Original Article

Utility of fine needle aspiration cytology in evaluation of lymphadenopathy – An audit from a Cancer Centre in South India

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Abstract

Background

Cytological evaluation and diagnosis of lymphadenopathy plays an important role in distinction between reactive hyperplasia and malignancy.Being a tertiary cancer care centre, lymph node enlargement clinically suspected to be due to malignancy constitute the commonest indication for fine needle aspiration cytology (FNAC) at our centre. The aim of this study was to determine the utility of FNAC in evaluating enlarged lymph nodes and to categorizethe causes of lymphadenopathy diagnosed byFNAC at our centre.

Material and Methods

Data was collected from the records of department of Pathology over a period of three months from January to March 2014. The data was analyzed and various parameters studied.

Results

There were 2000 aspirates over a period of three months of which 270 (13.5%) were from lymph nodes. Of these, 130cases (48.2%) have metastatic deposits.We also came across 16 cases (5.9%) of lymphoma, 5 cases(1.9%) of granulomatous lymphadenitis, 2 cases(0.7%) of suppurative lesion and 99 cases (36.7%) of reactive hyperplasia during this period. In 3 cases (1.1%), the lesion turned out to be of salivary gland origin. Aspirates were suboptimal for diagnosis in 15 cases (5.5%). Aspirates were more in males (181) as compared to females (89). The most common site of aspiration was the cervical lymph node(64.5%),followed by supraclavicular=81(30%), inguinal=33(12.22%), axillary=19(7.04%) sub mental=1(0.37%) and others=7(2.59%). Apart from metastatic carcinomas other metastatic malignancies we came across were malignant melanoma, neuroblastoma, germ cell tumor and synovial sarcoma.

Conclusion

FNAC of lymph nodes helps in rapid diagnosis of lymphadenopathy.Categorizingthe cause of lymph node enlargement as metastatic malignancy,lymphoma,reactive change,inflammatory cause,suppuration etc. can be done by FNAC.In patients with known histologically proven malignancy in whom a subsequent enlargement of lymph node occurs,a cytological diagnosis of metastasis helps in avoiding unwanted surgery for confirming metastasis.In patients without a previous diagnosis of malignancy, FNAC not only confirm metastatic deposit but in most conditions give a clue regarding site of primary. The use of immunocytochemistry and cell block preparations have increased the scope of FNAC.

Keywords

Fine needle aspiration cytology, lymph node, malignancy

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Introduction

Fine–needle aspiration cytology (FNAC), when performed by trained personnel is a safe and minimally invasive procedure with an excellent diagnostic yield.FNAC is now being usedworldwide as a first–line diagnostic procedure for triage of palpable masses, particularly peripheral lymphadenopathy[1] FNA and cytological examination of the yielded material help decide whether the lymphadenopathy is due to reactive hyperplasia, infective pathology, metastatic malignancy or lymphoma. Hence, FNAC is an excellent diagnostic tool for triaging cases of lymphadenopathy. Our centre is a tertiary cancer centre andthe most common indication for FNAC of lymph nodes is clinically suspected malignancy. In a known case of malignancy, cytological confirmation of metastasishelps avoid an unwanted surgery to confirm metastasis. In cases of unknown primary, a positive diagnosis of metastatic disease in lymph node helps not only to confirm malignancy but also gives an indication of the possible primary site. All clinically suspected cases may not necessarily be malignant. FNAC is extremely useful in differentiating reactive hyperplasia from malignancy. Since it is a rapid diagnostic tool, unwanted anxiety and further unnecessary investigations can be avoided and triaging of cases can be done.

Materials and Methods

This study was conducted in a tertiary cancer care centre catering to a large population. Being a referral centre with additional cases worked up in our centre, many cases are referred to the centre for FNAC.Data was retrieved from the records of Pathology department over a period of three months from 1st January 2014 to 31st March 2014. A total of 2000 aspirates were done during this period of which 270 were from lymph nodes.15 cases were suboptimal for reporting and hence were excluded while the remaining 255 cases were included in the study. A detailed history, clinical examination findings and relevant investigation results were documented. FNAC of the enlarged lymph node was performed by taking aseptic precautions. Aspiration technique using a 23 gauge needle is done. In cases of inaccessible sites, FNA is done under radiological guidance. Material is expressed on a glass slide and with another slide, the material is spread by applying optimal pressure on the slides. The fixative used was 95% ethanol. The smears are stained with Papanicolaou stain. Air dried smears are also taken and giemsa staining done.

Results

There were 2000 aspirates over a period of three months of which 270 (13.5%) were from lymph nodes. Aspirates were suboptimal for diagnosis in 15 cases (5.5%) and were excluded from the study. A total of 255 cases were evaluable for this study. These included 130 cases (48.2%) of metastatic deposits, 16 cases (5.9%) of lymphoma, 5 cases(1.9%) of granulomatous lymphadenitis, suppurative lesion in 2 cases (0.74%) and reactive change in 99 cases (36.7%). In 3 cases (1.11%)., the lesion turned out to be of salivary gland origin. The percentage wise distribution of the cases is shown in Figure 1. Aspirates were more in males (181) compared

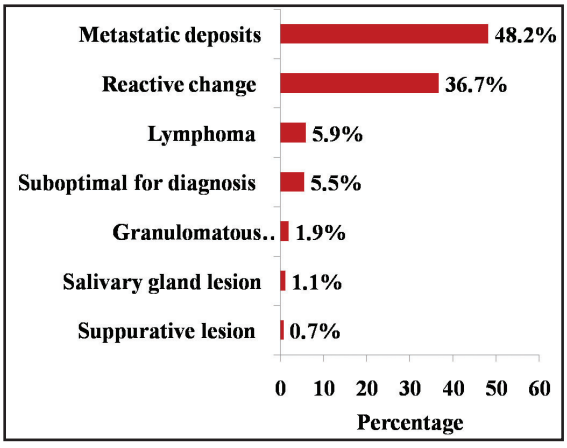

Figure 1. Percentage wise distribution of the cases

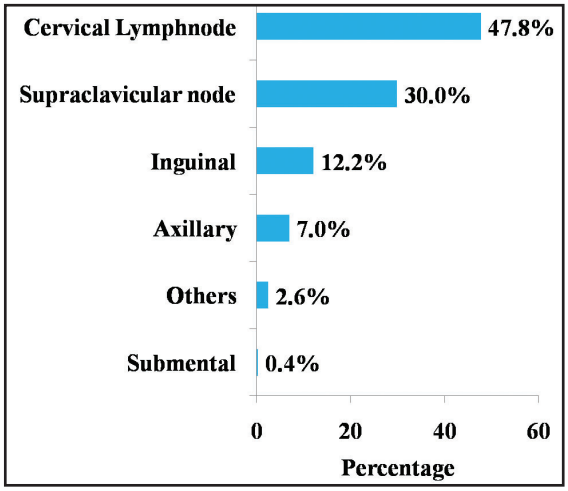

Figure 2. Site wise distribution of the lymphnodes with metastasis

tofemales (89). The age of our patients ranged from six years (a case of metastatic neuroblastoma) to 83 years (a case of metastatic squamous cell carcinoma). The most common age group for metastatic carcinoma was 50–80 years. The most common site of aspiration was the cervical lymph node=129 (64.5%), followed by supraclavicular node=81(30%), inguinal=33 (12.22%), axillary=19 (7.04%), sub mental=1(0.37%) and others= 7 (2.59%). The site wise distribution of the lymph nodes with metastasis is shown in Figure 2.

Of the 130 cases with metastatic deposits, the most common malignancy was metastatic squamous cell carcinoma (51cases) of which 40 cases have a primary in the head and neck region. Other less common sites of primary squamous cell carcinoma with metastasis that we came across during this period included esophagus (6 cases), lung (3 cases), penis (1 case), and anal canal (1 case). Table 2 shows the list of primary sites in case of metastatic squamous cell carcinoma. In squamous cell carcinoma, the characteristic cytological features noted were the dense cytoplasm, keratinization, intercellular bridges and dirty necrotic background (Figure 3a). However, poorly differentiated squamous cell carcinoma can be difficult to diagnose and a careful search for spindly keratinized cells should be made. Nonkeratinizing squamous cell carcinomaappears in sheets and has round to oval nuclei with coarse granular chromatin and prominent nucleoli. This makes a difficult differentiation from poorly differentiated adenocarcinoma. Mucin stains and immunocytochemistry may be required to differentiate difficult cases.

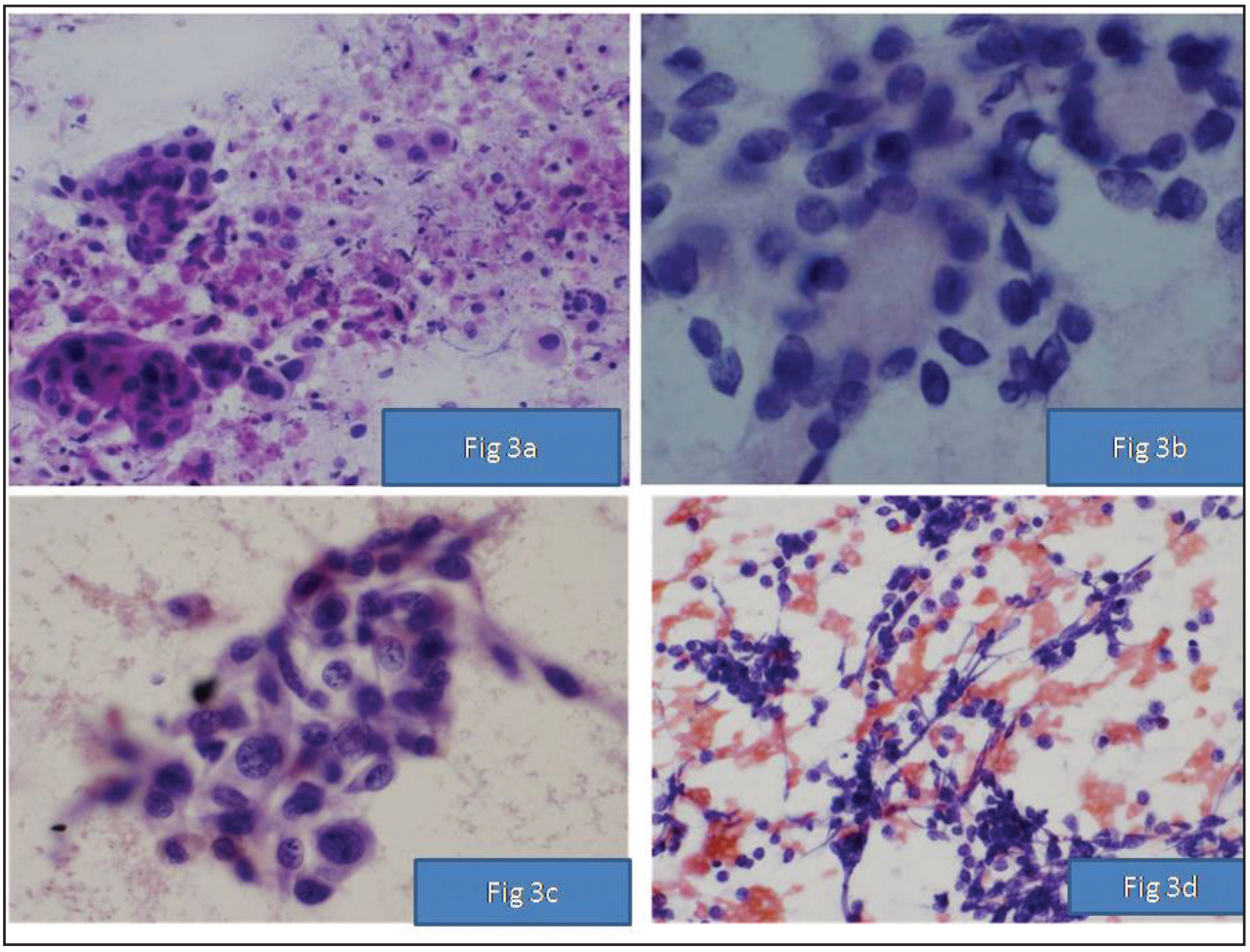

Figure 3a. Squamous cell carcinoma showing the dense cytoplasm, keratinization and dirty necrotic background (Papx400)

Figure 3b. Adenocarcinoma showing glandular pattern of cells (Papx400)

Figure 3c. Malignant melanoma showing malignant cells with intracytoplasmic pigment. (Papx400)

Figure 3d. Small cell carcinoma showing nuclear molding, streaking of nuclear material. (Papx200)

Primary site	Number of cases
Head and neck	40
Esophagus	6
Lung	3
Penis	1
Anal canal	1

Table 2. Distribution of the primary site in case of metastatic squamous cell carcinoma

There were 44 cases of metastatic adenocarcinoma which included 16 cases of metastasis from carcinoma breast, 12 cases of metastasis from lung carcinoma, 5 cases of metastasis from ovary, 3 cases of metastasis from carcinoma of pancreas, 2 cases each of metastasis from carcinoma stomach and prostate. There was also one case of metastasis from cervix. In the remainingthree cases, primary was not known at the time of diagnosis of metastatic malignancy, wherein malignancy was confirmed by FNA and possible primary site was suggested. Table 3 shows the list of primary sites of metastatic adenocarcinoma. The cytological features which were helpful in diagnosis of adenocarcinoma were glandular pattern, cells with vesicular nucleus, prominent nucleoli, intracytoplasmic mucin vacuoles, extravasated mucin, etc. (Figure 3b).

Primary site	Number of cases
breast	16
lung	12
ovary	5
pancreas	3
stomach	2
prostate	2
cervix	1
Unknown primary	3

Table 3. Distribution of primary site of metastatic adenocarcinoma

The other cases of metastatic malignancies we recorded were 3 cases of metastatic papillary carcinoma thyroid, 3 cases of metastatic neuroendocrine carcinoma, 12 cases of metastatic poorly differentiated carcinoma, 2 cases of metastatic malignant melanoma, 3 cases of small cell carcinoma lung, 8 cases of metastatic non–small cell carcinoma, lung, 2 cases of metastatic germ cell tumor, one case of metastatic neuroblastoma and one case of metastatic synovial sarcoma. Table 1 shows the distribution of cases with metastasis. Metastatic papillary carcinoma thyroid showed the characteristic nuclear grooves and intra nuclear

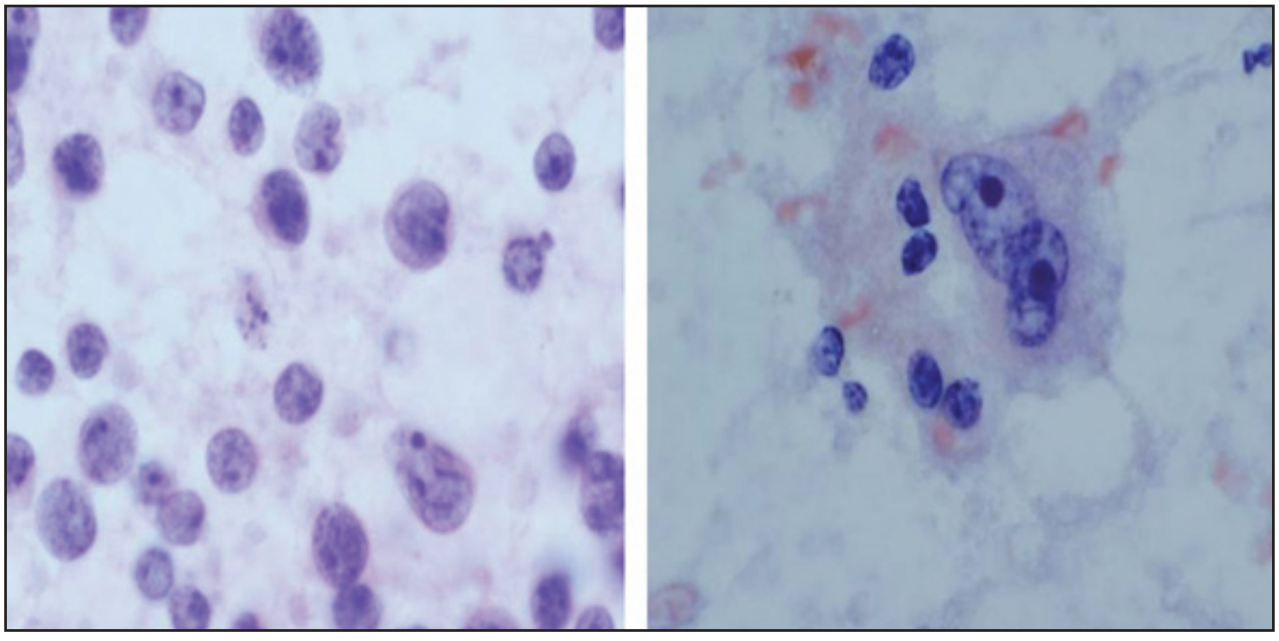

Figure 4a. Monotonous population of atypical lymphoid cells (Papx400)

Figure 4b. Reed–Sternberg cell in Hodgkin lymphoma (Papx1000)

Type of malignancy	Number of cases
Squamous cell carcinoma	51
Adenocarcinoma	44
Papillary carcinoma thyroid	3
Malignant melanoma	2
Germ cell tumor	2
Neuroendocrine carcinoma	3
Poorly differentiated carcinoma	12
Neuroblastoma	1
Synovial sarcoma	1
Small cell carcinoma lung	3
Non–small cell carcinoma lung	8

Table 1. Case distribution of metastasis to lymph nodes

inclusions. The most important cytological finding in neuroendocrine carcinoma was the salt and pepper, granular chromatin. The neuroendocrine carcinoma was confirmed by using immunocytochemistry which showed characteristic paranuclear dot positivity for cytokeratin and positivity for synaptophysin. Few casesof poorly differentiated carcinoma required immunocytochemistry with cytokeratin for confirmation.

Apart from metastatic carcinomas, other metastatic conditions we have noted were malignant melanoma, neuroblastoma, germ cell tumor and synovial sarcoma. In case of malignant melanoma, the presence of intracytoplasmic pigment gives a clue to diagnosis (Figure 3c). Both our cases of metastatic melanoma were known cases of primary malignant melanoma of skin. In small cell carcinoma, the features that helped in diagnosis were nuclear molding, streaking of nuclear material and above all adetailed clinical and radiological information (Figure 3d).

Of the 16 cases of lymphoma, 10 cases were initially diagnosed by FNA and in 6 cases relapse were confirmed. The cases where initial diagnosis was done by FNA include 8 cases of Non–Hodgkin lymphoma (NHL) and 2 cases of Hodgkin lymphoma (HL). Histopathological confirmation was available for 6 cases of NHL and 2 cases of HL. The cases where FNA was used to confirm relapse included 4 cases of NHL (2 cases of Diffuse large B–cell lymphoma, 1 case offollicular lymphoma, 1 case ofmantle cell lymphoma), 1 case of Hodgkin lymphoma and 1 case of lymphoblastic leukemia. Monotonous population of atypical lymphoid cells were observed in NHL (Figure 4a), while the presence of Reed–Sternberg cell helped in reaching a diagnosis of HL (Figure4b). Reactive lymphadenopathy was diagnosed in 99 cases. Of this total, 10 cases were patients with known malignancy where there was clinical suspicion of metastasis. We also recorded 5 cases of granulomatous lymphadenitis, wherein the smears showed granulomas composed of epithelioid histiocytes in a caseous background (Figure 5).

3 cases where clinical lymph node enlargement was suspected turned out to be salivary gland

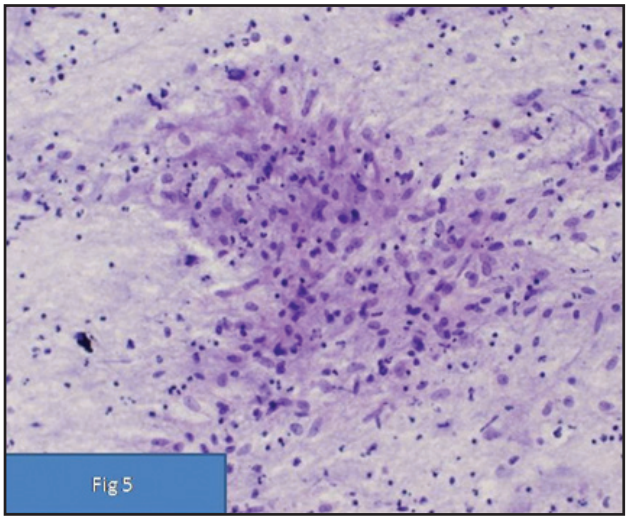

Figure 5. Smear showing granulomas composed of epithelioid histiocytes in a caseous background.(Papx400)

lesions, 2 cases of pleomorphic adenoma and 1 case of sialadenitis. Being a cancer centre, the most common cause of lymphadenopathy that we have on record in the present audit was metastatic carcinoma (48%). This was as expected for a cancer care centre. However, we also havea significant percentage of reactive change cases (36.7%). These included our patients as well as cases referred to us for FNA.

Discussion

Enlarged peripheral lymph nodes are a cause of anxiety to patients and constitute a significant proportion of cases coming for FNAC. Peripheral lymph nodes are easily accessible for FNACand the main purpose of cytopathological examination

is to decide whether the lymphadenopathy is due to reactive hyperplasia, inflammatory pathology, metastatic malignancy or lymphoma. This triaging of cases can be easily done at a peripheral centre and only appropriate cases need to be referred to specialized centers for further work up. In deep seated sites, like intra–abdominal location where accessibility is limited, material can be procured by guided FNA.

The diagnostic sensitivity and specificity of FNA in lymphadenopathy is high. [2, 3] Factors like size, location, fibrosis, etc. affects the nature of the aspirate. In cases of malignancy, extensive necrosis and tiny sub capsular deposits can lead to false negative FNA results. [4] Diagnostic accuracy however depends on other factors like experience of the person performing the procedure, representativeness of the aspirate, quality of the cytological preparations, etc. There are situations where a high yield aspirate becomes totally uninterpretable due to drying artifact or inadequate smearing. The application of adequate pressure while preparing smears is an art which has to be mastered. Both aspiration and non–aspiration techniques can be used. Non–aspiration technique has the added advantage that one can better appreciate the feel of the node by this technique. However in fibrous nodes aspiration is required to procure adequate material. We use 23 gauge needles for FNA of nodes. Depending on individual cases, one or a maximum of two passes are done at a time and smears are submitted for papinicolaou and giemsa stains.

The primary aim of FNA in lymphadenopathy is to categorize cases as either reactive, inflammatory, metastatic malignancy or lymphomas. Based on FNA diagnosis, a wait and watch policy can be adopted for reactive cases while appropriate treatment can be given for inflammatory conditions. Metastatic malignancy and lymphomas can be referred to specialized centers for further workup and sub typing. The primary finding in metastatic malignancy is the presence of foreign population of cells amidst a reactive population of lymphocytes. In some cases of metastatic malignancy, lymphadenopathy may be the initial presenting sign of an underlying malignancy, which is picked up by FNA. In patients with unknown primary FNAC of enlarged nodes not only confirm metastatic deposit but also give a clue regarding site of primary. The presence of columnar cells with nuclear palisading suggests a colonic primary, mucin containing signet ring cells suggest a primary in stomach. Large prominent central nucleoli are usually seen in hepatocellular carcinoma, large cell anaplastic carcinoma of lung, nasopharyngeal carcinoma and malignant melanoma. The presence of intracytoplasmic mucin helps in ruling out a primary of kidney, adrenal, thyroid and liver. Small cell carcinoma metastasing to node can be confused with lymphoma. A proper clinical history and the presence of nuclear molding often help to reach a correct diagnosis. However, immunocytochemistry may be required to sort out difficult cases.

We have recorded more cases of metastatic carcinoma (130 cases) than lymphoma (16 cases) in this audit. This is in agreement with the observation made in previous similar studies. [5, 6, 7] The most common carcinoma metastasizing to lymph node was squamous cell carcinoma in our audit and the most common lymph node involved by metastasis was cervical node. [8, 9] The most common primary was head and neck squamous cell carcinoma. This is also consistentwith the observations made in previous similar studies. [10] The age of our patients ranged from six years (a case of metastatic neuroblastoma) to 83 years(a case of metastatic squamous cell carcinoma).The most common age group for metastatic carcinoma was 50–80 years.We have a significant percentage (36.7%)of lymph nodes with reactive change. These included our patients as well as cases referred to us for FNA. We are of the opinion that if triaging of such cases is done at a peripheral centre, the overload at specialized centers can be reduced and resources can be channeled to cases which needs to be worked up at specialized centers.

When multiple smears are available immunocytochemistry on smears can help in identifying the primary site. Immunocytochemistry can also be used to arrive at a diagnosis when there is a poorly differentiated neoplasm involving lymph node.[11] In the case of malignant melanoma, presence of intracytoplasmic pigment gives a clue to diagnosis but thereare situations where the pigment may not be apparent. In such cases thorough screening for pigment or immunocytochemistry (S100, HMB 45) may be required for a diagnosis. A basic panel of markers consisting of CK, LCA, and S100 can

help to differentiate carcinoma, lymphoma and melanoma. We have used CK (AE1/AE3) to diagnose metastatic poorly differentiated carcinoma. Similarly LCA, CK and synaptophysin helps in differentiating small cell carcinoma from lymphoma. In sites were biopsy is not feasible when adequate material is procured by aspiration, cell blocks can be prepared and immunostaining done.

In patients with known malignancy, a cytological diagnosis of metastasis will help avoid further surgery to confirm metastasis. In case of lymphomas histopathology is still considered to be the gold standard because adiagnosis of lymphomaalone is not sufficient for starting treatment. Proper sub–typing is needed for planning treatment which is possible in histopathology sections. However when accessibility is a limitation for biopsy FNA with ancillary techniques such as immunocytochemistry and flow cytometry can help. [12] Also, in known cases of lymphoma FNA is sufficient to diagnose relapses in high grade lymphomas. However in case of low grade lymphoma it may be difficult to differentiate from reactive change and such situations a biopsy may be required.

Conclusion

Fine–needle aspiration (FNA) is a simple, safe, and costeffective procedure for the investigation of patients with lymphadenopathy. The turnaround time of FNA is much lower than biopsy and hence in case of emergency a faster report can be given. Availability of clinical and radiological details is of utmost importance in increasing efficacy of cytological diagnosis. The complications due to this procedure like hematoma andinfarction are minimal[13, 14]. If used judiciously it gives valuable information on which treatment can be planned and unnecessary surgeries avoided.

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