Original Article

DOI: 10.7860/JCDR/2022/57693.17355

Pathology Section

Diagnostic Utility of Proposed Sydney System of Lymph Node By Fine Needle Aspiration Cytology: A Cross-sectional Study

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ABSTRACT

Introduction: Fine needle aspiration cytology is the basic and simple technique for diagnosis and evaluation of lymphadenopathies. Although large numbers of conditions and cytomorphological overlapping may cause a challenging task in diagnosis. In 2020, an expert panel proposed the Sydney system for classification and reporting of lymph node based on cytology.

Aim: To evaluate the diagnostic utility of the recently proposed Sydney system of reporting for lymph node aspirations.

Materials and Methods: This retrospective cross-sectional study was conducted at M. P. Shah Government Medical College, Jamnagar, Gujarat, India, from January 2020 to January 2022. Total of 194 fine needle aspirations (FNA) of lymph node lesions performed were reviewed and cytologically re-evaluated and classified according to the Sydney system and were compared with its clinical and histopathological details. The statistical analysis was done with the help Statistical Package for Social Sciences (SPSS) version 26.0.

Results: Out of 194 FNA, 8 (4.12%) were inconclusive, 119 (61.34%) benign, 6 (3.09%) atypical lymphocytic lesions, 26 (13.4%) suspicious for malignancy and 35 (18.04%) were malignant including metastasis and lymphomas. Data of 82 cases of histopathological follow-up was available. The sensitivity was 95.2% and the specificity was 94.1%. The positive and negative predictive values were 98.3% and 84.21%, respectively. The Risk of Malignancy (ROM) in category L2 was 0.5%, in category L3 was 50% and in category L4 and L5 were 100%.

Conclusion: The proposed Sydney system for reporting lymph node cytology would be helpful in the improvement of quality of reports, better understanding and communication between clinician and pathologist and thereby improving patient care.

Keywords: Cytopathology, Granulomatous lymphadenitis, Lymphoma, Sensitivity, Specificity

INTRODUCTION

Fine needle aspiration cytology is most common method for evaluation of lymphadenopathy. It gives basic material for cytological evaluation as well as facilitates multitude of ancillary techniques such as, cell block preparation, flowcytometry and immunocytochemistry (ICC) [1]. The reporting of the lymph node cytology is a difficult task as many lesions of lymph nodes share similar cytopathological features. Hence, it becomes subjective for pathologists to interpret the lesion. Presently the diagnosis of lymphoma in FNA is still followed by histopathological confirmation in practice and also due to the lack of a uniform reporting system in LN cytology along with previous challenges, the LN fine needle aspiration cytology is not preferred by clinical practitioners in routine practices [1].

In the year 2020, a categorical system for performance, classification, and reporting of lymph node cytopathology was proposed at the 20th International Congress of Cytology in Sydney [2]. This system also referred to as the Sydney system, is based on well-documented international cytopathology studies, as well as years of experience of the contributing authors from all over the world. It allows for the categorisation of LN-FNA diagnoses, provides a management algorithm, and has been endorsed 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 communication among cytopathologists, haematopathologists, clinicians, surgeons, and other healthcare providers. It also provides the key diagnostic cytopathological features and management recommendations linked to the reporting categories [3].

The classification suggested two levels of diagnostic categories, in which first category is mandatory to categorise the lesion according to broad diagnosis from L1-L5, such as inadequate, benign and malignant. The second diagnostic level aimed at identification of specific diagnostic entities by using ancillary techniques like ICC, florescent *in situ* hybridisation, cell block is used to obtain more accurate diagnosis on cytopathological basis. The classification also recommended the format of lymph node reporting in cytopathological examination in which basic clinical data, radiological findings, site and basic diagnostic categories (L1-L5) are recommended. Additional data such as microscopic description, ancillary techniques and secondary diagnosis if any were also suggested [3]. However the Sydney system remains underutilised and there is limited data in literature to date [4,5]. Therefore the present study was aimed to cognise the diagnostic utility of Sydney reporting system in fine needle aspiration cytology for lymph node lesions.

MATERIALS AND METHODS

This was a retrospective cross-sectional study conducted at M. P. Shah Government Medical College, Jamnagar, Gujarat, India from January 2020 to January 2022. The ethical approval was not taken as the study was to re-evaluate the data and done as a part of departmental audit.

Inclusion criteria: Data of all the cases of Lymph node aspirates from both sexes and all age groups were included.

Exclusion criteria: Non lymph node aspirates were excluded from the study.

A total of 194 cases of lymph nodes FNA performed over last two years with detailed history and diagnosis given at that time were

examined. The cytopathological data of previously reported cases were analysed and classified according to the Sydney system of reporting [2].

Study Procedure

In all the cases the FNA was performed with patient consent,under aseptic conditions with 23 gauge needle. 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.

Atleast 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. Additional Immunohistochemical markers were also done for subtyping of 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 [2]. The first diagnostic level included cases from L1-L5 [2]:

- L1: inadequate/non diagnostic
- L2: benign
- L3: atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance (AUS/ALUS)
- L4: suspicious
- L5: malignant)

While, there was no case in the present study that fell under second diagnostic level.

To assess the diagnostic accuracy the FNA diagnosis, each diagnostic category was compared with histopathologic diagnosis; when no biopsy was performed,clinical follow-up was checked. Out of a total 194 FNA, data of 84 histopathological cases were available.

Risk of Malignancy (ROM) was calculated by dividing the number of cases with a confirmed malignant lesion by the total number of cases with a histological or clinical follow-up within each diagnostic category [4,6].

STATISTICAL ANALYSIS

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 and true negative 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.

RESULTS

Total 194 lymph node fine needle aspiration smears were reviewed during study period, in which 81.4% (n=158) were percutaneous aspiration and 18.6% (n=36) image guided aspirations were taken. The mean age of patients was 39.3 years with age range from 3 months to 90 years. Out of which, 112 (57.7%) were male and 82 (42.3%) were females. Most common site for FNA was cervical lymph nodes, comprising 67.5% (n=131) cases. Second most common site was axillary lymph nodes with 12.3% (n=24) cases, followed by inguinal lymph nodes, 5.15% (n=10) cases, submandibular lymph nodes 5.15% (n=10) cases and 9.7% (n=19) cases from other sites including submental, supraclavicular and infraclavicular lymph nodes.

A total of 4.12% (n=8) cases were reported as non diagnostic/ inconclusive (L1). The majority of them n=6 (75%) showed only blood and no cellularity. Remaining cases (n=2) showed only necrosis. Benign (L2) cytologic diagnosis was seen in 61.34% (n=119) cases, which included 63 (52.9%) cases of granulomatous lymphadenitis, 16 (13.4%) cases of non specific lymphadenitis, 24 (20.2%) cases of reactive lymphadenitis and 11 (9.2%) cases of necrotising lymphadenitis with 5 (4.2%) cases of acute suppurative lymphadenitis. Among granulomatous lymphadenitis, being tuberculosis was diagnosed as the most common cause based on their clinical as well as cytologic features consistent with epitheloid histiocytic cells, multinucleated Langerhans giant cells and areas of necrosis.

Atypia of undetermined significance (AUS) (L3) included 3.09% (n=6) cases with atypical lymphocytic population and atypical non lymphocytic population. Suspicious of malignancy-category L4 cytological diagnosis were rendered in 13.4% (n=26) cases including lymphomas in 8 (30.7%) cases and metastatic lesions in 18 (69.3%) cases.

Malignant lesions (L5) were seen in 35 cases. Amongst these 5 (14.3%) cases were reported as non Hodgkin's lymphoma, 1 (2.9%) case as lymphoproliferative disorder, 82.8% (n=29) cases as metastatic lesions. Among me tastatic lesions, 68.9% (n=20) cases were of metastastic squamous cell carcinoma from the oral cavity or lung and 31.0% (n=09) cases were of metastatic adenocarcinoma from breast, lung and thyroid.

Corresponding histopathological diagnosis were available for 42.3% (n=82) cases, which included benign as well as malignant lesions. Of 82 cases,17 cases were from category L2, 4 cases from category L3, 26 cases from category L4 and 35 cases from L5 category. In the category L2, 10 granulomas and six reactive lymphnodes were concordant with the same histopathological diagnosis, but one case of diffuse large B cell lymphoma was misdiagnosed as reactive lymphadenitis. Also, two cases of Hodgkin's lymphomas were classified as lymphoproliferative disorder and as atypical lymphocytes (L3), respectively in FNA [Table/Fig-1].

For the clinical follow-up of patients with category L2-out of 63 cases of granulomatous lymphadenitis, 10 cases were proven as granulomatous lymphadenitis in histopathological examination and 50 cases were Cartridge Based Nucleic Acid Amplification Test (CB-NAAT) proved cases with infection of M. Tuberculosis. Amongst the 24 cases of reactive lymphadenitis, 7 cases were followed-up based on histopathological biopsies and rest all (n=17) cases were followed-up with regression of lymph node size with antibiotic and anti-inflammatory therapy.

The sensitivity for the present study for Sydney system of reporting was 95.23%, specificity of 94.11%, the positive predictive value was 98.36% and negative predictive value was 84.21%. The details of cytopathological diagnosis according to Sydney reporting system categories along with follow-up histopathological diagnosis of each categories with ROM is mentioned in [Table/Fig-1].

S. No.	Category	Cytology diagnosis (n=194)	Histopathological diagnosis (n=82)	Risk of malignancy (ROM)
1.	L1-Inconclusive (n=8)	Blood-6 Necrosis- 2	-	-
2.	L2-Benign (n=119)	Granulomatous lymphadenitis-63 Reactive lymphadenitis-24 Non specific lymphadenitis-16 Acute suppurative lymphadenitis-5 Necrotising lymphadenitis-11	Granulomatous lymphadenitis-10 Reactive lymphadenitis -6 Diffuse large B cell lymphoma-1	0.5%
3.	L3-Atypia (n=6)	Atypical lymphocytes-3 Atypical non lymphocytic cells-3	Hodgkin's lymphoma -1 Metastasis from breast carcinoma-2 Metastasis from lung carcinoma-1	50%

4.	L4- Suspicious (n=26)	Lymphomas- 8 Metastasis- 18	Diffuse large B cell lymphoma-5 Mantle cell lymphoma- 1 Small cell lymphoma-1 Follicular lymphoma-1 Metastasis from Squamous cell carcinoma from oral cavity-9 Metastasis from Squamous cell carcinoma from lung-3 Metastasis from Ductal carcinoma of breast-3 Metastasis from Adenocarcinoma of lung-1 Metastasis from mucoepidermoid carcinoma-1 Metastasis from papillary carcinoma of thyroid-1	100%
5.	L5- Malignant (n=35)	Non Hodgkin's lymphoma-5 Lymphoproliferative disorder-1 Metastasis-29	Diffuse large B cell lymphoma-4 Follicular lymphoma-1 Hodgkin's lymphoma-1 Metastasis from Squamous cell carcinoma from oral cavity-18 Metastasis from Squamous cell carcinoma from lung-2 Metastasis from Ductal carcinoma of breast-3 Metastasis from Adenocarcinoma of lung-4 Metastasis from papillary carcinoma of thyroid-2	100%

[Table/Fig-1]: Distribution of lymph node FNA cases according to Sydney reporting system and corresponding risk of malignancy.

DISCUSSION

After the successful establishment of Bethesda system for cervical [7] and thyroid cytology [8] and Milan system for salivary gland cytology [9], in 2020 proposal of Sydney system for lymph node was proposed to keep uniform reporting and better communication [3]. The present study showed the diagnostic accuracy of Sydney system in Fine needle aspiration cytology of lymph node pathologies.

In the present study, 67.5% (n=131) patients were having cervical lymphadenopathy, both unilateral as well as bilateral. A study by Robert F suggested 55% of lymphadenopathy occurs at head and neck region [10] Similar findings were also suggested by Gupta P et al., Vigilar E et al., [4,5] [Table/Fig-2A].

In the present study, L2 category showed more prevalence (61.34%) which could be due to low sample size and also could be due to increased prevalence of tuberculosis in the area where study has been conducted. On the contrary, studies by Gupta P et al., Vigilar E et al., [4,5]. showed equal distribution between benign and malignant lesion catagories [Table/Fig-2B].

A. Site of lymphadenopathy	Present study	Gupta P et al., [4]	Vigilar E et al., [5]
Cervical group	67.5%	66.8%	45.3%
Axillary group	12.3%	14%	18.3%
Inguinal group	5.15%	8.1%	9.7%
Submandibular	5.15%	2%	13.3%
Others	9.7%	9.1%	13.4%
B. Categories	**Present study**	**Gupta P et al., [4]**	**Vigilar E et al., [5]**
L1-Non diagnostic	4.12%	4.1%	6.7%
L2- Benign	61.34%	48.6%	34.7%
L3- Atypical	3.09%	0.5%	8.3%
L4- Suspicious	13.4%	1.4%	4.3%
L5-Malignant	18.04%	45.5%	46%

[Table/Fig-2]: A. Comparison of sites of lymphadenopathy B. Distribution of cases in the present study with other studies [4,5].

No histopathological follow-up was rendered in the category L1 in the present study, as six cases showed only blood and two showed necrosis, and risk of malignancy could not be calculated. Whereas, in a study by Gupta P et al., [4] 11 aspirates from category L1 found to be malignant lesions on follow-up examination therefore, the risk of malignancy (ROM) was 27.1%, where as in study of Vigilar E et al., [5] ROM was 50%, which was comparatively higher.

In the category L2, only one case of the benign lesion was falsely interpreted as reactive lymphadenitis which on histopathological and IHC examination was diagnosed as diffuse large B cell lymphoma therefore the ROM was 0.5%. Vigilar E et al., [5] have reported ROM for this category as 1.92% which was similar to the present study.

On the contrary, in a study by Gupta P et al., 35 cases out of 304 cases were found to be malignant and the ROM of this category was 11.5% [4].

Maximum discordant results (false negative) results were found in category L3 where 3 cases were reported as atypical lymphoid and non lymphoid cells which later were diagnosed as Non Hodgkin's lymphoma in 2 cases and metastasis from epithelial malignancy in one of the case. Hence the ROM was 50%. Where as in study of Gupta P et al., [4] , total 16 cases were discordant in the category L3 and the ROM was 66.7. Similarly, the ROM for category L3 was 58.3% in a study by Vigilar E et al., [5]. In the category L4 and L5 the risk of malignancy was found to be 100% , similar to Vigilar E et al., [5] and Gupta P et al., [4] where the ROM was reported to be 88% for L4 and 99.6% for L5.

In the category L5, the sub typing of the Non Hodgkin's lymphoma were followed-up with histopathological examination and Immunohistochemistry (IHC), as IHC was the only ancillary technique which was available at the institute [11]. Due to lack of other ancillary methods like flowcytometry and cell block preparation, those results could not be correlated.

The sensitivity of lymph node FNA in the malignant lesions is variable and it has range from 75-99% [12] while other studies have found that core biopsies for suspicious lymph nodes are more useful in diagnosing malignant lymph node lesions [13]. The present study showed sensitivity and specificity of diagnosing FNA lymph node lesion by using Sydney system of reporting to be as 95.23% and 94.11%, respectively which is similar to the other studies by Vigilar E et al., and Cupato A et al., [4,5,14] [Table/Fig-3].

Variables	Present study	Gupta P et al., [4]	Vigilar E et al., [5]	Cupato A et al., [14]
Sensitivity	95.23%	79.9%	98.4%	97.9%
Specificity	94.11%	98.7%	95.3%	96.2%
Positive predictive value	98.36%	98.4%	96.3%	99.5%
Negative predictive value	84.21%	83.1%	98.1%	86.3%

[Table/Fig-3]: Comparison of various statistical parameters of present study with other similar studies [4,5,14].

Limitation(s)

Small sample size, less histopathological follow-up and lack of adequate ancillary techniques were the main limitations of this study.

CONCLUSION(S)

Lymph node fine needle aspiration cytology helps in the primary diagnosis of lymphadenopathy which is very useful for further management according to the lesions. 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.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 13, 2022
- Manual Googling: Aug 04, 2022
- iThenticate Software: Oct 04, 2022 (14%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **May 11, 2022**
Date of Peer Review: **May 31, 2022**
Date of Acceptance: **Oct 08, 2022**
Date of Publishing: **Dec 01, 2022**