphoid hyperplasia diagnosis on FNA turned out to be Non Hodgkin Lymphoma (NHL) on histopathology. The ROM for this category in our study was 5.9%. This was comparable with the study conducted by Rivas HE et al (3%)[7]. The value was lower compared to Gupta P et al (11.5%) and Shankar M et al (10%)[4,8]. The lower value in our study might be due to the smaller number of cases with histopathological correlation. After reviewing the cytology smear of the case which turned out to be NHL on histopathology we found out that there were both sampling as well as interpretation errors. The partially effaced lymph nodes, predominant reactive lymphoid cells in the background and smaller atypical lymphoid cells are some of the reasons for false negative diagnosis of NHL cases as reactive lymphoid hyperplasia on FNAC[4]. Our study substantiated the same diagnostic challenge which can be prevented by clinical correlation and application of flow-cytometry or immunocytochemistry in cases with clinical or radiological suspicion. Many studies have already proven the value of ancillary techniques such as flow cytometry and immunocytochemistry in diagnosis of lymphoma on FNA[10-12]. The proposed Sydney system also recommended clinical correlation and application of ancillary techniques wherever necessary for this category[6].

The L3 category of our study did not have any histopathological correlation. The L4 category had 2 cases with histopathological correlation and both were confirmed as malignant which made the ROM for this category as 100%. This overestimation might be because of lesser number of available histopathological correlation. We advised excision biopsy for such cases in view of high ROM. However the value was concordant with the studies conducted by Rivas HE et al (100%) and Shankar M et al (100%)[7,8].The study by Joshee A et al had slightly lower ROM (78.5%) for this category[1]. The Sydney system recommended repeating FNA to get material for ancillary tests or performing a core needle/excision biopsy on such cases[6].

15 cases in L5 category in our study had histopathological diagnoses. There were no false positive cases on cytology. Hence the ROM for L5 category was 100% in our study. This was comparable to the study results of Gupta P et al (99.6%), Rivas HE et al (100%) and Shankar M et al (100%)[4,7,8]. We recommended excision biopsy in view of very high ROM which was also the management guidelines by the Sydney system[6].

The sensitivity, specificity, PPV, NPV and diagnostic accuracy in the present study after considering all calculated values were 92.85%, 100%, 100%, 94.11% and 96.66% respectively. Comparison of our study values with other study results are depicted in Table 2.

Table – 2 Comparison Of Our Study Values (in Percentage) With Other Studies.

	Current study	Joshee A et al(1)	Vigliar E et al(3)	Shankar M et al(8)
Sensitivity	92.85	95.12	98.47	99.37
Specificity	100	90.32	95.33	98.31
Positive predictive value (PPV)	100	97.5	96.27	99.6
Negative predictive value (NPV)	94.11	82.35	98.08	98.5
Diagnostic accuracy	96.66	94.16	97.06	98.12

The Sydney system also recommended giving a second level specific diagnosis after primary basic diagnosis in benign and malignant cases[6]. In our study we have given second level diagnosis in benign conditions such as tubercular lymphadenitis after performing Zeihl Neelsen stain. Since ancillary methods like flow cytometry and immunocytochemistry haven't yet been established in our institute, we could not give a secondary specific diagnosis for malignant cases.

CONCLUSION:

Implementation of the proposed Sydney system of classification and reporting lymph node cytology helps in achieving a uniform standardized approach and improves diagnostic accuracy of lymph node FNAC reporting. The risk of malignancy and management recommendations help clinicians to understand the FNAC report in a better way and improve patient care.

Ethical Approval:

This study was reviewed and approved by the Institutional Ethics Committee (IEC) SIMS (Recognized by CDSCO vide Regn. No.ECR / 952 / Inst / KA / 2017 / RR-20 and Recognized by NECRBHR- DHR vide File No. EC / NEW / INST / 2020 / 922)

Limitation Of The Study:

Single institute retrospective study with lesser sample size. Other metacentric and prospective studies with larger sample size are necessary to assess the utility of the proposed Sydney system.

Financial Support And Sponsorship: Nil

Conflicts Of Interest: Nil

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