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APPLICATION OF THE NOVEL SYDNEY SYSTEM IN CLASSIFICATION AND REPORTING OF LYMPH NODE FINE NEEDLE ASPIRATION CYTOLOGY

Pathology

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ABSTRACT

Background: Fine Needle Aspiration Cytology (FNAC) is a useful, inexpensive and reliable tool in assessing the lymph node pathology. However, there is no uniform reporting system for lymph node cytology which hampers its vast acceptance among clinicians and cytopathologists. In May 2019, the 20th International Congress of Cytology held in Sydney proposed a categorical system for performance, classification and reporting of lymph node cytopathology, known as the Sydney System. It has been endorsed by the International Academy of Cytology and the European Federation of Cytology Societies. Current study aims at evaluating the applicability of the proposed system. **Methods:** The study was done at Department of Pathology, Gandhi Medical College, Bhopal from 1 January 2021 to June 2021. Overall, 100 FNACs were reviewed and categorized as per the Sydney system. The diagnostic accuracy and risk of malignancy was assessed in each category. **Results:** 100 FNACs were reviewed and categorized as following- L1 (Inadequate/Non diagnostic) n=02 (02%), L2 (Benign) n= 68(68%), L3 (Atypical cells of undetermined significance) n=02 (02%) L4(Suspicious for malignancy) n= 02 (02%), L5(Malignant) n=25(25%). FNACs were correlated with ancillary tests, histopathological diagnosis and clinical follow-up wherever necessary, to assess the diagnostic accuracy. Statistical analysis showed following results: sensitivity 86.2%, specificity 100%, positive predictive value 100%, negative predictive value 94.4%, accuracy 95.8%. **Conclusion:** FNAC coupled with various ancillary techniques ensures high diagnostic accuracy in diagnosing various lymph node pathology and the implementation of Sydney system may improve the practice among pathologists.

KEYWORDS

Sydney classification, reporting system, lymph node, fine needle aspiration.

INTRODUCTION:

Fine Needle Aspiration is a very common diagnostic technique, beside it being minimally invasive, rapid & cost effective, it also provides material for several ancillary techniques.[1]

It is highly useful in highly co-morbid patients where biopsy/more invasive procedures are not feasible. The earlier problems of FNACs being possible only in palpable lesions is now resolved by increasing frequency of guided aspiration. However, in minimum resource setting, aspiration of palpable lesions is still a very good investigation for early intervention and gather good patient compliance.

Nevertheless, lymph node FNACs are quite challenging in terms of interpretation. It is because of the large number of benign, reactive as well as malignant processes presenting as lymphadenopathy. A detailed clinical history, physical examination, radiological findings are key for cytopathologists as well as standardized categorization of lesions for better communication to the clinicians are pivotal. [2-4]

To overcome this limitation, in May 2019, the 20th International Congress of Cytology held in Sydney proposed a categorical system for performance, classification and reporting of lymph node cytopathology, known as the Sydney System. It has been endorsed by the International Academy of Cytology and the European Federation of Cytology Societies and has 5 diagnostic criteria: L1: Inadequate/ Non diagnostic, L2: Benign, L3: Atypical cells of undetermined significance/ atypical lymphoid cells of uncertain significance, L4: Suspicious for malignancy, L5: Malignant.

Aim:

Current study aims at evaluating the applicability of the Sydney system and assessing the risk of malignancy (ROM) in each category.

Material and Methods:

Study Design

This was a retrospective study, taken place at Department of Pathology, Gandhi Medical College, Bhopal from1 January 2021 to June 2021.100 FNACs were reviewed and categorized as per the Sydney system.

All the FNACs included in this study were done percutaneously without any radiological assistance. Informed consent was taken from patient and/or relative and confidentiality was maintained.

Aspiration and Smear preparation

A detailed clinical history and physical examination of the patient was done.

22G needle attached to 20ml syringe fitted into a metallic handle was used. 2 passes were done in cases with scanty aspirate and scant cellularity was suspected.

Aspirated material was directly spread onto the precleaned slide and fixed in methanol. Each case was stained with Hematoxylin and Eosin as well as Papanicolou staining as part of routine procedure. Slides were kept for special stains in suspected cases. Any discrepancy was resolved by discussing with at least two pathologists. Clinical follow-up and histopathological correlation were done wherever necessary.

RESULTS:

100 FNACs performed from patient of all ages ranging from 4months to 70 years.

Mean age was 33.6 years, with 55% (n=55) females and 45% (n=45) males.

Most common lymph node was cervical lymph node (69%) followed by pre-auricular(11%), supraclavicular(10%), axillary and inguinal (5%,5%). There was unilateral enlargement in 95.9% cases and only 4.1% cases had bilateral lymph node involvement. Also, majority (81.4%) cases presented as single enlarged node and only 18.6% cases had multiple lymph node enlargement. 41.2% patients presented with acute (<=3 months) symptoms while 35.1% patients had gradual onset for more than/equal to one year.

Diagnostic categories

The original diagnoses were reviewed and each case was classified according to the first diagnostic level of Sydney Classification. In the present study, n= 03/100 (3%) were categorized as L1, inadequate/nondiagnostic; n = 68/100 (68%) as L2, benign; n = 02/100

(2%) as L3, AUS/ALUS; n = 02/100 (2%) as L4, suspicious, both suspicious for NHL and finally, n=25/100 (25%) were categorized as L5, malignant. The second diagnostic level was provided in 89 cases, data is summarised in Table 1.

L1: In the present study, total 3% cases (n=3) reported as L1-considered non diagnostic / inadequate for interpretation. Majority of these samples contained blood, minimal to no lymphoid cells and extensive necrosis with no viable cells.

L2: Benign (L2) was given in 68% cases (n=68). Majority of cases (33.8%) reported were tubercular (n=23), further confirmed by AFB staining and CBNAAT testing. Cases reported as granulomatous lymphadenitis (n=12, 17.6%) were also later confirmed as tuberculosis by CBNAAT testing. 03 cases (0.04%) reported as acute suppurative lymphadenitis were also CBNAAT positive for tuberculosis. 07 cases were reported as abscess content, ancillary testing was done for 05 of them, 03 of which were CBNAAT positive for tuberculosis and 02 were culture positive for bacterial infection.03 cases were reported as inflammatory smear, out of which one patient being PLHA underwent biopsy and was confirmed as non-Hodgkin lymphoma on histopathology. No ancillary testing was done for 08 cases, these were clinically followed up.

L3: 02 cases reported as reactive with few atypical cells categorized under L3, on follow-up, 01 case reported as non Hodgkin lymphoma on histopathology while 01 case was reported as chronic hyperplasia of lymph node on histopathology.

L4: 02 cases reported as suspicious of malignancy categorized as L4 with both of them reported as non Hodgkin lymphoma on further histopathology.

L5:Total 25 cases categorized as L5, out of which 20 cases were metastatic deposits of Squamous cell Carcinoma,02 cases of non hodkin lymphoma, 01 case was reported of Hodgkin lymphoma and 01 case each of malignant spindle cell lesion and metastatic deposit of Infiltrating ductal carcinoma breast.

Histopathologic correlation:

In 89 cases out of 100 FNACs, second diagnostic level was done, out of which 31 cases (35.6%) had histopathological correlation. Mostly it was available for L5 category, all 25 cases in L5 category were confirmed malignant on histology. Similar findings are for L4 category. In L3 category (n=2), one patient on histology showed benign lesion and other showed Hodgkin lymphoma. As far as L2 is concerned, majority cases were benign on cytology and underwent only clinical follow-up, however, in two cases, histopathology was done, and one case was confirmed malignant later. Data is summarised in Table 2.

Statistical Analysis:

Statistical analysis showed sensitivity of 86.2%, specificity 100%, positive predictive value 100%, negative predictive value 94.4% and diagnostic accuracy 95.8%.

Table 1: Correlation between Sydney diagnostic category and second diagnostic level:

Diagnostic category	Second diagnostic level	Histopathological Diagnosis
L2 (n=68)	CBNAAT+ Culture= 58	02 (NHL= 01 Sinus Histiocytosis= 01)
L3 (n=02)		02 (Reactive Hyperplasia=01 NHL=01)
L4 (n=02)		02 (Metastatic deposit of SCC=01 NHL=01
L5 (n=25)		25 (Metastatic deposit of SCC= 20 NHL= 02 HL=01 IDC deposits= 01 RMS= 01)
Total	58	31

Table 2: Correlation between diagnostic categories and histology/clinical follow-up

	Clinical Followup	Histopathological Correlation	Lost	Total
L1	00	00	03	03
L2	58	02	08	68
L3	00	02	00	02
L4 NHL Metastases	00	02 01 01	00	02
L5 NHL HL Metastases	00	25 02 01 22	00	25

Table 3: Statistical analysis

Statistical Data	Value
Sensitivity	86.2%
Specificity	100%
Positive Predictive value	100%
Negative Predictive value	94.4%
Diagnostic accuracy	95.8%

Table 4: Stratification of Risk of Malignancy in Sydney System

Sydney System Diagnostic Category	Histological or Clinical Follow-up	Confirmed Malignant Lesion	Risk of malignancy (ROM)
L1(n=03)	00	00	NA
L2 (n=68)	60	01	1.4%
L3 (n=02)	02	01	50%
L4 (n=02)	02	02	100%
L5 (n=25)	25	25	100%

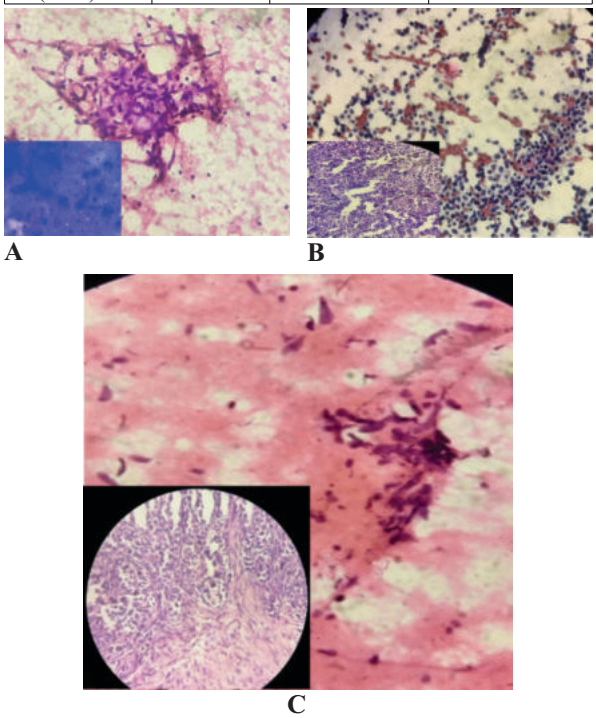

Figure 1: A: Smear from a case of tuberculosis, showing an epithelioid cell granuloma composed of epithelioid cells, lymphocytes against an inflammatory background (H&E,40x), inset shows multiple acid-fast bacilli (ZN stain; 40x), B: Smear from a case reported as likely Non Hodgkin Lymphoma showing small monomorphic population of atypical lymphoid cells against a haemorrhagic background (H&E,40x), on further histopathological correlation, it was confirmed as NHL (inset, H&E,10x), C: Smear from a case reported as spindle cell lesion, likely malignant (H&E,40x), on histopathological correlation, it was further confirmed as alveolar rhabdomyosarcoma (H&E, 10x)

Abbreviation: H&E-Hematoxylin and Eosin, NHL- Non Hodgkin Lymphoma, ZN stain- Ziehl-Neelsen stain.

DISCUSSION:

Lymph node FNAC has been an established diagnostic modality, especially in peripheral centres, however, the cytological evaluation of lymphadenopathies can be extremely challenging. Adequate clinical data coupled with ancillary techniques has proved to ensure satisfactory diagnostic accuracy. [1,2-4] With the introduction of a uniform reporting system, a decrease in the rate of clinical misinterpretation and inter-observer variation is expected. This study in a step forward in this matter. According to the proposed Sydney system [5-6] it is divided into two diagnostic levels, the first one is mandatory, while the secondary if achievable, provides additional and accurate diagnosis. The secondary diagnostic levels provide specific etiology in reactive processes, NHL and HL subtyping and specific primary tumour in case of metastasis. And although these are recommended, but only if available. In peripheral healthcare settings, availability of advanced ancillary testing might be questionable, but this study concludes that lymph node aspirations and their uniform classification can be a significant step in improving quality treatment and referral to higher centres when needed.

There was unambiguity in classification of cases into categories L1, L2 and L5. However, there was some inter-observer variation in L3 and L4 category amongst the two cytopathologists involved which warranted histopathological correlation for the two. In L1 category, all the three FNACs performed yielded scant material despite two passes; and thus, non-diagnostic, the average size of lymph node being very small could be the main reason. In our study, all these patients were lost to follow-up and hence risk of malignancy was not assessed. In other similar studies, L1 showed ROM to be 27.5% (P Gupta et al) and 50% (Vigliar E et al). [7-8] But there were significant false negatives and a smaller number of histological controls available in the following categories in both of these studies. P Gupta et al recommends that all category I aspirates, from clinically significant LNs, should be followed up with repeat aspiration by a more experienced cytopathologist, and preferably with the use of rapid onsite evaluation (ROSE) to definitively exclude the possibility of a malignancy. [6] The application of ROSE for the reporting of LN cytopathology has also been recommended by the proposed Sydney system. In addition, according to the proposed guidelines, ROSE can reduce the inadequacy as well as the false-negative rates.

In L2 category, as expected, the Risk of Malignancy (ROM) came out to be least (1.4%). Major cause was tuberculosis (77.9%). In other similar study by P Gupta et al (2021) major infective cause also appears to be tuberculosis (94.9%). There was one case of PLHA patient which was misclassified as L2 on cytomorphology, but the patient was still advised for biopsy to rule out malignancy. On histomorphology, it was diagnosed as NHL. Plausible reason for this misclassification could be the very small size of the lymph node, faulty aspiration technique or interpretation error.

Table 5: Details of a case misclassified as L2, later revealed to be malignant on histology

Category	Age/ Sex	Site	Medical History	Provisional Diagnosis	Cytological Diagnosis	Histological Diagnosis
L2	35/ M	Inguinal (1x1x1cm)	PLHA	? Lympho-reticular malignancy	Inflammatory smear (Few small mature lymphocytes against acute inflammatory and hemorrhagic background)	NHL

Abbreviations: PLHA- People living with HIV/AIDS, NHL- Non-Hodgkin lymphoma

Possible areas of interpretation errors according to P Gupta et al include smaller size of atypical lymphoid cells, the presence of a mixed population of lymphoid cells in a partially involved lymph node and the background showing florid reactive lymphoid cells. L3 category being the indeterminate category represents the heterogenous group, in our study, ROM came out to be 50%. This could be also be due to the low number of cases (n=02) with limited ancillary controls available. As discussed by Vigliar E et al (2021) (ROM= 58.3%), the false positive cases in L3 were based on the presence of excess of large cells with enlarged and slightly irregular nuclei, prominent nucleoli and scant cytoplasm, while histopathology revealed benign reactive hyperplasia.[7] In our study both cases reported having atypical cells, however only one was diagnosed as NHL on histopathology. However, the management in L3 category require either excisional biopsy or repeat FNAC at the least to establish the proper evaluation.

Both L4 and L5 category showed 100% Risk of malignancy, which is in consistence with similar studies. Management recommendations in L4, including FNAC repetition with acquisition of additional material for ancillary techniques or core-needle/excision biopsy, is substantiated by a highly expected ROM value. There were interobserver variation in category 3 and 4, however no statistical analysis was done for the same. Histopathological correlation was done for final outcome. Few studies that have compared the diagnostic utility of FNAC and core needle biopsies in the diagnosis of malignancies, especially lymphoma have found that the overall rate of diagnosis and subclassification of lymphoma is lower for the FNAC group alone and improves significantly when both FNAC and biopsy are used together.[9] Although, in this study, when ROM was calculated without using histopathological correlation, it was same in L4 and L5. Although L3 and L2 showed decrease in ROM, but it was not much significant. P Gupta et al (2021) in their study suggested that if ROM in each diagnostic category is calculated on the basis of cytomorphology alone, it would not differ significantly.Furthermore, a systematic review, performed on all the published studies in English literature from 1989-2012, concluded that neither the type of sampling procedure (whether FNAC or CNB or both) nor the use of ancillary techniques (like FCM or molecular tests), significantly affected definite lymphoma classification.[10] Overall, the diagnostic accuracy of this study was 95.8%, which was comparable to study done by Vigliar et al (97.06%).

CONCLUSION:

FNAC coupled with appropriate ancillary techniques is effective in evaluating lymphadenopathies with diagnostic accuracy of 95.8% and positive predictive value of 100% By implementation of Sydney system, more standardized system of reporting and categorization can be done. Even with limited sources of ancillary techniques, cytomorphology alone is sufficient for malignant stratification in low-cost settings.

Limitation:

Small sample size
Non availability of higher-level ancillary studies

Conflict of interest:

Nil

Abbreviations:

CNB- Core needle biopsy, FCM- Flow cytometry, FNAC- Fine needle aspiration cytology, ROM- Risk of Malignancy, ROSE- rapid onsite evaluation

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