Diagnostic value of lymph node fine-needle aspiration cytology

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ABSTRACT

Objectives: This study aims to assess the diagnostic accuracy of cytology by comparing the results of fine-needle aspiration cytology (FNAC) and histopathologic examination.

Material and Methods: A 4-year retrospective study design was conducted on FNAC samples from the lymph nodes of patients in our hospital between January 2015 and December 2018. The cytopathological diagnoses were compared with the histopathological results of the same excised lymph nodes. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy rate were calculated.

Results: A total of 392 lymph nodes were aspirated during the study period. Cytologic analysis of the lymph nodes revealed the following: Reactive lymphoid hyperplasia, 239 (61%); metastatic, 61 (15.6%); granulomatous lymphadenitis, 24 (6.1%); suspicious, 24 (6.1%); pyogenic abscess, 10 (2.6%); necrosis, 4 (1%); non-Hodgkin lymphoma, 2 (0.5%); and non-diagnostic, 28 (7.1%). Immunohistochemical analysis was performed on 26 (6.6%) cases to the cell block samples. Histopathological correlation was available in 73 (18.7%) cases. The overall diagnostic sensitivity, specificity, PPV, and NPV of FNAC of lymph nodes were 87.9%, 100%, 100%, and 89.7%, respectively. The overall diagnostic accuracy was 94.1%. In case of malignancies, the histopathological correlation was 100%. Of four cases with false negative, three were low-grade non-Hodgkin lymphoma and one was granulocytic sarcoma.

Conclusion: FNAC of lymph nodes is a safe, easy, cheap, quick diagnostic tool and reduces the need for diagnostic excisional biopsy in many patients. Cytological diagnosis can be supported with immunohistochemical analysis of cell block samples. However, lymphomas, particularly low-grade non-Hodgkin lymphomas, are a diagnostic challenge and additional studies such as flow cytometry are required in cases with suspicious for lymphoma.

Keywords: Fine-needle aspiration, Cytology, Lymph nodes

INTRODUCTION

Fine-needle aspiration cytology (FNAC) of lymph nodes has been widely used in the diagnosis and staging of non-lymphoid malignancies, diagnosis of lymphoma, and evaluation of reactive lymphadenopathies.[1] The fine-needle aspiration technique is a rapid, inexpensive, minimally invasive, reliable, and convenient procedure that is often used in the initial evaluation of enlarged lymph nodes.[2] Lymph node FNAC is excellent in the diagnosis of metastatic malignancy, reducing the need for diagnostic excision biopsy in many patients.[3] However, the role of FNAC for the initial diagnosis and subclassification of primary lymphoid malignancy is still controversial and the cytological diagnosis of lymphoma on FNAC is still very often followed by tissue biopsy in most cases.[4,5]
In this study, we aimed to investigate the results of lymph node FNAC and to correlate the results of FNAC and histopathologic diagnosis.

MATERIAL AND METHODS

A total of 392 lymph node FNAC materials evaluated between 2015 and 2018 were included in the study. The patients were examined for age, gender, lymph node location, and cytological diagnoses which were compared with the histopathological diagnoses of the biopsy materials. The slides of all cases were examined to determine the cytomorphological features. Hypocellular slides were excluded from the present study. Immunohistochemical analysis was performed on 26 (6.6%) cases to the cell block samples.

Cytological diagnoses were categorized as reactive lymphoid hyperplasia, metastatic, granulomatous lymphadenitis, pyogenic abscess, lymphoma, and suspicious.

The cases that are rich in monotonous small lymphocytes were evaluated as suspicious for low-grade lymphoma. The cases that are rich in large lymphoid cells were evaluated as suspicious for high-grade lymphoma. The cases are revealed Reed-Sternberg and Hodgkin-like cells were evaluated as suspicious for Hodgkin lymphoma.

The cytological diagnoses were compared with the histopathologic results of the same excised lymph nodes. For all discordant cases, special attention was focused on the cytomorphological features.

Statistics

SPSS software (version 15.0 for Windows) was used for all statistical analyses. Descriptive statistics were given as number and percentage for categorical variables, and given as mean, standard deviation, and minimum and maximum for numerical variables. The results were analyzed by Cohen's Kappa test. $P<0.05$ was considered statistically significant.

RESULTS

A total of 392 lymph node FNACs were analyzed. Two hundred and fifty-seven cases (65.6%) were female and 135 (34.4%) cases were male with the male-to-female ratio 1:1.9. In this study, the age of the patients ranged from 6 months to 86 years with the mean age of 47.8. Seventeen cases (4.3%) were in the age group between 0 and 19 years. One hundred and eleven cases (28.3%) were in the age group between 20 and 39 years. One hundred and fifty-eight cases (40.3%) were in the age group of 40–59 years. Ninety-eight cases (25%) were in the age group of 60–79 years. Eight cases (2%) were above the age of 80.

The most common site of the involved lymph node was cervical constituting 145 cases (37%) followed by involvement of the axillary lymph nodes in 83 cases (21.2%). The remaining cases were distributed as follows: 67 (17.1%) submandibular, 35 (8.9%) jugular, 24 (6.1%) supraclavicular, 17 (4.3%) parotis, 8 (2%) inguinial, 6 (1.5%) submental, 2 (0.5%) mediastinal, and 5 (1.3%) others sites.

| Table 1: General demographic information and cytological/histopathological diagnoses. |
|---------------------------------|---------|---------|---------|
| Age               | Mean±SD | Min-Max |
| Gender            |         |         |         |
| Male              | 135     | 34.4    |
| Female            | 257     | 65.6    |
| Site of lymph node|         |         |         |
| Axilla            | 83      | 21.2    |
| Inguinal          | 8       | 2       |
| Jugular           | 35      | 8.9     |
| Parotid lymph node| 17      | 4.3     |
| Cervical          | 145     | 37      |
| Submandibular     | 67      | 17.1    |
| Supraclavicular   | 24      | 6.1     |
| Submental         | 6       | 1.5     |
| Mediastinal       | 2       | 0.5     |
| Other             | 5       | 1.3     |
| Cytological diagnosis |     |         |         |
| Suspicious        | 24      | 6.1     |
| Reactive hyperplasia | 239  | 61      |
| Pyogenic abscess  | 10      | 2.6     |
| Metastatic        | 61      | 15.6    |
| Granulomatous     | 24      | 6.1     |
| Necrosis          | 4       | 1       |
| Non-Hodgkin lymphoma | 15  | 20.5    |
| Non-diagnostic    | 28      | 7.1     |
| Biopsy            |         |         |         |
| No                | 317     | 81.3    |
| Yes               | 73      | 18.7    |
| Histopathological diagnosis |     |         |         |
| Reactive hyperplasia | 28  | 38.4    |
| Metastatic        | 15      | 20.5    |
| Granulomatous     | 10      | 13.7    |
| Non-Hodgkin lymphoma | 15  | 20.5    |
| Hodgkin lymphoma  | 2       | 2.7     |
| Granulocytic sarcoma | 1   | 1.4     |
| Melanoma          | 1       | 1.4     |
| Plasmacytoma      | 1       | 1.4     |
Cytologic analysis of the lymph nodes revealed the following: Reactive lymphoid hyperplasia, 239 (61%); metastatic, 61 (15.6%); granulomatous lymphadenitis, 24 (6.1%); suspicious, 24 (6.1%); pyogenic abscess, 10 (2.6%); necrosis, 4 (1%); non-Hodgkin lymphoma, 2 (0.5%); and non-diagnostic, 28 (7.1%) [Table 1].

The cytological diagnoses were found to be benign in 277 cases (76.1%) and malignant in 87 cases (23.9%). Immunohistochemical analysis was performed on 26 (6.6%) cases to the cell block samples. Histopathological correlation was available in 73 (18.7%) cases.

Carcinoma metastasis (breast carcinoma, thyroid papillary carcinoma, lung carcinoma, gastric carcinoma, prostate carcinoma, nasopharyngeal carcinoma, and renal cell carcinoma metastasis) was the most common in the metastatic category [Figure 1]. Histopathological correlation was 100% in the metastatic category. Granulomatous lymphadenitis was detected in 24 cases (6.1%) and histopathological correlation was 100% [Figure 2 and Table 2]. Thirty patients (90.9%) of 33 patients in the category of reactive hyperplasia were compatible with histopathological diagnosis [Figure 3]. False negative three cases were low-grade non-Hodgkin's lymphoma (follicular lymphoma) [Figure 4].

In the biopsy of a case interpreted as pyogenic abscess, coagulative necrosis as well as large amounts of neutrophil leukocytes and rare monocyctoid cells were observed. In the patient with a history of chronic myelomonocytic leukemia, granulocytic sarcoma was suspected. Bone marrow biopsy and skin biopsy were diagnosed as acute myelomonocytic leukemia [Figure 5].

Of 13 patients in the category of suspicious, 9 were non-Hodgkin lymphoma (diffuse large B cell lymphoma, Burkitt lymphoma, follicular lymphoma, chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL], and marginal zone lymphoma), 2 were Hodgkin lymphoma, 1 was plasmacytoma, and 1 was melanoma [Figures 6 and 7].

| Cytological diagnosis | n | Histopathology correlated | Histopathology not correlated | Percentage of accuracy of cytology histopathology correlation (%) |
|----------------------|---|---------------------------|-----------------------------|---------------------------------------------------------------|
| Reactive hyperplasia | 33 | 30                         | 3-NHL                       | 90.90                                                         |
| Pyogenic abscess     | 1  | 1                          |                             |                                                               |
| Metastatic           | 14 | 14                         |                             | 100                                                           |
| Granulomatous        | 5  | 5                          |                             | 100                                                           |
| NHL                  | 2  | 2                          |                             |                                                               |
| Suspicious           | 13 | 9-NHL                      | 2–NHL                       | 100                                                           |

![Figure 1](breast-carcinoma-metastasis, Pap stain, ×400 (a), hematoxylin and eosin (H&E) stained cell block, ×200 (b), GATA-3 immunohistochemistry (IHC), ×400 (c), prostate carcinoma metastasis, Pap stain, ×200 (d), H&E stained cell block, ×200 (e), PSA immunohistochemistry, ×400 (f).)
In two cases, non-Hodgkin lymphoma (diffuse large B-cell lymphoma and CLL/SLL) was diagnosed with cytological findings and immunohistochemical study on the cell block [Figure 8]. Histopathological diagnosis of these cases was consistent with cytological diagnosis. Accordingly, the overall diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FNAC of lymph nodes were 87.9%, 100%, 100%, and 89.7%, respectively. The overall diagnostic accuracy was 94.1% [Table 3].

**DISCUSSION**

Lymph node FNAC is a commonly used method for initial evaluation of lymphadenopathies. However, it is important to know the clinical and laboratory information.
In our study, 392 lymph nodes were included in the study. 28/392 (7.1%) cases were non-diagnostic. The incidence of inadequate or unsatisfactory samples in various studies ranged from 0 to 25%. Inadequate specimens were examples of cytological detail which could not be evaluated due to diffuse crush artifact and hypocellularity. Adequacy was also attributable to the small size or nature of lesion, that is, fibrosis, necrosis, or cystic degeneration.

Reactive hyperplasia was found to be the most frequent diagnosis with 239/392 (61%) cases. The criteria on which the diagnosis of reactive hyperplasia was established were a combination of clinical and epidemiological data, patient age, symptoms, number, location of lymph nodes, and laboratory findings. Cytological criteria included highly cellular smears, polymorphic patterns of cells like lymphocytes at different maturation stage, and a considerable number of tingible body macrophages. It was also the most frequent diagnosis in other studies, where its incidence ranged from 7.5% to 86.4%. 

Thirty patients (90.9%) of 33 patients in the category of reactive hyperplasia were compatible with histopathological diagnosis. Three false negative cases were low-grade non-Hodgkin’s lymphoma (follicular lymphoma).

Metastatic tumors were detected in 61 cases (15.6%) and histopathological correlation was 100%. In these cases, if enough sample was present in the cell block, the diagnosis was supported by immunohistochemical study. This rate varies between 87 and 100% in other studies. The diagnosis of metastatic tumor to the lymph node on cytological

| Table 3: Cytology sensitivity, specificity, and accuracy rates. |
|---------------------------------------------------------------|
| Cytology | Biopsy | Total |
|          | Benign | Malign |          |
| Benign   |        |        |          |
| n        | 35     | 4      | 39       |
| % Row    | 89.7   | 10.3   | 100      |
| % Column | 100    | 12.1   | 57.4     |
| Malign   |        |        |          |
| n        | 0      | 29     | 29       |
| % Row    | 0      | 100    | 100      |
| % Column | 0      | 87.9   | 42.6     |
| Total    |        |        |          |
| n        | 35     | 33     | 68       |
| % Row    | 51.5   | 48.5   | 100      |
| % Column | 100    | 100    | 100      |
| McNemar  | Measure of agreement Kappa | Sensitivity | Specificity | PPV | NPV | Accuracy |
| Test P   | 0.125  | 0.882  | 87.90%    | 100% | 100% | 89.70%    | 94.10% |

PPV: Positive predictive value, NPV: Negative predictive value
smear is crucial and highly reliable. Most of the metastatic carcinoma cases can be identified by their cytomorphologic characteristics alone.\[^5\]\n
In our study, granulomatous lymphadenitis was found in 24 cases (6.1%) and the histopathological correlation was 100%. Diagnostic accuracy of granulomatous lymphadenitis varies between 70 and 100% in the literature.\[^5,6,11\]\n
Pyogenic abscess/acute suppurative lymphadenitis was found in 10 cases (2.6%) in our study. In the biopsy of a case interpreted as pyogenic abscess, coagulative necrosis as well as large amounts of neutrophil leukocytes and rare monocytoid cells were observed. In the patient with a history of chronic myelomonocytic leukemia, granulocytic sarcoma was suspected. Bone marrow biopsy and skin biopsy were diagnosed as acute myelomonocytic leukemia. Therefore, it is important to evaluate the cases with clinical findings and the presence of neutrophil leukocytes as well as other myeloid series cells.

In 4 cases (1%), only necrotic material was observed without any malignant cell or granuloma. This rate varies between 2 and 4.1% in other studies.\[^6\] Necrosis can be seen in malignancy or necrotizing granulomatous lymphadenitis.

Of 13 patients in the category of suspicious, 9 were non-Hodgkin lymphoma (diffuse large B cell lymphoma, Burkitt lymphoma, follicular lymphoma, CLL/SLL, and marginal zone lymphoma), 2 were Hodgkin lymphoma, 1 was plasmacytoma, and 1 was melanoma. These cases have been interpreted as suspicious because of the limitation of cytological material and crush artifact.

In two cases, non-Hodgkin lymphoma (diffuse large B-cell lymphoma and CLL/SLL) was diagnosed with cytological findings and immunohistochemical study on the cell block. Histopathological diagnosis of these cases was consistent with cytological diagnosis.

FNAC of lymph node is used mainly to assess the staging of primary lymphoid malignancies as well as to recognize the residual and recurrent lymphoid malignancies.\[^12\] The role of FNAC for the initial diagnosis and subclassification of primary lymphoid malignancy is still controversial and cytological diagnosis of lymphoma on FNAC is still often followed by tissue biopsy in most cases.\[^4,13,14\]

The majority of recent studies describe the usefulness of a combined approach using FNAC and immunophenotyping by flow cytometry (FC) or immunohistochemistry.\[^4,13,14\]

The main arguments against the use of FNAC for lymphoma diagnosis insist on the fact that FNAC does not provide an architecture assessment, precluding accurate subclassification, or grading in some lymphoma subtypes.\[^14\]

In the present study, the overall diagnostic sensitivity, specificity, PPV, and NPV of FNAC of lymph nodes were 87.9%, 100%, 100%, and 89.7%, respectively. The overall diagnostic accuracy was 94.1%.

The accuracy rate of lymph node FNAC in the literature varies between 82% and 94.4%.\[^15-7\] Cytological diagnosis of metastatic lesions and granulomatous lymphadenitis can be given with high accuracy. However, lymphomas, particularly low-grade non-Hodgkin lymphomas, are a diagnostic challenge and additional studies such as FC are required in cases with suspicious for lymphoma.

The diagnostic accuracy of lymph node FNAC can be further improved when used with other special techniques such as immunohistochemistry, FC, and molecular studies.

**CONCLUSION**

Despite its limitations and pitfalls, FNAC appears as a good first-line method for investigating the cases of lymphadenopathy. The evaluation of FNAC in a patient with no previously diagnosed malignancy should be interpreted with clinical, radiological, and laboratory findings. Additional investigations should be performed in cases with suspicious for lymphoma.

**COMPETING INTEREST STATEMENT BY ALL AUTHORS**

The authors declare that they have no competing interests.

**AUTHORSHIP STATEMENT BY ALL AUTHORS**

All authors of this article declare that we qualify for authorship as defined by ICMJE http://www.icmje.org/#author. Each author has participated adequately in the work and takes public responsibility for appropriate portions of the content of this article. OTE and AAO conceptualized and designed the study. OTE and RU contributed in data collection, analysis and interpretation of data. OTE, RU, AAO and FK drafted and critically analyzed the article. All authors read and approved the final manuscript. Each author acknowledges that this final version was read and approved.

**ETHICS STATEMENT BY ALL AUTHORS**

This study was conducted with approval from the Institutional Review Board of the institution associated with this study. Authors take responsibility to maintain relevant documentation in this respect.

**LIST OF ABBREVIATIONS (IN ALPHABETIC ORDER)**

FNAC - Fine needle aspiration cytology
PPV - Positive predictive value
NPV - Negative predictive value
NHL - Non-Hodgkin's lymphoma
IHC - Immunohistochemistry
FC - Flow cytometry

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