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Pathology

CYTOPATHOLOGY OF LYMPH NODES USING THE SYDNEY SYSTEM FOR REPORTING LYMPH NODE CYTOLOGY: A SINGLE INSTITUTE EXPERIENCE

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ABSTRACT **Background:** Various spectrum of diseases result in the enlargement of lymph node (LN) and its evaluation is required for proper management of the patients. Fine needle aspiration cytology (FNAC) has been routinely used as a diagnostic tool in the first-line evaluation of any lymphadenopathy and aid in differentiating reactive causes from malignant causes. The standardization of a reporting format is required for a uniform assessment. This paper highlights the adoption of the Sydney System for classification and reporting LN cytopathology in our institute. **Objective:** To analyse and categorize the lymph node aspirates as per the proposed Sydney system and evaluate its applicability. **Materials and Methods:** This retrospective study included lymph node FNAC cases over six years duration. Data on the patient's age, sex, lymph node location, clinical details, the FNAC slides, and reports were retrieved from the Department's record section. FNAC slides were re-evaluated as per new reporting system. Statistical analysis was done. **Results:** A total of 1732 lymph node FNAC cases were evaluated with age ranging between 4 months to 92 years. During the study period, female patients were more in number (53.75%) and the cervical group of LNs was the most encountered site (%). Each case was revised using the proposed Sydney System and categorized appropriately into L1, L2, L3, L4, and L5 as the first diagnostic level, and the second level was applied wherever feasible. 69 cases (3.98%) belonged to the L1 category, 1242(71.71%) in L2, 16(0.92%) in L3, 24(1.39%) in L4 and 381(22.0%) in L5. Regarding the second diagnostic level, special stains like ZN stain for AFB, and PAS stain for fungal elements were applied to provide specific etiology in infective lymphadenopathy and PAP stains to specify the origin of the primary tumor in metastatic LNs. **Conclusion:** The use of a standard categorical cytology reporting system (Sydney system) will allow a uniform and better reports for further patient management.

KEYWORDS : Sydney system, Lymph node, FNAC

INTRODUCTION:

Fine needle aspiration cytology (FNAC) has been routinely used as a diagnostic tool in the first-line evaluation of any lymphadenopathy. Lymph nodes (LN) are considered one of the most common sites targeted by FNA.[1] Documented advantages of FNAC include minimum invasiveness, rapidity, cost-effectiveness, staging malignancy, and also provide material for ancillary techniques which contribute to improving its accuracy.[1,2,3] By combining cytological features with ancillary techniques like immunocytochemistry (ICC), flow cytometry (FC), microbiological analysis, and molecular data, most benign lymphadenopathies may be reliably diagnosed and thus, help to avoid unnecessary diagnostic surgical interventions. Moreover, FNAC is especially useful in elderly patients not eligible for surgery and in cases of tumor metastasis.[2] Nonetheless, excisional biopsy remains the mainstay for the diagnosis of malignant lymphadenopathies.[4,5]

The current WHO classification of lymphoproliferative disorders incorporates clinical, morphological, and ancillary data.[6] FNAC can provide cytomorphological information as well as material for ancillary testing, highlighting its vital role.[1] Even though many conditions present as lymphadenopathy, LN-FNAC is still challenging[2] and a standardized categorization is not established yet.

Despite the tremendous progress made in performing and interpreting LN-FNAC and its correlation with ancillary tests, it is still not uniformly accepted by clinicians and pathologists, mainly due to a lack of widely shared and accepted guidelines and a cytopathological classification that directly relates to management. A consensus in the classification system is required to improve reliability, efficiency, reproducibility, and acceptance. Considering the wide spectrum of pathology represented in LN, a single classification system, like thyroid Bethesda, salivary Milan, and urine Paris, is not adequate.[1]

In this view, an expert panel proposed the Sydney System for classification and reporting LN cytopathology into the first diagnostic level of 5 categories and a second diagnostic level aimed at the identification of specific etiologies with help of ancillary methods. It integrated clinical and imaging information with key diagnostic cytopathological features and ancillary techniques and linked to a management algorithm.[1]

However, the proposed system is still underutilized, and limited data is available in the literature.[7] So, to fill this knowledge gap, the present study aims to introduce the proposed Sydney System and evaluate its applicability.

MATERIALS AND METHODS:

A cross-sectional study was carried out in the Department of Pathology, RIMS, Imphal for a study period of 6 years from January 2016 to December 2021, and all lymph node FNACs done within the period were included in the study. Data on the patient's age, sex, lymph node location, clinical details, the FNAC slides, and reports were retrieved from the Department's record section. The slides and original diagnoses for all the cases were reviewed, reassessed, and categorized as per the Sydney System of reporting.

Routinely practiced standard protocol of FNAC procedure was followed with a 23-24G needle and the required number of passes were performed. ROSE (Rapid On-Site Evaluation) with Toluidine blue stain was done to check for the adequacy of the specimen. Multiple passes were carried out in cases yielding no/scant material with the cooperation of the patient.

The smears were stained with May Grunwald- Giemsa stain. At our institute, available ancillary techniques with special stains like Ziehl-Neelsen (ZN), Papanicolaou (PAP), and Periodic acid- Schiff (PAS) stains were applied whenever necessary.

Cases in which single/ repeated passes yielded predominantly blood, minimal to no lymphoid cells, no atypical cells, and only necrosis with no viable cells were grouped into L1. L2 included acute/ chronic/ non-specific reactive/ granulomatous/ tubercular/ suppurative/ fungal lymphadenitis/ Kimura's/ Kikuchi/other benign conditions. L3 included cases with atypical cells that could not be classified into other groups. Diagnosis of lymphoproliferative lesion/disorder were categorized into L4 (suspicious). L5 (malignant) included cases of hematolymphoid malignancy/ HL/ NHL/ metastasis.

Each case was reassessed according to the first diagnostic level of the proposed Sydney System (L1: inadequate/non-diagnostic; L2: benign; L3: atypical cells of undetermined significance/ atypical lymphoid cells on uncertain significance, AUS/ALUS; L4: suspicious; L5: malignant). The second diagnostic level was recorded wherever applicable. Any discrepancies in the revision were resolved by consensus between at least two Pathologists.

Descriptive statistics were used, and the numbers were expressed as percentages. Institutional ethics committee approval was obtained.

RESULT:

A total of 1732 LN-FNACs were performed within the period of 6 years (357 in 2016, 454 in 2017, 324 in 2018, 260 in 2019, 101 in 2020, and 166 in 2021). There was a wide range of age at presentation (4 months- 92yrs) with a mean age of 34±16. The size of the lymph nodes ranges from 0.5cm to 7cms in diameter with a mean diameter of 2.2 cms. During the study period, female patients were more in number with female to male ratio of 1.16:1.(Fig-1)

The cervical group of LNs was involved in the maximum number of cases with 1396 cases (80.6%)

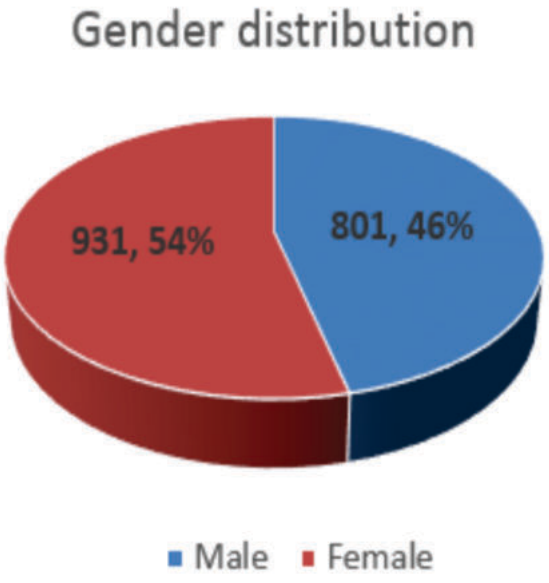

Fig-1: Showing the gender distribution of the cases.

"The distribution of various cases falling into Sydney categories viz. L1, L2, L3, L4, L5 along with the year wise cases are shown in table-1." The most common category belongs to the L2 with 1242 cases (71.71%) followed by L5 with 381 cases (22%). The least number of cases belong to the category L3 with 16 cases (0.92%)

Table 1: Categorisation of cases using the Sydney System by first diagnostic level.

Year (n)	Diagnostic category				
	L1 (%)	L2 (%)	L3 (%)	L4 (%)	L5 (%)
2016 (357)	18 (5.0)	255 (71.4)	6 (1.7)	3 (0.8)	75 (21.0)
2017 (454)	11 (2.4)	341 (75.1)	5 (1.1)	4 (0.9)	93 (20.5)
2018 (394)	10(2.5)	296 (75.1)	2 (0.5)	7 (1.8)	79 (20.1)
2019 (260)	14 (5.4)	178 (68.4)	1 (0.4)	8 (3.1)	59 (22.7)
2020 (101)	5 (4.95)	60 (59.4)	1 (0.99)	1 (0.99)	34 (33.66)
2021 (166)	11 (6.6)	112 (67.5)	1 (0.6)	1 (0.6)	41 (24.7)
Total=1732	69(3.98)	1242(71.71)	16(0.92)	24(1.39)	381(22.0)

Regarding the second diagnostic level, special stains like ZN stain for AFB, and PAS stain for fungal elements were applied to provide specific etiology in infective lymphadenopathy and PAP and PAS stains to specify the origin of the primary tumor in metastatic LNs (table 2).

Table 2: Relevant second diagnostic level (additional diagnostic information)

Year	ZN stain		PAS stain	PAP stain
	Total (n)	AFB positive (%)		
2016	54	19 (35.2)	1	40
2017	76	40 (52.6)	1	52
2018	68	32 (47.1)	2	48
2019	32	11 (34.4)	1	34
2020	15	2 (13.3)	-	24
2021	29	10 (34.5)	-	28
Total	274	114(41.61)	4	226

Among the Level 2 group, nonspecific reactive lymphadenitis was the most common lesion followed by granulomatous lesion (Fig-2) as shown in table-3.

Figure 3 shows Level 4 group displaying features of a lymphoproliferative lesion.

A predominance of metastatic squamous cell carcinoma (Fig-4) is seen within the Level 5 category.

Out of the 25 cases of hematolymphoid malignancies, 17 cases were correlated with histopathology and 12 cases were diagnosed as Non Hodgkin Lymphoma and 5 cases of Hodgkin disease.

Table 3: Various lesions seen in Level 2 and Level 5 category

Category	Year	2016	2017	2018	2019	2020	2021
Level-2	Total cases (1242)	255	341	296	178	60	112
	Non specific reactive (947)	198(77.65)	261 (76.54)	222 (74.32)	141 (79.21)	43 (71.67)	82 (73.21)
	Granulomatous (151)	33 (12.94)	33 (9.67)	35 (11.82)	20 (11.24)	12 (20.0)	18 (16.07)
	Tubercular (AFB+ve) (114)	19 (7.45)	40 (11.73)	32 (10.81)	11 (6.18)	2 (3.33)	10 (8.93)
	Suppurative (18)	3 (1.18)	4 (1.17)	4 (1.35)	3(1.69)	2 (3.33)	2 (1.78)
	Fungal(05)	1 (0.39)	1 (0.29)	2 (0.68)	1 (0.56)	-	-
	Rosai Dorfman (02)	1 (0.39)	-	-	1 (0.56)	-	-
	Kimura(02)	-	1 (0.29)	1 (0.34)	-	-	-
	Kikuchi(01)	-	-	-	-	1 (1.67)	-
	Cat scratch(02)	-	1 (0.29)	-	1 (0.56)	-	-
Level-5	Total cases (381)	75	93	79	59	34	41
	Hematolymphoid malignancy (25)	6 (8.0)	11 (11.83)	3 (3.8)	1 (1.69)	1 (2.94)	3 (7.32)
	Metastatic SCC (214)	40 (53.33)	52 (55.91)	45 (57.0)	30 (50.85)	22 (64.71)	25 (60.98)
	Metastatic Adenocarcinoma (122)	27 (36.0)	24 (25.81)	28 (34.44)	24 (40.68)	9 (26.47)	10 (24.39)
	Metastatic Undifferentiated carcinoma (20)	2 (2.67)	6(6.45)	3 (3.8)	4(6.78)	2(5.88)	3 (7.32)

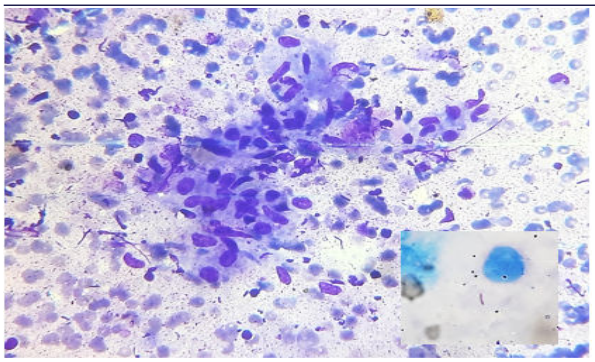

Fig-2: Phtomicrograph of lymphnode aspirate showing a granuloma with AFB positive bacilli(inset) [Level 2]; MGG stain 100X

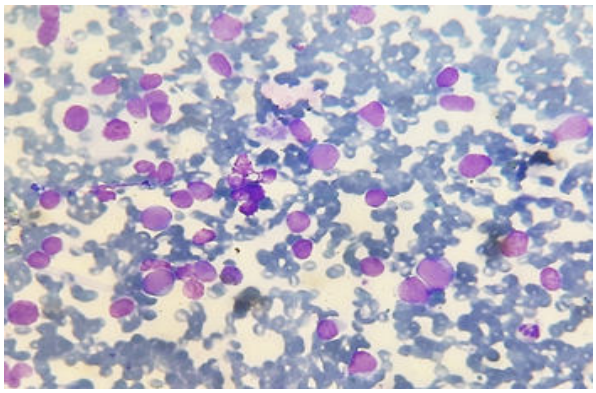

Fig-3: Phtomicrograph of lymphnode aspirate showing immature lymphoid series displaying a lymphoproliferative lesion [Level 4]; MGG stain 100X

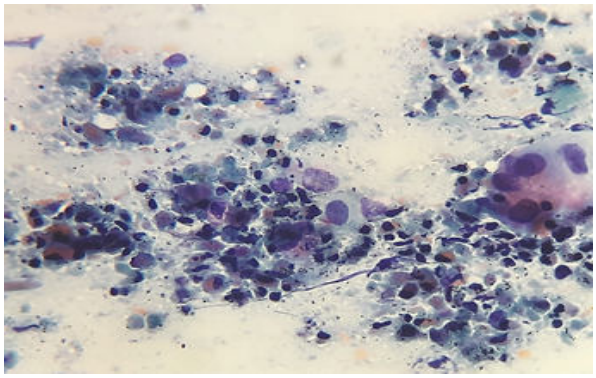

Fig-4: Phtomicrograph of lymphnode aspirate showing malignant squamous cells displaying a metastatic Squamous cell carcinoma [Level 5]; PAP stain 100X

DISCUSSION:

A wide spectrum of non-neoplastic and neoplastic conditions presents as lymphadenopathy. FNAC is considered the first line of evaluation and provides material for ancillary techniques. The knowledge of clinical history, physical examination, and radiological features is pivotal. Nonetheless, reporting of LN cytopathology remains a challenging scenario, coupled with a lack of standardized categorization. To fulfill the requirement, an expert panel published the proposal of the Sydney System for reporting lymph node cytopathology. It introduces 2 diagnostic levels and recommendations for post-FNAC management. The first diagnostic level classifies LN cytopathology into 5 diagnostic categories- L1 (inadequate/ insufficient), L2 (benign), L3 (atypical cells undetermined significance/ atypical lymphoid cells of uncertain significance, AUS/ ALUS), L4 (suspicious) and L5 (malignant). The second diagnostic level helps in providing specific diagnoses using applicable ancillary techniques. Finally, post-FNAC management is recommended as a means of communication with the treating clinicians.[1,2,8,9]

After categorization with 1st diagnostic level, each case should have a diagnosis established, or, if not possible, a preferred diagnosis with a discussion of possible differentials. When the combination of 1st and 2nd diagnostic levels is achieved, corresponding findings should be reported in one final integrated cytopathology report with the specific diagnosis.[1]

The Sydney system has been proposed to bring forth uniformity in reporting and to guide management.[1] As with any other newly proposed classification system, its validity, reproducibility, and clinical utility need to be ascertained before it can be recommended for routine use.[7]

In our study, despite ROSE, cases were still categorized as L1 (4%) due to non-compliance by the patients for repeat aspiration as well as guided aspirations which were performed without a cytopathologist and smear revealing only blood or few mature small lymphocytes. Proper counseling of the patients and the presence of a cytopathologist is recommended to minimize cases of L1. This is necessary as the observed risk of malignancy (ROM) associated with L1 is quite high (50%[2], 27.5%[7]). Most of the cases in our study belonged to L2 (71.7%) and lower L5 cases (21.9%), in contrast to other studies with a lower proportion of L2 and higher L5 (34.7% vs 46%[2], 48.6% vs 45.4%[7]). The high proportion of malignant diagnoses in both the above studies may be presumably related to the place of study being a referral institute. Lower cases of L3 and L4 in our study (0.9%, and 1.4% respectively) may be the result of limited ancillary techniques available in our institute to provide additional information to guide the diagnosis.

Studies indicate classification into categories L1, L2, and L5 was deemed to be unambiguous. On the contrary, interobserver variability was noted for categories L3 and L4.[2,7] This may probably be because clear-cut identification was possible for L1, L2, and L5. However, categorization of the cells presents as either atypical or suspicious and not as frank malignant may need expertise, in conjunction with available ancillary tests. This may represent either inadequate sampling or non-representative sampling or interpretational error.

Proper handling of diagnostic material to perform ancillary techniques, coupled with cytopathological features and clinical data, ensures satisfactory diagnostic accuracy. However, it is not uniformly accepted, mainly due to a lack of guidelines and reporting system. The application of a standardized reporting system will enable to limit interobserver variability and to communicate clinically relevant information in a reproducible manner.[8,9] Moreover, the rate of clinician misinterpretation of cytological reports might be reduced by using management recommendations, specific to each diagnostic category. It is also crucial to perform risk stratification and to identify ROM values.[2]

The etiology of LAP correlates with the patient's age and clinical history, and the clinical relevance varies between adults and children.[10] Rates of malignancy increase with age and size of the LN. Metastatic cancers were diagnosed in 4% of patients with unexplained LAP aged > 40 years versus 0.4% of those < 40 years.[11] Abnormal LNs are typically defined by size, consistency, and/or imaging findings. Palpation of enlarged LN may suggest a pathologic process, such as soft fluctuant suggesting infection or firm to hard suggesting a malignant neoplasm. The etiologies of LAP can be grouped into malignancies, infections, autoimmune disorders, miscellaneous and unusual conditions, and iatrogenic causes (MIAMI).[12,13]

Imaging evaluation, particularly by ultrasound (US), is a key tool for the initial evaluation of LN, as well as to guide FNAC of non-palpable or challenging lesions. US devices have become less expensive and portable, thus more available in hospitals and used more often in pathologist-performed FNACs. US can provide information like echogenicity, echotexture, and focal infiltration of the involved LN.[14,15] It also helps in approaching the target LN, avoiding adjacent vascular structures and the LN hilum. In case of multiple enlarged LNs, the US helps in selecting the most significant or the most approachable LN to be targeted, where additional passes can be performed.[1]

In our study, guided FNAs (US/CT) were performed for tiny LNs or those located in inaccessible areas. The majority of the aspirations were done percutaneously (96%) and only 4% were performed under radiological guidance. Other studies had a higher number of guided aspirations (100%[2], 11.8%[7]), likely to avoid a high diagnosis of L1. Despite performing ROSE even with guided aspirations, if the material

was still scant and non-diagnostic, repetition was inadvisable. In such cases, Sydney system management recommends that, in cases of L1, rather than repetition, core needle or excision biopsy may be performed under a specific clinical context.[1] As studies have found relatively higher ROM associated with L1, repeat image-guided FNA with ROSE or excision biopsy are recommended to reduce inadequacy and false negative rates.[2,7]

Ancillary methods like basic laboratory tests such as complete blood count, peripheral blood smear, chemical serum analytes, such as lactate dehydrogenase, beta-2-microglobulin, creatinine, serum immunoglobulins, hepatic and renal function tests, urine analysis, Acid-fast bacilli stain (ZN stain for *Mycobacterium tuberculosis* and Wade-Fite stain for *M. leprae*), PAP, PAS stains, PCR, culture, and skin tuberculin test, serologic evaluation, titres for specific infections or antibodies may help in the evaluation of LNP.[1]

LN-FNAC is an accurate, quick, and cost-effective procedure, often making excisional biopsy an unnecessary and costly alternative. FNAC can determine whether a palpable or impalpable mass is an LN and distinguish a benign from a malignant entity, or a hematolymphoid from a non-hematolymphoid process. It can be the first-choice procedure for patients who are poor candidates for surgical biopsy or with abnormal LN in deep or inaccessible locations. However, without widely accepted guidelines on technical procedures and diagnostic criteria, the use of FNAC and the value of diagnoses varies between countries and institutions. LN-FNAC diagnosis made in conjunction with appropriate ancillary techniques, when necessary, and in a proper clinical context does not require histopathological confirmation in cases of benign reactive lymphoid hyperplasia, specific infections, recurrent lymphoproliferative disorders, and metastases. It can be particularly useful in staging and follow-up, including the response to treatment, in patients with known malignant processes. It can also obtain tissue for immunophenotypic and molecular studies and procure cellular and genetic material for storage.[1,16-22]

Histological/ clinical follow-up is required for confirmation of the cytopathological diagnosis and for calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and risk of malignancy-related to the proposed diagnostic category. The ROM values for each category will help in the further management of the patient. However, limited research has been done so far in the field.

Studies have shown high sensitivity (98.47%[2], 79.87%[7]), specificity (95.33%[2], 98.71%[7]), PPV (96.27%[2], 98.40%[7]), NPV (98.08%[2], 83.15%[7]) and accuracy (97.06%[2], 89.32%[7]). However, the ROM associated with each category of different studies[2,7] had varied results (L1: 50% vs 27.5%; L2: 1.92% vs 11.5%; L3: 58.3% vs 66.7%; L4: 100% vs 88%), except for L5 (100% vs 99.6%). The varying results of ROM may be due to the non-availability of ROSE or cytopathologists for the procedure, the institute being a tertiary referral center, sampling/ interpretational error, less sample size, and less histological/ clinical follow-up. Hence, multiple studies with large sample sizes and strict histological correlation, and clinical follow-up are needed to establish the accurate ROM for each diagnostic category of the proposed system.

High ROM in L1 perhaps reflect deficiencies in the aspiration technique, which is known to correlate with the expertise of the cytopathologist. Inadequate smears may also be obtained when the lymph nodes are fibrotic. However, considering the relatively higher ROM in L1, all clinically significant LNs, should be followed up with repeat aspiration by a more experienced cytopathologist, and preferably with the use of ROSE to definitively exclude the possibility of a malignancy.[2,7] 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.[1,7]

It is also recommended that cases with predominant necrosis and degenerated cells on the smears should be closely followed up either by a repeat image-guided FNA from a viable area or an excision biopsy to exclude malignancy.[7] The false-negative rates reported previously in studies on LN-FNAs range from 1.4% to 23.6% and have been attributed to a variety of causes such as inadequate aspirates, non-representative sampling, and interpretational errors.[23-26]

Our study attempted in introducing the proposed system for reporting LN-FNAC and categorized the cytopathology of lymphadenopathy with the 1st diagnostic level and apply the 2nd diagnostic level wherever feasible. However, due to the limited number of cases with confirmed histopathological correlation, a high number of cases lost during clinical follow-up and the retrospective nature of the study, the calculation for appropriate statistical analysis was not possible. Further studies are required to confirm the usefulness of the Sydney System.

CONCLUSION:

Our study aimed to assess the proportion of cases encountered in each category of the proposed Sydney system for performance, classification, and reporting of LN cytopathology. Its implementation with the introduction of standardized categorization can help in achieving uniformity and reproducibility in cytologic diagnoses, improve diagnostic accuracy and also help in risk-stratification in cytology. It will also improve the quality of the procedure, handling of material, and understanding of the report and inter-disciplinary communication, thereby improving patient care. Future multicentric studies with a larger sample size need to be conducted for the validation of results and to assess the reliability and validity of this system.

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