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RESEARCH ARTICLE

APPLICABILITY OF THE PROPOSED SYDNEY SYSTEM: CLASSIFICATION AND REPORTING OF LYMPH NODE FINE-NEEDLE CYTOLOGY

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Abstract

Most of the disease conditions whether benign or malignancypresents as lymphadenopathy. Therefore, first line evaluation of lymphadenopathy of unknown etiology, fine-needle aspiration cytology (FNC) act as an important diagnostic tool. Recently, an expert panel published the proposal of the Sydney system for reporting and classification of lymph node cytopathology. The aim of the present study was to evaluate the applicability of Sydney system of classification and reporting.

Material and method: It is retrospective study done in tertiary health care center in which FNC diagnoses were correlated with histopathological and clinical follow-up, to assess the diagnostic accuracy and the risk of malignancy (ROM) for each diagnostic category. A total of 1204 lymph node FNCs that were performed between 1st of January 2021to 31st of August 2021 were reviewed.

Results: Out of 1204 cases, n=127 cases (10.5%) were re-categorized as L1-inadequate/non-diagnostic; n = 805 (66.8%) as benign (L2); n = 12 (0.99%) as atypical (L3); n = 15 (1.24%) as suspicious (L4), and n = 241 (20%) as malignant (L5). Statistical analysis: Sensitivity 99.37%, specificity 98.31%, positive predictive value 99.6%, negative predictive value 98.5%, and accuracy 98.12%. The ROM was 100% for L4 and L5category, 66.6% for L3, 1.51% and 0.66% for L1 and L2 categories, respectively.

Conclusion:In lymph node FNC reporting, diagnostic accuracy can be improved by the implementation of Sydney system of classification and reporting. Moreover management recommendation specific for each categories with increased ROM that enables the clinician with better management of patient care.

Introduction:-

For diagnosis of cause of lymphadenopathy Fine-needle cytology (FNC) is considered as very important modality. Moreover, it has other advantages such as minimum invasiveness, rapidity, and cost effectiveness. The material aspirated can be used for several ancillary techniques and thus contribute to improve lymph node FNC diagnostic accuracy.[1] However, FNC done forbenign and malignant conditions if combine with ancillary technique like microbiological analysis,immunocytochemistry (ICC), with flow cytometry(FC) and molecular testing data can be

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almost accurately diagnosed.[2-12] Therefore, unnecessary diagnostics surgical procedures can be avoided. Hence psychological and economical burden is reduced to a greater extent. However, confirmation of a malignancy is still done on histo-pathological evalution.[13,14] When a surgery is not feasible or inadvisable as in elderly patients with comorbidities or in metastatic carcinoma, FNC really helpful for nonsurgical management. Most of the disease conditions whether infection (acute, chronic) and malignanciespresent as lymphadenopathy, hence lymph node cytology represents a challenging scenario. To report and to make a diagnosis the clinical history, physical examination, and radiological/ultrasonographic(USG) features are of paramount importance for a cytopathologists.[15,16] In 2020, Sydney system for classification and reporting of lymph node cytopathology was published by expert panels. They proposed the introduction of use of five diagnostic categories.[17] However, due to limited data available in literature, this Sydney system is still not uniformaly used by most of the institutions.[18]

Aim:-

The aim of the present study was to evaluate the applicability of the Sydney system of lymph node FNC and to assess the diagnostic accuracy and the risk of malignancy (ROM) for each diagnostic category.

Materials And Methods:-

This retrospective study was conducted in pathology department in North India tertiary health care center. A search of the database was carried out focusing on patients who underwent lymph node FNC between 1st January 2021 to 31st August 2021.Their cyto and histopathology records were retrieved. Data were recorded like age, sex, clinical history, lymph node location, ancillary studies and final diagnosis.

Every patients's original diagnosis was reviewed and then it was reclassified according to the first diagnostic level of the Sydney system classification like L1 (inadequate/nondiagnostic), L2 (benign), L3(atypical cells of undetermined significance/atypical lymphoid cells of uncertain significance){AUS/ALUS}, L4 (suspicious), L5(malignant). The second diagnostic level, whenever possible, was also recorded.

To assess the risk of malignancy (ROM) and diagnostic accuracy first cytohistopathologicalcorrelation was done when patient managed conservatively, clinical follow-up was done.

Statistical analysis

In statistical analysis specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy of lymph node FNC were assessed. Any histologically or clinically confirmed malignant lesion in categories L3,L4 and L5 was defined as true positive.Also, any histologically or clinically confirmed benign lesion (L2 category) was defined a true negative.Any histologically confirmed malignant lesion with an L2 benign cytological diagnosiswas defined asa false negative case.Any histologically confirmed benign lesion in L5, L4, or L3 categories was defined asfalse positive case. FNC samples yielding (L1) inadequate/nondiagnostic material were excluded from these analyses.

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.

Results:-

Overall, 1204 lymph node FNCs were performed from patients of all ages, ranging from 2 months to 85 years (mean age 26.6 years) and both sex (n = 463 females (38.4%)and n = 741 men (61.5%). lymph node size ranged from 6 to 65 mm (mean size 22 mm).[Table 1] In 16 cases, ancillary techniques were done, in particular, n = 10 ICC analysis, n = 6 FC analysis were performed.

Table 1:- Clinico-pathological summary of patients.

		N=1204	**Percentage**
Gender	Female/male	463/741	38.5%/61.5%
Age			
	Range	2months -85years	
	Mean	26.6 years	
	Median	27.1years	
Location			

	Cervical	716	59.4%
	Submandibular	303	25.1%
	Supraclavicular	110	9.13%
	Axillary	54	4.48%
	Inguinal	21	1.7%
Ancillary test	ICC	10	0.8%
	FC	6	0.5%

Diagnostic Categories

In the present series, n = 127/1204 (10.5%) were re-categorized as L1, inadequate/non- diagnostic; n = 805/1204 (66.86%) as L2, benign; n = 14/1204 (1.2%) as L3, AUS/ALUS; n = 17/1204 (1.4%) as L4, suspicious, including n = 3 suspicious for NHL, n = 14 for metastasis. Finally, the 20% of cases were categorized as L5, malignant (n = 241), further classified into NHL (n = 24), HL (n = 3) and metastasis (n = 214). Being a tertiary health care center we have higher cases belonging to L5 category. Summary of second diagnostic level was shown in Table 2.

Table 2:-Summary of Diagnostic categories.

	N=1204	**PERCENTAGE**
Inadequate/Non-diagnostic (L1)	127	10.5%
Benign; (L2)	805	66.86%
AUS/ALUS; (L3)	14	1.2%
Suspicious (L4)	17	1.4%
Malignant (L5)	241	20%

Histopathological Correlation and Clinical Follow-Up

We had 208 (17.3%) patients with clinico-histopathological correlation mostly for L5 diagnostic category; in fact, in 109 cases, were histologically confirmed malignant cytological diagnoses. Whereas in the L2 diagnostic category, we had only 40 histopathologicalcorrelations were available out of these four cases found to be false negative diagnoses. On histopathology of these cases showed the presence of adenocarcinoma of breast metastases. In L3 category (Atypical or undetermined significance) we had histopathological correlation in 12 cases, 3 of which showed a reactive lymph node hyperplasia therefore, three false positive diagnoses were recorded in the L3 category. Instead, in L4n = 11 cases, were histopathological confirmed the cytological diagnosis. Finally, n = 24 histologic controls were available in L1 cases. N = 525(43.6%) cases were confirmed clinically by follow-up, in L2 category. L4-L5 (n = 103) diagnosis, that did not undergo surgery due to advance stage of disease, co-morbidity, disease relapse. Finally, n = 362 cases (30%) were lost to follow-up. (Table 3)

As far as the second diagnostic level is concerned, histo-pathological correlation was available and confirmed cytological diagnoses in n = 196 samples.

Table 3:- Correlation between Sydney system diagnostic categories and histopathological/clinical follow-up.

	Clinical follow up	**Histopathological correlation**	**Lost to follow up**	**Total**
L1	18	24	85	127
L2	525	40	240	805
L3	0	12	2	14
L4	4	11	2	17
NHL	1	3		
HL	0	0		
Metastases	3	8		
L5	99	109	33	241
NHL	10	14		
HL	1	2		
Metastases*	88	93		

Total	646	196	362	1204

*Metastasis included Squamous cell carcinoma from head and neck, poorly differentiated carcinoma, adenocarcinoma from breast, colon, germ cell tumor, melanoma. Sensitivity 99.37%, specificity 98.31%, positive predictive value 99.6%, negative predictive value 98.5%, and accuracy 98.12%.(Table-4)

Table 4:- Statistical analysis of lymph node FNC.

STATISTIC	**VALUE**	**95%CI**
Sensitivity	99.37%	94.51% to 99.81%
Specificity	98.31%	89.43% to 98.47%
Positive predictive value	99.6%	91.64% to 98.38%
Negative predictive value	98.5%	92.80% to 99.51%
Accuracy	98.12	94.03% to 98.81%

When histo-pathological correlation or clinical follow-up were available: then ROM was calculated for each diagnostic category, category L4 and L5 had the higher ROM (100%); the lower value of ROM was observed in category and L1 (2.38%) and L2 (0.7%) . whereas intermediate ROM values was observed with category L3 (66.6%) [Table 5].

Table 5:- Risk of malignancy (ROM) in the Sydney system diagnostic categories.

Sydney system diagnostic categories	**Histological or Clinical Follow-Up**	**Confirmed Malignant Lesion**	**Risk of Malignancy (ROM)**
L1	42	1	2.38%
L2	565	4	0.7%
L3	12	8	66.6%
L4	15	15	100%
L5	208	208	100%

Discussion:-

For cytopathologist reporting of lymphadenpathies is sometime very challenging. However, when FNC is done with proper technique, correlating it with clinic-radiological finding and coupled with ancillary techniques accurate diagnosis can achieved. In this present study we observed high diagnostic accuracy in L3, L4, L5 categories. Moreover, there is absence of uniform reporting system or guidelines for lymph node FNC enabling clinicians for better management of patients. Furthermore, to limit interobserver variability and to communicate clinically relevant information in a reproducible mannerthe standardized reporting systems is utmost required.[15,16]. It is critical to identify ROM valueand risk stratification common to several entities to minimize the rate of misinterpretation of cytological reports by clinician. Therefore, if for each diagnostic category by giving management recommendations at end mismanagement can be reduced to a greater extent.

In the present study, we observed the applicability of the Sydney system to classify lymph node FNCs into categories with increasing ROMs. ROM of L1 and L2 categories was remarkably low. However, this extremely low value was probably due to the small number of histological controls available. Noteworthy In few cases, despite performing repeat aspiration material was scant and non-diagnostic, thus, a repetition was inadvisable. Therefore, our study also showed that in L1 category that management recommendation are repeat FNC, core-needle biopsy or excision biopsy, based on the specific clinical diagnosis.[17]Also in L1category, rapid on site evaluation (ROSE) by an experienced cytopathologist is required and the use of advanced methods such as liquid-based cytology, may be consideredtoimprove the scant material and hence diagnostic accuracy can be improved.

In this study, among L2 category most of the cases were infective (acute and chronic) lymphadenopathies. However, the role of FNC as a non- invasive procedure cannot be overemphasized in many hospital settings.[18] Interestingly, the four FNC from axillary lymph nodes misdiagnosed as benign instead of breast adenocarcinoma metastases, which may be due partial involvement of lymph nodal hence clinical correlation is advisable.

Like in other cytological reporting systems, presence of an "indeterminate" category in the classification of lymph nodes FNC advisable to maintain a high negative and positive predictive value in the L2 and L5 categories, respectively. Therefore, this L3 category represents anheterogenous group of entities that, in our observation, showed an intermediate ROM (66.6%). In L3category diagnosis was rendered based on the presence of large cells with high nucleo/cytoplasmic (N/C) ratio, enlarged and irregular nuclei, prominent nucleoli, and scant cytoplasm. In L3 category mostly repeat aspiration is not recommended but based on clinical suspicion of malignancy excision is recommended.[17,19]

However, 100% ROM was observed in both categories L5 and L4, it is possible that this L4 represents an overestimation probably due less number of histopathological co-relation was available. Despite that repeat FNC with acquisition of additional material for ancillary techniques or core-needle/excision biopsy, can safely be assume management recommendations in L4 category, which is validated by a highly expected ROM value. A core needle biopsy (CNB) can be considered as "second-line" approach. In fact, this core needle biopsy enables to collect additional material in the L3 and L4 categories for further subtyping of disease.The Sydney system recommends providing, in addition to giving basic diagnosis,a specific benign or malignant second level diagnosis.

The second diagnostic level was given mostly in malignant conditions (L4 and L5) Moreover, the application of ICC panels and flowcytometry coupled with clinical data enabled the identification of primary site in metastatic cases.

Conclusion:-

To conclude, in FNC lymph node reporting, diagnostic accuracy can be improved by the implementation of Sydney system of classification and reporting, by using standardized categories. Moreover management recommendation specific for each categories with increased ROM that enables the clinician with better management of patient care.

Limitation of the study:

Our study was retrospective in nature. So prospective and metacentric studies are required to confirm the Sydney system's usefulness.

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Conflicts of interest:

There are no conflicts of interest.

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