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ORIGINAL ARTICLE

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

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KEYWORDS

Cervical lymph nodes;
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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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Conclusion: The overall diagnostic accuracy of FNAC of cervical lymph nodes was 82.2% while the overall discordance rate was 17.8%. The evaluation of FNA in patients with no previously diagnosed malignancy should be interpreted by an experienced cytopathologist in the context of clinical, radiological, and laboratory finding and if any of these findings is suspicious, further investigation is justified to overcome the limitations and pitfalls of the cytomorphological features when applied alone.

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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 cytodiagnostic 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 supraclavicular 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.

Reactive lymphoid hyperplasia, chronic necrotizing lymphadenitis, and chronic granulomatous lymphadenitis were

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

Site	Age range (years)					Total
	0–20	21–40	41–60	61–80	> 80	
Upper deep cervical	16	20	15	8	0	59 (37.6%)
Supraclavicular	2	13	16	10	3	44 (28%)
Lower deep cervical	0	9	9	5	0	23 (14.6%)
Submandibular	0	1	5	4	0	10 (6.4%)
Preauricular	0	9	0	0	0	9 (5.7%)
Mid cervical	0	1	3	3	0	7 (4.5%)
Occipital	0	5	0	0	0	5 (3.2%)
Total	18 (11.5%)	58 (36.9%)	48 (30.6%)	30 (19.1%)	3 (1.9%)	157 (100%)

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

Cytological diagnoses	No. of cases	Size	
		≤ 2 cm	> 2 cm
<i>Benign cases</i>	<i>48 (30.6%)</i>	<i>42</i>	<i>6</i>
Reactive lymphoid hyperplasia	20 (12.7%)	20	0
Chronic necrotizing lymphadenitis	18 (11.5%)	15	3
Chronic granulomatous lymphadenitis	10 (6.4%)	7	3
<i>Malignant and suspicious cases</i>	<i>109 (69.4%)</i>	<i>23</i>	<i>86</i>
Metastatic malignant tumors	31 (19.7%)	2	29
Diagnostic of NHL	9 (5.7%)	3	6
Suspicious for NHL	51 (32.5%)	9	42
Diagnostic of HL	4 (2.6%)	1	3
Suspicious for HL	14 (8.9%)	8	6
Total	157 (100%)	65	92

NHL: non Hodgkin lymphoma; HL: Hodgkin lymphoma.

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

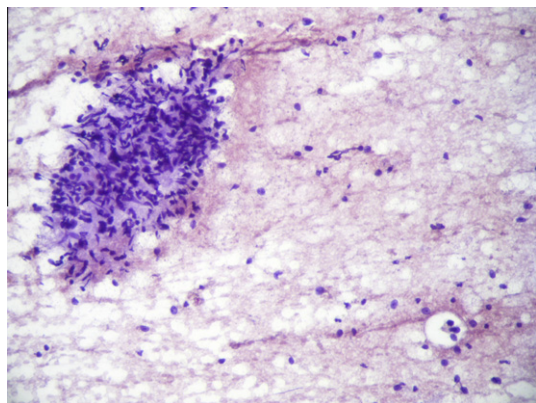


Figure 1 Chronic granulomatous lymphadenitis correlated well with the histopathology. Smears shows tight aggregate of epithelioid histiocytes which is surrounded by lymphocytes, plasma cells, and histiocytes (Papanicolaou stain 200×).

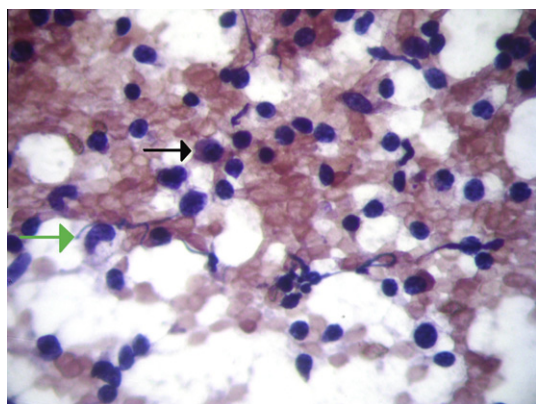


Figure 2 Reactive lymphoid hyperplasia correlated well with the histopathology. Smear reveals plasma cell (black arrow) and tingible body macrophage (green arrow) scattered through small lymphocytes (Papanicolaou stain 400×).

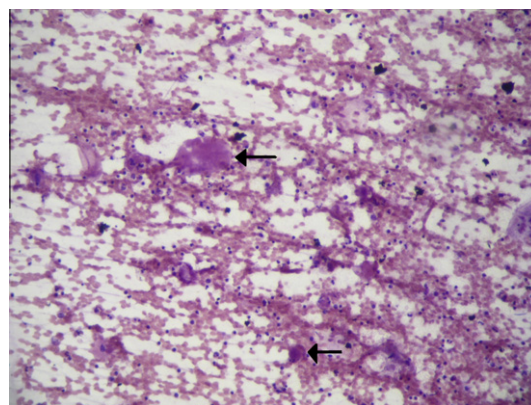


Figure 3 Misdiagnosed cytologically as chronic necrotizing lymphadenitis and proved histopathologically as metastatic squamous cell carcinoma. Smear shows mixed inflammatory cells with scattered amorphous eosinophilic debris (arrows) (Papanicolaou stain 100×).

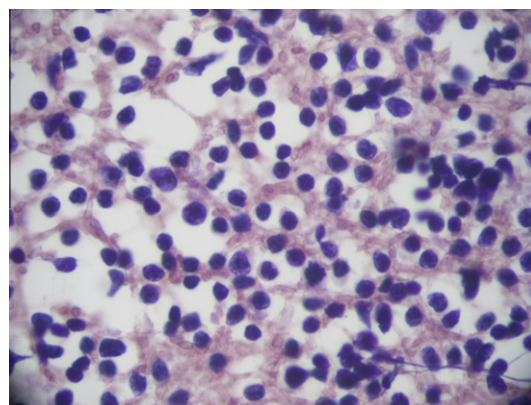


Figure 4 Cytologically was suspicious for small cell NHL and proved histopathologically as follicular lymphoma, low grade (Papanicolaou stain 400×).

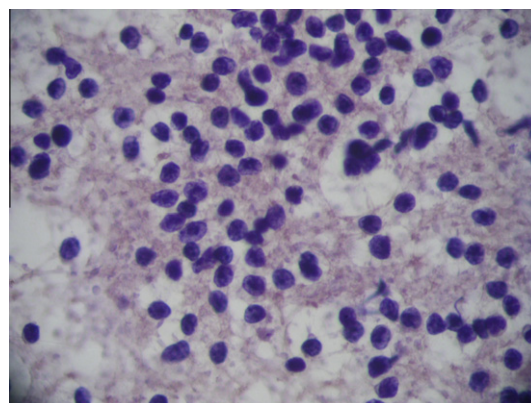


Figure 5 Cytologically was suspicious for small cell NHL and proved histopathologically as mantle cell lymphoma (Papanicolaou stain 400×).

FNAC of cervical lymph nodes were 90.9%, 67.2%, 82.6%, and 81.3%, respectively. The overall diagnostic accuracy was

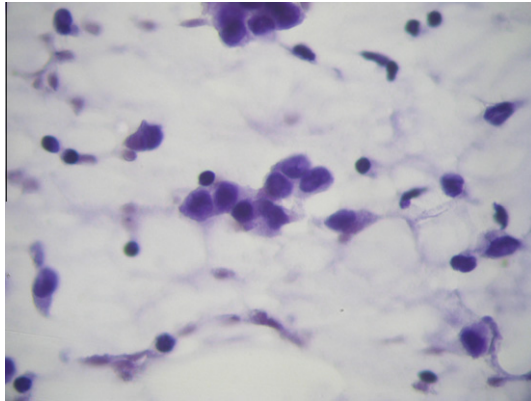


Figure 6 Cytologically diagnosed as metastatic adenocarcinoma and correlated well with the histopathology (Papanicolaou stain 400x).

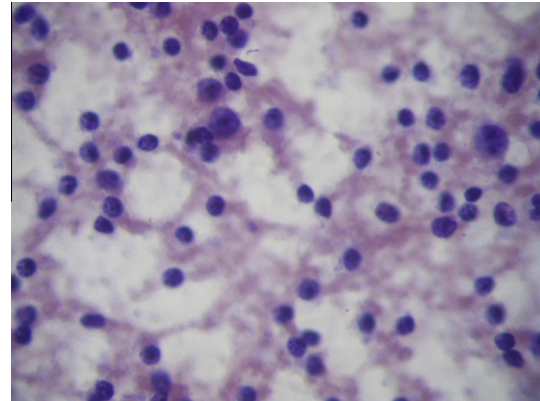


Figure 9 Cytologically diagnosed as suspicious for NHL, large cell type and proved histopathologically as infectious mononucleosis (Papanicolaou stain 400x).

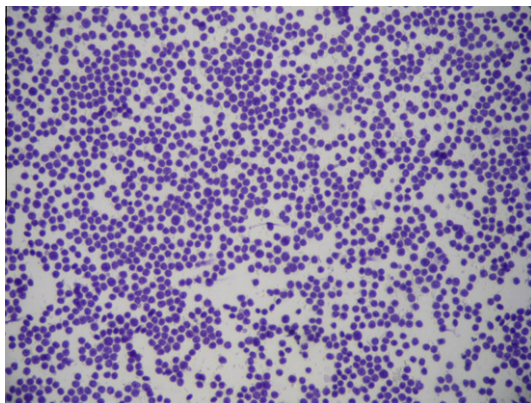


Figure 7 Cytologically diagnosed as large cell NHL and confirmed by histopathology (Papanicolaou stain 200x).

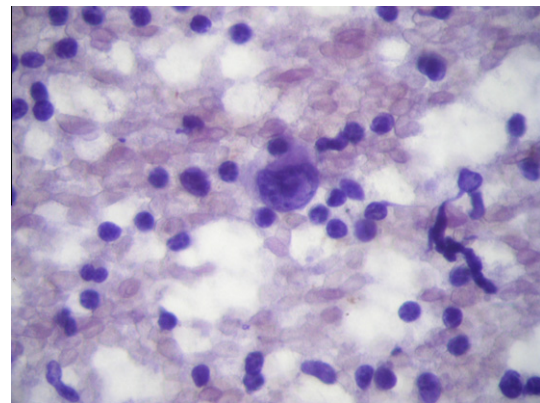


Figure 10 Cytologically was suspicious for HL (mononuclear R-S cell) and correlated well with the histopathology (Papanicolaou stain 400x).

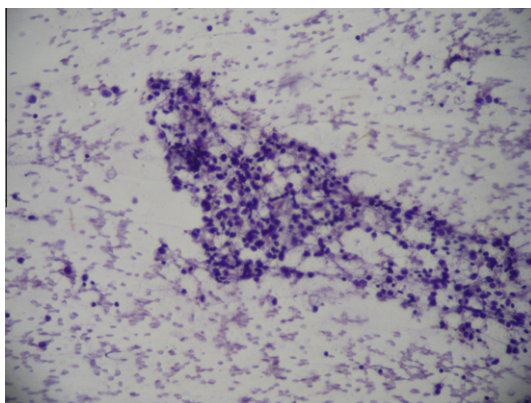


Figure 8 Cytologically diagnosed as large cell NHL and histopathologically proved as metastatic undifferentiated large cell carcinoma (Papanicolaou stain 100x).

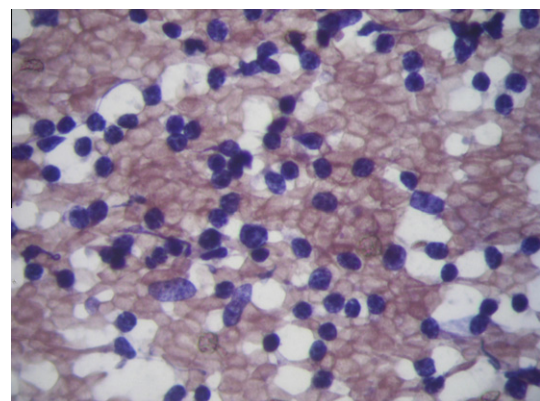


Figure 11 Misdiagnosed cytologically as suspicious for HL and diagnosed histopathologically as granulomatous lymphadenitis (Papanicolaou stain 400x).

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,

Table 3 Comparative analysis of cytological diagnoses by histopathological diagnoses in patients with cervical lymphadenopathy.

Cytopathological diagnoses	Histopathological diagnoses		Total
	Benign	Malignant	
Benign	39 (81.3%) TN	9 (18.7%) FN	48
Malignant	19 (17.4%) FP	90 (82.6%) TP	109

TN: true negative cases; FN: false negative cases; FP: false positive cases; TP: true positive cases.

Table 4 Diagnostic reliability of cytopathological diagnoses of cervical lymph nodes as compared with histopathological diagnoses in patients with cervical lymphadenopathy.

Statistical parameters	Percentage (%)	95% CI (%)
Sensitivity	90.9	83.0–95.5
Specificity	67.2	53.4–78.7
PPV	82.6	73.9–88.9
NPV	81.3	66.9–90.6
Accuracy	82.2	75.1–87.6
Discordance	17.8	12.4–24.9

PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval.

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 5 Comparison of detailed cytopathological diagnoses with the corresponding detailed histopathological diagnoses in patients with cervical lymphadenopathy.

Cytologic diagnoses	No. of cases	Final histopathological diagnoses					Accuracy (%)
		Reactive hyperplasia	Granulomatous lymphadenitis	Metastatic carcinoma	NHL	HL	
Reactive hyperplasia	20	17	–	–	1	2	85
Necrotizing lymphadenitis	18	–	15	2	1	–	83.3
Granulomatous lymphadenitis	10	–	7	2	–	1	70
Metastatic carcinoma	31	–	–	31	–	–	100
NHL	60	9	6	1	44	–	75
HL	18	1	3	–	–	14	77.8

NHL: non Hodgkin lymphoma; HL: Hodgkin lymphoma.

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 cytologically 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 cytologically 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 response 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, remember 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 heterogeneous 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 findings 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 cytodiagnosis 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 increase 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%. 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 AlAlwan 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]. Shakya 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

- [1] Hirachand S, Lakhey M, Akhter J, Thapa B. Evaluation of fine needle aspiration cytology of lymph nodes in Kathmandu Medical College, Teaching hospital. Kathmandu Univ Med J 2009;7(26):139–42.
- [2] Keith VE, Harsharan SK, Jerald GZ. Fine needle aspiration biopsy of lymph nodes in the modern era: reactive lymphadenopathies. Pathol Case Rev 2007;12(1):27–35.
- [3] Das DK. Value and limitation of fine-needle aspiration cytology in diagnosis and classification of lymphomas: a review. Diagn Cytopathol 1999;21:240–9.
- [4] Howlett DC, Harper B, Quante M, Berresford A, Morley M, Grant J. Diagnostic adequacy and accuracy of fine needle aspiration cytology in neck lump assessment: results from a regional cancer network over a one year period. J Laryngol Otol 2007;121(6):571–9.
- [5] Kollur SM, El Hag IB. Fine needle aspiration cytology of metastatic nasopharyngeal carcinoma in cervical lymph nodes: comparison with metastatic squamous cell carcinoma and Hodgkin' and Non Hodgkin' lymphoma. Diagn Cytopathol 2003;28:18–22.
- [6] Al-Mulhim AS, Al-Ghamdi AM, Al-Marzooq HM, Mohammad HA, Gharib IA. The role of fine needle aspiration cytology and imprint cytology in cervical lymphadenopathy. Saudi Med J 2004;25:862–5.
- [7] Haque MA, Talukder SI. Evaluation of fine needle aspiration cytology of lymph node in Mymensingh. Mymensingh Med J 2003;12(1):33–5.
- [8] Raghuveer CV, Leekha IL, Pai MR, Adhikari P. Fine needle aspiration cytology versus fine needle sampling without aspiration. A prospective study of 200 cases. Indian J Med Sci 2002;56:431–9.
- [9] Shakya G, Malla S, Shakya KN, Shrestha R. A study of fine needle aspiration cytology of cervical lymph nodes. J Nepal Health Res Counc 2009;7(14):1–5.
- [10] Jeffers MD, Milton J, Herriot R, McKean M. Fine needle aspiration cytology in the investigation on Non Hodgkin' lymphoma. J Clin Pathol 1998;3:189–96.
- [11] Troxell ML, Charles DB, Athena MC, Yasodha N. Cytologic diagnosis of Burkitt lymphoma: role of ancillary techniques. Cancer Cytopathol 2005;105:310–8.
- [12] Sun HB, Zheng XF, Zhang J. Diagnostic accuracy of fine needle aspiration biopsy of cervical lymph node: a study of 580 cases. Zhonghua Bing Li Xue Za Zhi 2008;37(10):693–7.
- [13] Narang R, Pradhan S, Singh R. Place of fine needle aspiration cytology in the diagnosis of lymphadenopathy. Ind J Tuberc 1990;37(1):29–31.
- [14] Chieng DC, Cangiarrella JF, Cohen JM. Fine needle aspiration cytology of Hodgkin disease: a study of 89 cases with emphasis on false negative cases. Cancer 2001;93(1):52–9.
- [15] Wakely PE. Fine needle aspiration cytopathology of malignant lymphoma. Clin Lab Med 1998;18(3):541–7.
- [16] Tilak V, Dhadel AV, Jain R. Fine needle aspiration cytology of the head and neck masses. Ind J Pathol Microbiol 2002;45(1):23–30.
- [17] Ahmad SS, Akhtar S, Akhtar K, Naseen S, Mansoor T. Study of fine needle aspiration cytology in lymphadenopathy with special reference to acid fast staining in cases of tuberculosis. J K Sci 2005;7(1):1–4.

- [18] Sarda AK, Bal S, Singh MK, Kapur MM. Fine needle aspiration cytology as a preliminary diagnostic procedure for asymptomatic cervical lymphadenopathy. *JAPI* 1990;38(3):46–9.
- [19] Saluja JG, Ajinyka MS. Comparative study of fine needle aspiration cytology, histology, and bacteriology of enlarged lymph node. *Bombay Hosp J* 2000;42(2):1–7.
- [20] Rakhshan M, Rakhshan A. The diagnostic accuracy of fine needle aspiration cytology in Neck lymphoid masses. *Iranian J Pathol* 2009;4(4):147–50.
- [21] Steel BL, Schwartz MR, Ibrahim R. Fine needle aspiration biopsy in the diagnosis of lymphadenopathy in 1,103 patients. *Acta Cytol* 1995;39:76–81.
- [22] Egea AS, Gronzalez MAM, Cohen JM. Usefulness of light microscopy in lymph node fine needle aspiration biopsy. *Acta Cytol* 2002;46:368–9.
- [23] AlAlwan NA, AlHashimi AS, Salman MM, AlAttar EA. Fine needle aspiration cytology versus histopathology in diagnosing lymph node lesions. *East Mediterr Health J* 1996;2(2):320–5.
- [24] Khajuria R, Goswami KC, Singh K, Dudey VK. Pattern of lymphadenopathy on fine needle aspiration cytology in Jammu. *JK Sci* 2006;8(3):145–9.
- [25] Alam K, Khan A, Siddiqui F, Jain A, Haider N. Fine needle aspiration cytology, a handy tool for metastatic lymphadenopathy. *Internet J Pathol* 2010;10(2).
- [26] Kumari TRR, Rajalakshmi T. Fine needle aspiration cytology in the diagnosis of Hodgkin lymphoma: Hits and misses. *J Cytol* 2008;25(1):10–2.
- [27] Jogai S, Dey P, Jassar AI, Amanguno HG, Adesina AO. Role of fine needle aspiration cytology in nodular sclerosis variant of Hodgkin's lymphoma. *Acta Cytol* 2006;50:507–12.
- [28] Hehn ST, Grongan TM, Miller TP. Utility of fine needle aspiration as a diagnostic technique in lymphoma. *J Clin Oncol* 2004;22(15):3046–52.
- [29] Linda M, Sandhaus MD. Fine needle aspiration cytology in the diagnosis of lymphoma. *Am J Clin Pathol* 2000;113:623–7.
- [30] Brandao GD, Rose R, McKenzie F. Grading of follicular lymphoma in fine needle aspiration biopsies: The role of thin preparation of slide and FCM. *Cancer* 2006;108(5):319–23.
- [31] Dong HY, Harris NL, Preffer FI, Pitman BP. Fine needle aspiration biopsy in the diagnosis and classification of primary and recurrent lymphoma: a retrospective analysis of the utility of cytomorphology and flow cytometry. *Mod Pathol* 2001;14(5):472–81.
- [32] Saboorian MH, Ashfaq R. The use of fine needle aspiration biopsy in the evaluation of lymphadenopathy. *Semin Diagn Pathol* 2001;18(2):110–23.
- [33] Ciatto S, Brancato B, Risso G, Ambrogetto D, Maddau C, Turco P. Accuracy of fine needle aspiration cytology of axillary lymph nodes as a triage test in breast cancer staging. *Breast Cancer Res Treat* 103(1):85–91.
- [34] Mendon ME. Fine needle aspiration cytology of lymph nodes. *Prog Diagn Cytol* 1999;32:453–6.
- [35] Malakar D, Jajoo N, Gupta OP, Jain AP. A clinical evaluation of fine needle aspiration cytology in the diagnosis of lymphadenopathy. *Ind J Tuberc* 1991;38(17):17–8.
- [36] Zhang JR, Raza AS, Greares TS, Cobb CJ. Fine needle aspiration diagnosis of HL using current WHO classification, review of cases from 1999–2004. *Diagn Cytopathol* 2006;34(6):397–402.
- [37] Landgren O, MacDonald AP, Tani E, Ost A, Wedelin C. A prospective comparison of fine needle aspiration cytology and histopathology in the diagnosis and classification of lymphomas. *Hematol J* 2004;5:69–76.
- [38] Nasuti JF, Yu G, Boudousquie A, Gupta P. Diagnostic value of lymph node FNAC: an institutional experience of 387 cases observed over a 5 years period. *Cytopathology* 2000;11:18–31.