Reliability of fine needle aspiration cytology (FNAC) as a diagnostic tool in cases of cervical lymphadenopathy

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KEYWORDS
Cervical lymph nodes; FNA morphology; Reliability and accuracy

Abstract  Purpose: The aim of this work is to evaluate the reliability and diagnostic accuracy of fine needle aspiration cytology (FNAC) of cervical lymph nodes with an emphasis on discordant cases between the cytology and the histopathology.

Patients and methods: This retrospective study was conducted on 157 selected patients with cervical lymphadenopathy that had undergone FNAC. Cervical nodal enlargement was the first clinical manifestation of the patients in all cases. Hypocellular slides were excluded from the current study. The cytopathological diagnoses were compared with the histopathological results of the same excised nodes. For all discordant cases, special attention was focused on the cytomorphological features. Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and discordance rate were calculated.

Results: The cytological diagnoses were found to be benign in 48 cases (30.6%) and malignant in 109 cases (69.4%). The overall diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of FNAC of cervical lymph nodes were 90.9%, 67.2%, 82.6%, and 81.3%, respectively. The overall diagnostic accuracy was 82.2% (129/157), while the overall discordance rate was 17.8% (28/157). The diagnostic accuracy of reactive lymphoid hyperplasia, chronic necrotizing lymphadenitis, chronic granulomatous lymphadenitis, metastatic carcinoma, Hodgkin lymphoma, and Non Hodgkin lymphoma was 85%, 83.3%, 70%, 100%, 77.8%, and 75%, respectively.

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Introduction

Lymphadenopathy is one of the commonest clinical presentations of patients, attending the outdoor clinics in most hospitals. The aetiology varies from an inflammatory process to a malignant condition [1].

Fine needle aspiration cytology (FNAC) of lymph node has become an integral part of the initial diagnosis and management of patients with lymphadenopathy due to early availability of results, simplicity, and, minimal trauma with less complication [2]. FNAC has also been advocated as a useful method in comparison to more expensive surgical excision biopsies in developing countries with limited financial and health care resources [3]. It almost offers an accurate diagnosis for reactive lymphoid hyperplasia, infectious disease, granulomatous lymphadenitis, and metastatic malignancy. Thus, it can avoid the need for excisional biopsy in most cases and allow rapid onset of therapy [4].

The diagnosis of metastatic tumor to the lymph node on cytological smear is crucial and highly reliable. This would be the sole indication for searching the primary tumor, especially in cases of occult carcinoma [5]. However, in most of these cases, the primary tumor is clinically known and FNAC is used widely for the follow up of these patients. Most of metastatic carcinoma can be identified by their cytomorphological characteristics alone. However, there are some instances where features of different tumors overlap and the precise diagnosis of the primary tumor remains obscure [6]. Ancillary techniques, such as immunocytochemistry, are used to overcome these difficulties and support the cytdiagnostic interpretation [7].

FNAC is used mainly to assess the staging of primary lymphoid malignancies as well as to recognize the residual and recurrent lymphoid malignancies [8]. Shakya et al. [9] also mentioned that the cytology is more readily accepted for the evaluation of deeply seated lymph nodes (i.e. surgically inaccessible) with primary lymphoma or for medically unfit patients for surgery. 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 [10]. Since the latest World Health Organization (WHO) lymphoma classification is based not only on the architectural pattern, but also on cellular morphology, phenotype, and genotype of malignant lymphoid cells; and all of which can be assessed on cytology. Therefore, FNAC in combination with immunophenotypic and genotypic studies is gaining respect in providing an accurate diagnosis of malignant lymphoma in selected risk patients [11].

Enlarged palpable cervical lymph nodes are common and worrying presentation in adults as well as in children. Cervical lymph nodes are involved most often in all types of lymphadenopathy particularly reactive hyperplasia and Hodgkin lymphoma [9]. Although the reliability of FNAC of cervical lymph node has been shown in some studies [12,13] but there are also some reports in contrary [14,15].

Therefore, the aim of the current work is to report the results of FNAC of cervical lymphadenopathy, that depend on the cytomorphological features alone, in comparison to the results of histopathology in an attempt to highlight the diagnostic accuracy and reliability of FNAC of lymph nodes with an emphasis on discordant cases between the cytology and the histopathology.

Patients and methods

This retrospective study on 157 selected patients with cervical lymphadenopathy was conducted at the Cytology Unit, Pathology Department, National Cancer Institute, Cairo University from January 2007 to June 2010. Cervical nodal enlargement was the first clinical manifestation of the patients in all cases.

This study was limited to the selected cases that had undergone FNAC from the enlarged cervical lymph nodes, which were stained with Papanicolaou stain, followed by subsequent excisional biopsy of the same neck node with definitive histopathological diagnosis.

In each studied case, a brief clinical history was carried out including age, sex, size, and site of enlarged cervical nodes. The slides of all cases were examined to determine the cytomorphological features. These features included adequacy, cellularity, arrangement of cells, and nuclear as well as cytoplasmic features. The background was noted in all slides for the presence of necrosis and granuloma formation as well as for the type of inflammatory cells. Hypocellular slides were excluded from the present study.

The cytologic results included four main diagnoses; (a) “benign diagnosis with recommendation of follow up” that deal with smears presenting no malignant tumor cells, (b) “Malignant metastatic diagnosis with recommendation of searching for the primary tumors” that comprised smears showing malignant metastatic tumor cells, (c) “Malignant primary lymphoma (non Hodgkin lymphoma, large cell type or Hodgkin lymphoma) with recommendation of excision for confirmation and immunophenotyping” that showed large malignant-looking lymphoid cells or typical Reed–Sternberg (R–S) cells, (d) “Suggestive of or suspicious for lymphoid malignancy with a recommendation of biopsy and immunophenotyping” that revealed atypical small or large lymphoid cells or revealed R–S and Hodgkin-like cells. In the current study, we considered suggestive or suspicious cases as positive for malignancy as all these cases were investigated and managed seriously.

The histopathological assessment was advocated in the included cytologically benign cases either due to clinical persistent, multiple, or enlarging lymphadenopathy or due to suspicious...
radiological or laboratory features. The histopathological examination was performed in the included malignant metastatic cases as the metastatic work up of such cases failed to identify the primary tumors. The cytopathological diagnoses then were compared with the histopathological results of the same excised nodes. In cases of discrepancy, histopathologic results were considered the gold standard. For all discordant cases, special attention was focused on the cytomorphological features.

Statistics

Diagnostic sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and discordance rate were calculated. All these values were compared with other studies.

Results

Among the 157 studied cases with cervical lymphadenopathy that had underwent FNAC, 84 cases (53.5%) were females and 73 cases (46.5%) were males with male: female ratio of about 1:1.2. Eighteen cases (11.5%) were in the pediatric age group (between 0 and 20 years). Fifty-eight cases (36.9%) belonged to the age group between 21 and 40 years. Forty-eight cases (30.6%) were in the range of 41–60 years. Thirty cases (19.1%) were in the group between 61 and 80 years. Only three cases (1.9%) were above the age of 81 years.

The commonest site of the involved cervical lymphadenopathy was the upper deep cervical lymph nodes constituting 59 cases (37.6%) followed by involvement of the supravacular lymph nodes in 44 cases (28%). Among the remaining cases, 23 cases (14.6%), 10 cases (6.4%), 9 cases (5.7%), 7 cases (4.5%), and 5 cases (3.2%) were in lower deep cervical lymph nodes, submandibular, preauricular, midcervical, and occipital lymph nodes, respectively (Table 1).

The size of the lymph nodes was found to be ≤2 cm in 87.5% of the benign cases, 42 out of 48 cases; and >2 cm in 78.9% of the malignant cases, 86 out of 109 cases.

The cytological diagnoses were found to be benign in 48 cases (30.6%) and malignant in 109 cases (69.4%) (Table 2). Among the malignant cases, thirty-one FNA smears (19.7%) were diagnosed as malignant metastatic tumors. Cases with cytologic features diagnostic of or suspicious for malignant lymphoma constituted the largest group in the present study; 78 smears (49.7%). Of them, 60 cases (38.2%) were NHL and 18 cases (11.5%) were HL (Table 2).

Metastatic cases were seen most often over the age of 45 years, 24 cases (77.4%). Out of the 31 metastatic cases to the lymph nodes, 14 cases (45.2%) were metastatic squamous cell carcinoma, 8 cases (25.8%) were metastatic adenocarcinoma, 7 cases (22.6%) were metastatic undifferentiated carcinoma, and 2 cases (6.5%) were metastatic small cell carcinoma. Lymphoma cases were distributed over wide age range.

Table 1 Age and topographic distribution of the 157 studied cases among the different groups of cervical lymphadenopathy.

<table>
<thead>
<tr>
<th>Site</th>
<th>Age range (years)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–20</td>
<td>21–40</td>
</tr>
<tr>
<td>Upper deep cervical</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>Lower deep cervical</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Submandibular</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Preauricular</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Mid cervical</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Occipital</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>18 (11.5%)</td>
<td>58 (36.9%)</td>
</tr>
</tbody>
</table>

Table 2 Size and cytological diagnoses of the 157 studied cases with cervical lymphadenopathy.

<table>
<thead>
<tr>
<th>Cytological diagnoses</th>
<th>No. of cases</th>
<th>Size ≤2 cm</th>
<th>&gt;2 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive lymphoid hyperplasia</td>
<td>48 (30.6%)</td>
<td>42</td>
<td>6</td>
</tr>
<tr>
<td>Chronic necrotizing lymphadenitis</td>
<td>20 (12.7%)</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Chronic granulomatous lymphadenitis</td>
<td>18 (11.5%)</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Malignant and suspicious cases</td>
<td>109 (69.4%)</td>
<td>23</td>
<td>86</td>
</tr>
<tr>
<td>Metastatic malignant tumors</td>
<td>31 (19.7%)</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>Diagnostic of NHL</td>
<td>9 (5.7%)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Suspicious for NHL</td>
<td>51 (32.5%)</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>Diagnostic of HL</td>
<td>4 (2.6%)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Suspicious for HL</td>
<td>14 (8.9%)</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>157 (100%)</td>
<td>65</td>
<td>92</td>
</tr>
</tbody>
</table>

diagnosed in 20 cases (12.7%), 18 cases (11.5%), and 10 cases (6.4%), respectively (Table 2). Reactive lymphoid hyperplasia was seen most often under the age of 40 years, 12 cases (60%) and all cases of chronic lymphadenitis (necrotizing or granulomatous) were seen in the third and fourth decades.

Males showed predominance of reactive lymphoid hyperplasia and lymphoma, while chronic lymphadenitis and metastatic carcinoma showed female predominance.

The cytopathological results were then compared with the histopathological diagnoses of the corresponding excised lymph nodes. Among the 48 cytologically benign cases, 39 cases (81.3%) were proved histopathologically to be benign, true negative (Figs. 1 and 2), and 9 cases (18.7%) were diagnosed histopathologically as malignant, false negative (Fig. 3). Ninety cases (82.6%) out of the 109 cytologically diagnosed malignant cases were proved histopathologically to be malignant, true positive (Figs. 4–8 and 10), and 19 cases (17.4%) were benign by histopathology, false positive (Figs. 9 and 11) (Table 3).

Accordingly, the overall diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of FNAC of cervical lymph nodes were 90.9%, 67.2%, 82.6%, and 81.3%, respectively. The overall diagnostic accuracy was
82.2% (129 / 157) while the overall discordance rate was 17.8% (28/157) (Table 4).

The calculated 95% confidence interval of the sensitivity was from 83.0% to 95.5%, the specificity was from 53.4% to 78.7%, the PPV was from 73.9% to 88.9%, the NPV was from 66.9% to 90.6%, the accuracy was from 75.1% to 87.6%, and the discordance was from 12.4% to 24.9% (Table 4).

On focusing on the detailed correlation between cytological and histological diagnoses, it was found that, of the 20 cases that were cytologically diagnosed as reactive lymphoid hyperplasia,
3 cases were turned out to be malignant lymphoma on histological examination. This result showed 85% diagnostic accuracy of reactive lymphoid hyperplasia (Table 5).

In the 18 cases that were diagnosed cytologically as chronic necrotizing lymphadenitis, 3 cases were found to be malignant on histopathological base. The diagnostic accuracy of such cases was 83.3% (Table 5). Three cases out of the 10 cases that were diagnosed cytologically as chronic granulomatous lymphadenitis were diagnosed histopathologically as malignant. The diagnostic accuracy was 70% (Table 5).

In cases of metastatic carcinoma to the lymph nodes, all the 31 cases showed exact correlation with the histopathology. The diagnostic accuracy of the metastatic cases was 100% (Table 5).

Sixty aspirates were considered suggestive (n = 51) or diagnostic (n = 9) of non Hodgkin lymphoma (Table 2). Of these, 15 cases were histopathologically diagnosed as benign either reactive lymphoid hyperplasia in 9 cases or granulomatous lymphadenitis in 6 cases and the remaining 45 cases were correlated well with histopathology. The diagnostic accuracy of such cases was 75% (Table 5). One case, which was diagnosed cytologically as suspicious for NHL, was proved to be malignant metastatic undifferentiated large cell carcinoma on histopathological examination (Table 5). This case was considered as a minor discordant case with minor clinical relevance, as regard the typing of the malignant tumor.

Eighteen aspirates were considered suggestive (n = 14) or diagnostic (n = 4) of Hodgkin lymphoma (Table 2). Of these, 4 cases were reclassified histopathologically as benign, reactive lymphoid hyperplasia and granulomatous lymphadenitis. This result showed 77.8% diagnostic accuracy (Table 5).

**Discussion**

The lesion arising in lymph nodes can be found in patients ranging from an early to advanced age [16]. This was correlated with our findings where we found that the youngest patient in the present study was 4.5 years old and the oldest one was 82 years old, the mean age was 46 years. These figures came in close comparison to other workers [1]. We observed that the peak incidence of benign lesions was in the 3rd decade while the peak incidence of malignant lesions was in the 5th decade. These findings correlated with that of Ahmad et al. and Sarda et al. [17,18]. Saluja and Ajinyka [19] attributed the cause of the presence of more malignancy in older age to the fact that adult or elderly patients often react to the infection with only slight to moderate lymph node enlargement; therefore, distinct lymphadenopathy in an elderly patient would arouse suspicion of malignancy and justify immediate needle biopsy.

In the current study, the size of benign nodes was mostly equal or less than 2 cm in 87.5% of all benign cases, whereas malignant nodes were over 2 cm in 78.9% of all malignant cases. These results were in accordance with that of Tilak et al. [16].

In the present study, out of a total 157 studied cases, 109 cases (69.4%) were malignant and 48 cases (30.6%) were benign (Table 2). These findings did not correlate well with most of other similar studies that reported that the benign lesions were more frequent than the malignant lesions due to the high

<table>
<thead>
<tr>
<th>Cytologic diagnoses</th>
<th>No. of cases</th>
<th>Final histopathological diagnoses</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive hyperplasia</td>
<td>20</td>
<td>17</td>
<td>85</td>
</tr>
<tr>
<td>Necrotizing lymphadenitis</td>
<td>18</td>
<td>–</td>
<td>83.3</td>
</tr>
<tr>
<td>Granulomatous lymphadenitis</td>
<td>10</td>
<td>–</td>
<td>70</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
<td>31</td>
<td>–</td>
<td>100</td>
</tr>
<tr>
<td>NHL</td>
<td>60</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>HL</td>
<td>18</td>
<td>1</td>
<td>77.8</td>
</tr>
</tbody>
</table>

frequency of tuberculous and reactive hyperplastic cases, in their study [1,17,20]. However, our results came in close comparison with the results reported by Steel et al., [21] who found that the majority of their cases were malignant (59%) and 34% of the cases were benign. They attributed the cause to the fact that the western countries, where their study was carried out, show predominance of malignant lesions over the benign conditions. Although our study was carried out in eastern country where most of the cases are due to infections and tuberculosis, the predominance of malignant cases, in the present study, was attributed to the fact that we selected our cases that had undergone lymph node excision after FNAC either due to clinical, radiological, or cytological suspicion. Our cases were not randomly selected.

The majority of our studied cases were malignant lymphoma, 78 cases (49.7%). This observation was much higher than that reported by Ahmad et al. [17] who reported 4.5% cases were malignant lymphoma in their study. They considered the cause of this lower lymphoma incidence to the fact that their study included mainly children with large percentage of non-specific infection. Egea et al. [22] also reported a lower incidence of lymphoma, 9.5% of their cases. Rakhshan and Rakhshan [20] also reported 22.4% incidence for malignant lymphoma in their series. The cause of the large percentage of lymphoma in our study may be attributed to two factors: (1) we studied the suspicious cases only; (2) our study was carried out in cancer institute where most referral cases have serious complaints.

In the present study, all cases of metastatic carcinoma to the lymph nodes showed exact corroboration with the histopathology. The diagnostic accuracy of these cases was 100%. This finding showed exact correlation of other workers [1]. Our finding came in close comparison to most investigators who reported more than 90% accuracy rate [6,17,23]. While Khajuria et al. [24] reported 87% diagnostic accuracy. Most of the studied metastatic nodes were metastatic squamous cell carcinoma followed by metastatic adenocarcinoma. Similar findings had been documented by other researchers [1,17,25].

According to the histopathological diagnosis, the overall diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of FNAC of cervical lymph nodes were 90.9%, 67.2%, 82.6%, and 81.3%, respectively. Rakhshan and Rakhshan [20] in their similar study reported sensitivity, specificity, positive predictive value, and negative predictive value of 75.8%, 96.6%, 94%, and 85%, respectively. It was found that the sensitivity in our study was much higher than the sensitivity reported by them. This was attributed to the less false negative results in malignant cases in our study (9/157) compared to their study (15/151). Thus, the negative results had a high validity. The specificity in our results was much lower than that reported by them. This was attributed to the larger number of the false positive cases in our study (19/157) compared to theirs (3/151). The large number of the false positive cases, in our study, was because any atypical lymphoid cells in the included smears were reported with recommendation of excision and immunophenotyping in order to avoid discharging any patient with a possible lymphoma diagnosis.

In the present study and based on the cytomorphology alone, the overall diagnostic accuracy of FNAC in cases of lymphadenopathy was 82.2%. Our observation was lower than that reported by many other authors in similar studies who reported an accuracy rate of 85% to 94.4% [9,20,23–25]. Ahmad et al. [17] observed a much higher accuracy rate (97.6%) in their series.

The overall discordance rate was 17.8%. Among the 28 discordant cases, 9 cases were false negative and 19 cases were false positive.

Regarding to the 9 false negative cases, it was found that 3 cases were underdiagnosed as reactive lymphoid hyperplasia on FNAC and re-diagnosed as malignancy on histopathology. The first case was re-diagnosed as Hodgkin lymphoma of nodular lymphocyte predominant subtype where no R–S cells were detected in the smear, after careful re-examination, making the diagnosis by cytology impossible. The second case was re-classified as Hodgkin lymphoma of nodular sclerosis subtype. The cytomorphological features of this case were still favoured the reactive rather than the neoplastic process with no classic R–S cells or their variants were detected in the smear after careful search. The only significant feature on cytology was the presence of eosinophils in significant number. The third case was re-diagnosed as follicular non Hodgkin lymphoma, grade 2. Careful examination of the smear revealed polymorphous lymphoid population; small lymphocytes were the predominant cell type. Scattered plasma cells as well as histiocytes were also detected.

Kumari and Rajalakshmi [26] attributed the absence of any cytomorphological features of either Hodgkin or non Hodgkin lymphoma on cytology to the focal involvement of the lymph nodes by the disease that may be not aspirated (sampling error). The sampling error is a particular hazard in Hodgkin lymphoma nodular sclerosis subtype possibly because of the fibrosis that interferes with the cell yield [27]. However, sampling error is uncommon in actual practice because varying the angle of entry of the aspirated needle with each pass usually adequately samples the majority of enlarged lymph nodes [2]. Hehn et al., [28] concluded that Hodgkin lymphoma might be missed on cytology as R–S cells and their variant may be relatively sparse or may be masked by preponderance of reactive lymphoid cells. It is fair to say that the diagnosis of nodular lymphocyte predominant Hodgkin lymphoma is extremely challenging to make by FNA [29].

AlAlwan et al. [23] concluded that the low-grade non Hodgkin lymphomas, including follicular lymphoma grade 1 and grade 2, with minimal cytomorphological atypia remain very difficult to be evaluated cytopologically and they are usually mis-diagnosed as reactive lymphoid hyperplasia. Flow cytometry is essential in distinguishing them as it demonstrates the monoclonality in neoplastic B-cells. Brandao et al. [30] reported that the follicular lymphoma might present a particular difficulty in FNAC specimens because neoplastic element itself was polymorphous (centrocytes and centroblasts), and there might be a significant population of T-lymphocytes and, less commonly, histiocytes. Almost the same observations were reported by Dong et al. [31] who concluded that the difficulty to distinguish follicular lymphoma from reactive hyperplasia was largely due to the fact that the interfollicular areas in follicular lymphoma might contain large number of small lymphocytes as well as histiocytes that aspirated with the neoplastic cells. Saboorian and Ashfaq [32] reported that the key to the diagnosis of reactive lymphoid hyperplasia was the presence of plasma cells, macrophages, and lymphoblasts.

The diagnostic accuracy of reactive lymphoid hyperplasia in the current study was 85%. This finding was in agreement
with experience of Keith et al. [2] who reported 88% diagnostic accuracy. However our finding was much lower than that reported by Al-Mulhim et al. [6] who reported 100% diagnostic accuracy for such cases.

Three cases out of the 9 false negative cases, in the current study, were interpreted cytopathologically as chronic necrotizing lymphadenitis and proved histopathologically to be diffuse large B-cell lymphoma in one case and metastatic squamous cell carcinoma in the remaining 2 cases. Re-examination of the smears of the first case revealed marked necrotic background associated with scattered epithelioid cells, histiocytes, and small lymphocytes. Careful examination failed to identify any malignant or suspicious lymphoid cells. Extensive necrosis, in some cases of diffuse large B cell lymphoma, may yield necrotic material with sparsely suspicious lymphoid cells that might be degenerated and crushed. Knowledge of this pitfall needs careful searching for viable atypical lymphoid forms [33].

Review of one of the metastatic squamous cell carcinoma smears showed features of necrotic inflammation. Careful examination revealed few amorphous orangophilic debris scattered along the slide edge with very few anucleated keratinized cells. Examination of the other smear revealed mixed inflammatory cells with ghost of necrotic cells in the background. No viable atypical or malignant tumor cells could be detected after a meticulous examination. Mendon [34] in his study reported that the necrotic and cystic metastatic squamous cell carcinoma to the lymph node might constitute an example of a diagnostic problem in cytology. He considered that these cases were not rare in neck nodes and when considered both cytological characteristics and neck ultrasound, it is possible to suspect the true diagnosis of the lymph node even if the primary tumor is occult.

In the present study, the diagnostic accuracy of the chronic necrotizing lymphadenitis was 83.3%. This result was much lower than that reported by Keith et al. [2] and Ahmad et al. [17] who concluded 100% and 97.4% diagnostic accuracy, respectively. Also Al-Mulhim et al. [6] reported 93% diagnostic accuracy for such cases.

In the current study, the last 3 false negative cases were diagnosed on FNAC as chronic granulomatous lymphadenitis, but on follow up biopsy, the cases proved to be Hodgkin lymphoma mixed cellularity type in the first case, metastatic squamous cell carcinoma in the second case, and metastatic adenocarcinoma in the last case. Careful review of all aspirates failed to detect any atypical lymphoid or metastatic malignant cells. Kumari and Rajalakshmi [26] explained that the presence of exuberant granulomatous reaction in association with Hodgkin lymphoma or metastatic disease to the lymph node might distract the observer from the underlying pathology. Mendon [34] reported that when a cytological diagnosis of granulomatous lymphadenitis was done, one should, however, remembered that it does not exclude the possibility of associated malignancy. Therefore, one should recommend the tissue biopsy if the clinical, radiological, or laboratory data are not consistent with granulomatous disease to exclude a granulomatous response to a malignant neoplasm within the node.

In the present study, the diagnostic accuracy of chronic granulomatous lymphadenitis was 70%. This result was much lower than that concluded by Keith et al. [2] and Ahmad et al. [17] who reported 100% and 97.4% accuracy rate, respectively.

It is very important to mention that, the cytopathologist and the clinician should be aware that the negative cytologic results do not exclude malignancy, especially lymphoma, in patients with unexplained lymph node enlargement and the biopsy should be considered [9]. Based on this rule, the nine false negative cases in our study were subjected to biopsy in spite of the negative cytologic results.

Regarding to the 19 false positive cases, 4 cases had an initial cytologic diagnosis suggestive of Hodgkin lymphoma, while the histopathology showed granulomatous lymphadenitis in 3 cases and reactive lymphoid hyperplasia in one case. Review of the smears revealed heterogenous population of small and large lymphoid cells in various stage of maturation. Scattered large mononuclear atypical lymphoid cells with conspicuous nucleoli in some nuclei and smudged chromatin in others were also observed in all smears and these finding raised the question of Hodgkin lymphoma. Binucleated R-S like cells with no or small nucleoli as well as multinucleated cells were observed in only one case. No classic R-S cells with large prominent nucleoli were detected.

Malakar et al. [35] concluded that the cornerstone of the cytodagnosis of Hodgkin lymphoma on cytology was the finding of the classic R-S cells in an appropriate polymorphous cellular background. The sole presence of mononuclear cells (Hodgkin cells) or apoptotic cells was only suspicious but not diagnostic for Hodgkin lymphoma. However, if the diagnosis of Hodgkin lymphoma had already been established, the findings of these cells were sufficient to make a diagnosis. However, Zhang et al. [36] concluded that classic binucleated or multinucleated R-S cells were infrequent in many cases and the clue to the diagnosis of Hodgkin lymphoma in such situation was the frequently encountered atypical mononuclear R-S cell variant with prominent macronucleoli and granuloma together.

In the current study, the diagnostic accuracy for Hodgkin lymphoma was 77.8%. Similar finding was reported by AlAlwan et al. [23] who concluded 76.9% accuracy rate. However, our result was much lower than that recorded by Al-Mulhim et al. [6] and Das [3] who reported 92% and 90% diagnostic accuracy for Hodgkin lymphoma on cytology, respectively.

In the present study, 15 false positive cases were overdiagnosed by cytology as positive for non Hodgkin lymphoma and turned to be benign on follow up tissue biopsy. Eleven cases had highly cellular smears with presence of numerous individually scattered large atypical lymphoid cells demonstrating conspicuous nucleoli in reactive lymphoid background having plasma cells. The cytological diagnosis was suggestive of non Hodgkin lymphoma, large cell type. On histopathology, they were diagnosed as reactive lymphoid hyperplasia in 5 cases and granulomatous lymphadenitis in 6 cases. One case was proved to be infectious mononucleosis on follow up. Mendon [34] concluded that if the aspiration of the reactive node is derived from the large germinal center, the proportion of the large cells (centroblasts and dendritic cells) as well as the number of mitoses might be impressive enough to suggest malignant lymphoma. However, Hehn et al. [28] in their series concluded that in such germinal center aspiration, a full range of lymphocyte transformation was still present in larger proportion. Landgren et al. [37] reported that immature lymphoid cells might increased in reactive lymphoid hyperplasia due to the presence of hyperplasia of lymphoid cells and therefore cell division. They concluded that lymphoma should be diagnosed when these immature cells account greater than 50% of the cell population. Viral lymphadenitis, particularly infectious mononucleosis, may constitute diagnostic problem on cytology as it
may misinterpret as non Hodgkin lymphoma, large cell type, when large number of immunoblasts are present and it may also be misinterpreted as Hodgkin lymphoma when R–S like cells are prominent [34].

The last four false positive cases that were suggested to be non Hodgkin lymphoma, small cell type, on cytology; were proved to be reactive lymphoid hyperplasia on histopathology. Examination of these smears showed multiple areas of monotonous population of small lymphoid cells with rounded slightly enlarged nuclei having coarse chromatin pattern. The other areas showed polymorphic cell population including few tingible body macrophages. Some authors reported that some cases of reactive lymphoid hyperplasia showed numerically predominant small or slightly enlarged lymphocytes in the interfollicular tissue, if these areas were focally aspirated it would lead to the predominance of small lymphocytes in the smears with variable but much smaller number of the other components. In the same way, Nasuti et al. [38] concluded that the cytodiagnosis of small cell lymphoma should be avoided in the small nodes unless there is immunologic proof of clonality as the smear of small quiescent lymph nodes might show monotonous population of small lymphocytes that can mimic low-grade lymphoma. Hehn et al. [28] recorded that the presence of macrophages with tingible bodies favours the reactive process but do not rule out lymphoma especially in high grade with high turnover of cells. They concluded that if there were numerous mature lymphocytes and clearly visible plasma cells, one should not diagnose lymphoma.

Diagnostic accuracy of our non Hodgkin lymphoma cases was 75.3%. This matched with 73.8% as reported by Landgren et al. [37]. Our finding was much lower than that reported by Keith et al. [2], Al-Mulhim et al. [6], and AlAwlan et al. [23] who reported 82%, 86%, and 88.5% diagnostic accuracy for non Hodgkin lymphoma cases, respectively. Dong et al. [31] concluded lower diagnostic accuracy (67%).

In the current study, one case that was misdiagnosed cytologically as NHL, large cell type was proved histopathologically to be metastatic undifferentiated large cell carcinoma to the lymph node. Careful review of the case revealed total dissociation of the tumor cells. Nuclei were large rounded with dense uniform chromatin and small nucleoli. Some cells formed loose aggregates and no true sharply delineated grouping. Alam et al. [25] found that the dissociation pattern, that could occur in metastatic carcinoma cases, could be indistinguishable from diffuse large cell NHL or anaplastic large cell lymphoma. They concluded that the presence of lymphoid globules (cytoplasmic fragments) in the smear background as well as lobulated nuclei favoured the lymphoma diagnosis. Nevertheless, some degree of cell aggregation favoured the metastatic carcinoma diagnosis [37]. Shyakya et al. [9] concluded that poorly differentiated tumors were difficult to interpret on FNAC even in histopathology and immunostaining was required in such cases to reach a definite diagnosis.

**Conclusion**

Despite its limitations and pitfalls, FNAC appears as a good first line method for investigating the cases of cervical lymphadenopathy. The overall diagnostic sensitivity, specificity, positive predictive value, and negative predictive value were 90.9%, 67.2%, 82.6%, and 81.3%, respectively. The overall diagnostic accuracy was 82.2% (129 / 157) while the overall discordance rate was 17.8% (28/157). The evaluation of FNA in patient with no previously diagnosed malignancy should be interpreted by experienced cytopathologist in the context of clinical, radiological, and laboratory finding and if any of these findings is suspicious, further investigation is justified.

**References**


