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Comparative Study of Fine Needle Aspiration Cytology and Cell Block Technique in Lymphadenopathy

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Abstract

Lymphadenopathy is recognized as a common sign of infectious, autoimmune, or malignant disease. Most of the times, infection is the main cause of lymphadenopathy but proper treatment can be persuaded by exact diagnosis. Fine needle Aspiration Cytology plays important role in diagnosing lymphadenopathy having high sensitivity and specificity. But there are conditions in which fine needle aspiration cytology fails to give exact diagnosis. In these cases the diagnostic utility of fine needle aspiration cytology can be reckoned with use of cell block technique. Thus, the present study was conducted with aim to compare fine needle aspiration cytology and cell block technique in lymphadenopathy and to study advantages of cell block technique. Total 91 patients were studied and results revealed maximum number cases in the age group of 20-40 years with nearly equal M:F ratio and cervical lymph node being commonest aspirated one. Malignant cases outnumbered benign conditions on both fine needle aspiration cytology and cell block technique. 4 cases were inconclusive on fine needle aspiration cytology while only one case was inconclusive on cell block technique. Tuberculous lymphadenitis and metastasis of squamous cell carcinoma were commonly diagnosed conditions both on fine needle aspiration cytology and cell block. Cell block picked one more case each of reactive lymphadenitis, tubercular lymphadenitis and metastasis of squamous cell carcinoma. Two cases of squamous cell carcinoma were misdiagnosed on fine needle aspiration cytology. One case was reported as metastasis of adenosquamous carcinoma and other one reported as squamous cell carcinoma with tuberculous lymphadenitis on cell block. These results concluded that cell block has higher sensitivity and specificity than fine needle aspiration cytology. Thus fine needle aspiration cytology in conjunction with cell block technique can increase the diagnostic accuracy of the disease with the advantage of providing cell block section for immunocytochemistry and immunohistochemistry.

Keywords: Cell block, fine needle aspiration cytology, lymphadenopathy.

Introduction

Human body has approximately 600 lymph nodes. Lymphadenopathy i.e abnormal size, shape and consistency is one of the commonest clinical presentations of all age groups. The etiology can vary from an

inflammatory process to a malignant condition.[1] Most common tool used for diagnosis of lymphadenopathy is fine needle aspiration cytology (FNAC). FNAC facilitate early availability of result, simplicity and minimal trauma with fewer complications. FNAC offers accurate diagnosis of reactive lymphoid hyperplasia, infectious diseases, granulomatous lymphadenitis, and metastatic malignancy, follow up of primary tumor and assess staging of primary lymphoid malignancies. Image guided (CT, USG, MRI) FNAC plays an immensely beneficial role in intra abdominal, retroperitoneal, pelvic, thoracic, and other deep seated lesions.[2] One of the constraints of conventional FNA smears is limited material available for adjuvant diagnostic investigations including immunohistochemistry. Cell block (CB) preparation has long been useful complementary method for examination of cytology material. Large amount of material remains after smear preparation. This can be used in cell block preparation, thus, increasing sensitivity of detecting malignancy and also has the ability to reduce false positive interpretation. Cases that are suspicious or equivocal on the smear can be diagnosed definitively on cell block.[3] The cell block technique employs the retrieval of small tissue fragments from FNA specimens which are processed to form paraffin block. Thus it can provide advantage of taking multiple sections of the same material which may be processed for routine stains like hematoxylin and eosin, special stains that may serve for immunocytochemistry and for identification of mucin, melanin, bacteria and fungi. It increases cellular yield and improves diagnostic accuracy which is useful for categorization of tumors with optimal preservation of histochemical & immunocytohemical properties.[4] In cases where FNAC material is hemorrhagic, cell block can provide an alternative mean for diagnosis. Routine FNA smears yield sufficient material for cytologic evaluation but the architecture of small pieces of tissues is lost during smear preparation, however on cell block, tissue architecture is well preserved. [5] Thus examination of cell block preparation along with FNA smears yield two differing, complementary view of same cell population increasing sensitivity and decreasing false positive results. Richardson et al [6] have shown that additional diagnoses of cancer can be obtained in 5% of fluid specimens if smear technique is supplemented by cell block sections of residual material.

The present study has been undertaken to assess the utility of the cell block preparation in increasing the sensitivity of cytodiagnosis of lymph node lesions which is a useful method for comparison of routine cytology. This study will bear impact mainly in correct diagnosis of lymphadenopathy and hence patients management and prognosis.

Aim and Objectives

1. To study comparative cytopathology in conventional smears and cell blocks.
2. To study advantages of cell block technique over conventional FNAC smears.

Material and Methods

The present study was carried out on 91 patients of either sex and any age who presented with enlarged lymph nodes. The patients with bleeding tendencies, low platelet count, deranged coagulation profile and unwilling patients were excluded from the study. A written informed consent was taken from patients. A detailed history with complete general physical and local examination of swelling was carried out. Under all aseptic precautions FNAC was performed, 3-4 smears were made and stained with hematoxylin and eosin (H&E), papanicolaou (Pap), May Grunwald Giemsa (MGG) and ziehl-neelsen stain (ZN) in cases needed. Cell block samples obtained by flushing needle hub were transported to laboratory as soon as possible in normal saline. It is transferred to a tube and centrifuged at 3000 rpm for 10 min, supernatant fluid is

decanted off. To the sediment equal amount of thromboplastin is added and mixed and allowed to stand undisturbed for 10-15 minutes. The clot formed is subjected for paraffin embedding and cell blocks were made. 4-5 u thick sections are to be cut, mounted on slides and stained with H&E stain. Cell block sections were reported as per the criteria described by CE Bales (Koss's diagnostic cytology and its histologic basis) and by Orell SR & Whitaker D (Fine Needle Aspiration cytology). Biopsy was performed for final diagnosis especially in inconclusive cases.

Results

The present study included total 91 patients that showed M:F ratio of 1:1.06. (Fig. 1) The range of age was 10 to 85 years and maximum number of cases were found in the age group of 20 40 years. (Fig. 2) Cervical lymph node was the commonest group aspirated followed by axillary and submandibular lymph nodes. (Fig.3)

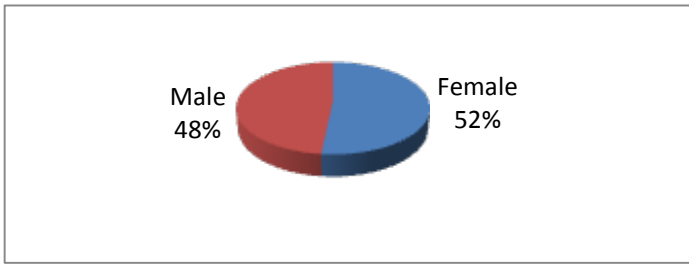

Fig. 1: Pie diagram showing sex distribution in present study

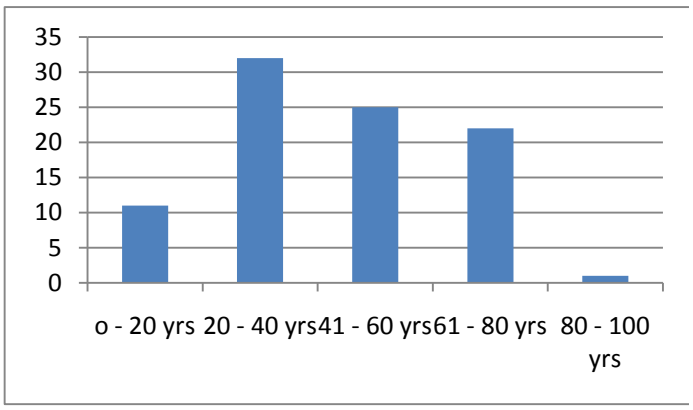

Fig. 2: Age wise distribution of cases in present study

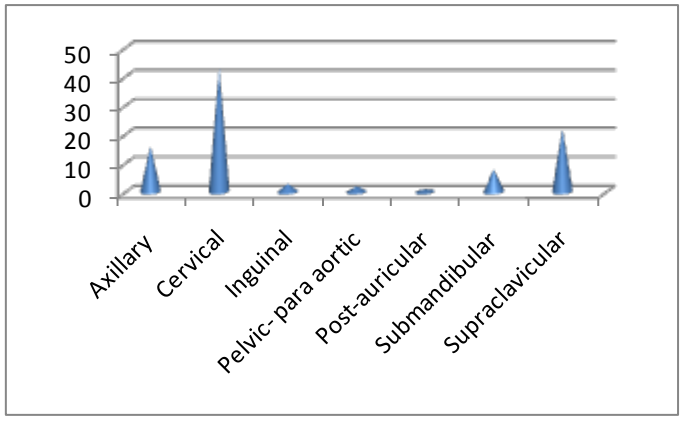

Fig. 3: Chart showing site wise distribution of lymph node lesions aspirated

In the present study, out of 91 cases, 43 were benign, 44 were malignant and 4 were inconclusive on FNAC smears. While on cell block preparation, 44 were benign lesions, 46 were malignant and only one was inconclusive. (Table 1)

Table 1: Incidence of benign and malignant lesions on FNAC and Cell block

Cases	FNAC	Cell Block
Benign	43 (47.25%)	44 (48.35%)
Malignant	44 (48.35%)	46 (50.55%)
Inconclusive	4 (4.39%)	1 (1.09%)
Total	91 (100%)	91 (100%)

Table 2 showed that out of 91 cases, maximum number of cases diagnosed were of tubercular lymphadenitis (Fig. 4) followed by granulomatous lymphadenitis. 7 cases were of reactive lymphadenitis (Fig. 5) and 1 case of lymph nodal abscess (Fig. 6) was also diagnosed.

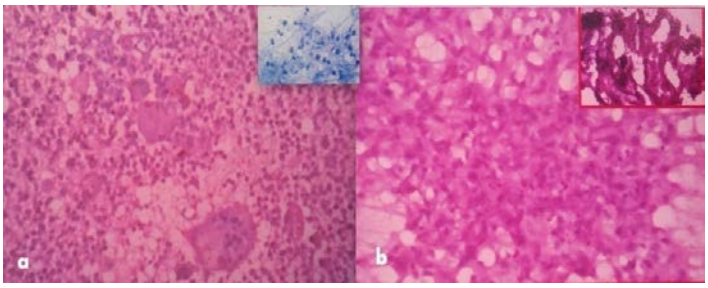

Fig. 4: Tuberculous lymphadenitis a) CB section showing granuloma with langhan's giant cell in necrotic background (H&E 100X) Inset- Tubercle bacilli (AFB)

(ZN 1000X) b) FNAC smear showing granuloma. Inset- caseous necrosis (H&E 400X)

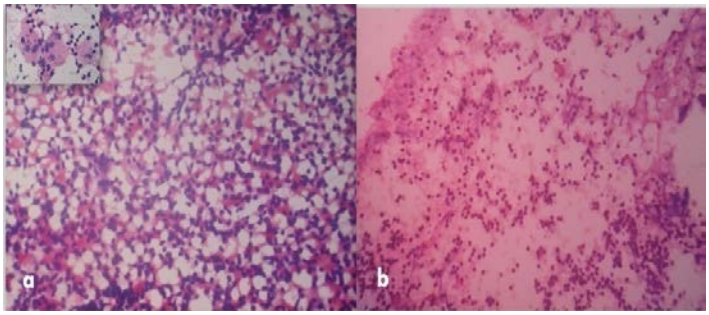

Fig. 5: Reactive lymphadenitis a) FNAC smear showing mixed population of reactive lymphoid cells (H&E 400X). Inset- Tingible body macrophage (H&E 1000X) b) CB section of reactive lymphadenitis (H&E 100X)

Among benign conditions cell block picked up one case more of both tubercular and reactive lymphadenitis whereas one case more of Granulomatous lymphadenitis was picked up by FNAC. Cell block picked up two malignant cases more than FNAC. Total four cases were inconclusive on FNAC whereas it was only one on cell block. Number of inconclusive cases was more on FNAC smears than cell block. One case was diagnosed as metastatic deposit of squamous cell carcinoma (SCC) with tubercular lymphadenitis and one case of fungal granulomatous lymphadenitis (Fig. 7)

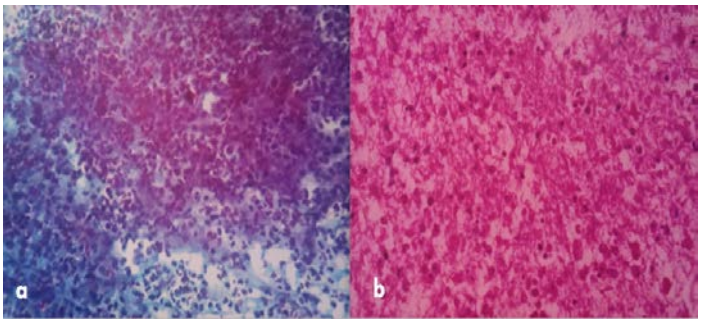

Fig. 6 : Lymph nodal abscess a) FNAC smear showing dense acute & chronic inflammatory infiltrate in necrotic background (Pap 400X) b) CB section showing neutrophils, lymphocytes, few plasma cells and macrophages in necrotic background (H&E 100X)

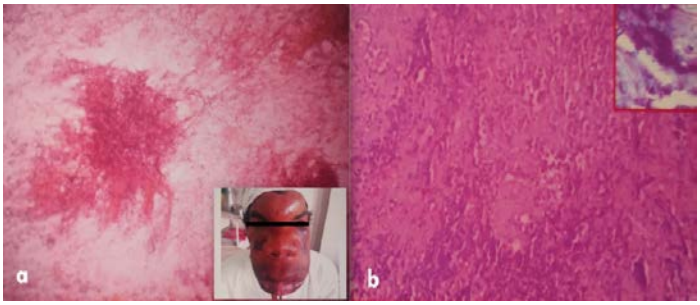

Fig. 7 : Fungal Granulomatous lymphadenitis a) FNAC smear showing granuloma in the background of necrosis and hemorrhage (Pap 100X) Inset- Clinical photograph showing diffuse swelling over face with hyper pigmented and dry skin b) CB section showing inflammation, necrosis Inset- Septated fungal hyphae (H&E 100X)

Equal number of Non Hodgkins (NHL) (Fig. 8) and Hodgkins lymphomas (HL) (Fig. 9) were diagnosed on FNAC and cell block. But in metastatic deposits, cell block has two more cases on its list as compared to FNAC. Out of 39 cases of metastatic deposits on FNAC, SCC (Figure 10) was commonest followed by adenocarcinoma (Fig.11).

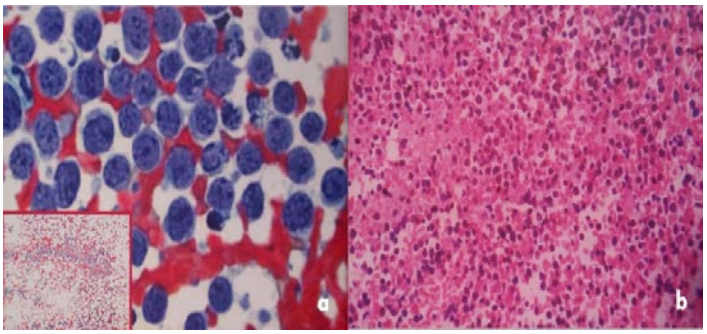

Fig. 8 : Metastasis of NHL a) FNAC smear showing uniform population of large neoplastic lymphoid cells (Pap 1000X). Inset- Dispersed population of cells (Pap 100X) b) CB section showing scattered, uniform population of neoplastic lymphoid cells (H&E 400X)

Table 2: Cytopathological diagnosis on FNAC and Cell block

Cases	FNAC	Cell block
Reactive	7 (7.69%)	8 (8.79%)
Granulomatous	11 (12.08%)	10 (10.98%)
Fungal granulomatous lymphadenitis	0	1 (1.09%)
Tubercular	21 (23.07%)	22 (24.17%)

Abscess		1 (1.09%)		1 (1.09%)	
Necrotizing		3 (3.29 %)		3 (3.29 %)	
Malignant	Metastasis	39 (42.85%)	44 (48.35%)	40 (43.9%)	46 (50.54%)
	Lymphoma	5 (5.49%)		5 (5.49%)	
	Metastasis of SCC with TB	0		1 (1.09%)	
Inconclusive		4 (4.39%)		1 (1.09%)	
Total		91 (100%)		91 (100%)	

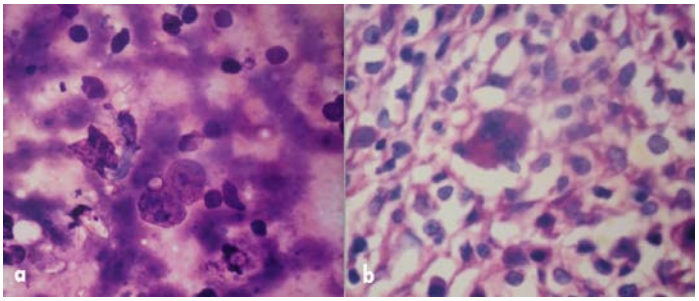

Fig. 9: Metastasis of HL a)FNAC smear showing large, bilobed Reed Sternberg (RS)cell with eosinophilic cytoplasm and prominent nucleoli (H&E 1000X) b) CB section showing RS cell and monomorphic lymphoid population (H&E 1000X)

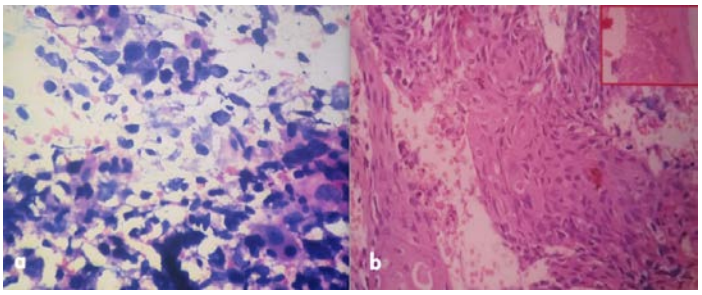

Fig. 10: Mets of SCC a) FNAC smear showing malignant squamous cells with abundant keratinized cytoplasm (H&E 400X) b) CB section showing malignant squamous cells with moderate atypia (H&E 400X). Inset- well differentiated malignant squamous cells (H&E 100X)

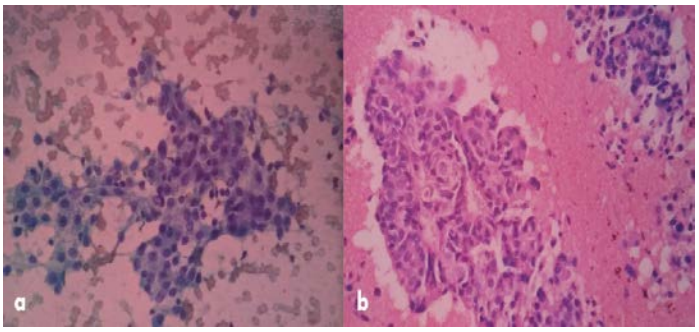

Fig. 11 : Mets of adenocarcinoma a) FNAC smear showing cuboidal to columnar cells with moderate amount of cytoplasm, prominent nucleoli and anisonucleosis (Pap 400X) b) CB section showing glandular arrangement of cells with moderate cytoplasm, vesicular nuclei (H&E 400X)

One case was categorized under germ cell tumor (GCT) metastatic deposit that was further diagnosed as embryonal carcinoma on cell block (Fig. 12). On cell block all the epithelial malignancy deposits diagnosed on FNAC fell under deposits of SCC. One case, each of metastasis of papillary carcinoma thyroid (PTC) (Fig.13) and metastasis of malignant melanoma (MM) arising from congenital lumbar nevus was also observed (Fig. 14). (Table 3)

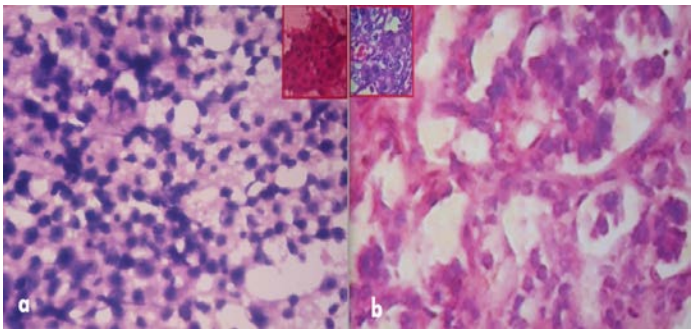

Fig. 12: Metastasis of germ cell tumor a) FNAC smear showing monomorphic tumor cells with hyperchromatic nuclei with moderate cytoplasm in background of lymphocytes. Inset- cluster of monomorphic cells (H&E 400X) b) CB section showing pleomorphic cells arranged in pseudoglandular and alveolar pattern. Inset- cells with hyperchromatic nuclei and prominent nucleoli in some (H&E 400X)

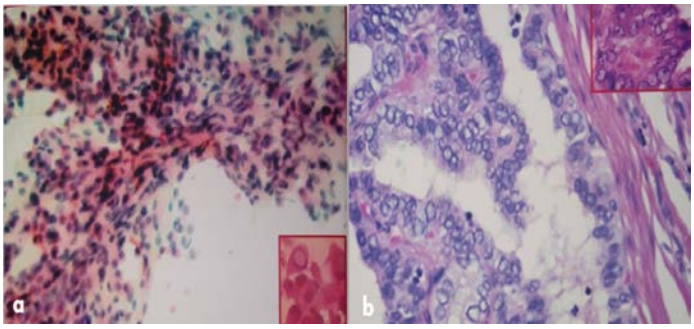

Fig. 13: Metastasis of papillary carcinoma thyroid a) & b) FNAC smear and CB section showing papillary fragments (Pap 100X), (H&E 400X) respectively. Inset- a) & b) Cells showing intranuclear inclusion (H&E 1000X)

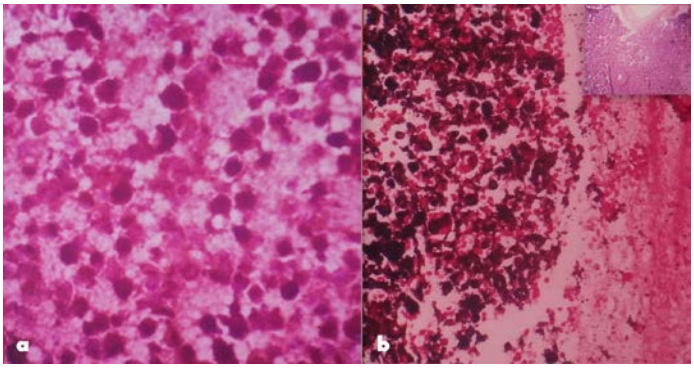

Fig. 14: Metastasis of Malignant melanoma a) FNAC smear showing scattered , pleomorphic cells with hyperchromatic nuclei (H&E 400X) b) Melanin pigment in malignant cells (Masson's Fontana 400X). Inset- Biopsy from congenital lumbar nevus showing features of malignant melanoma (H&E 100X)

Table 3: Incidence of malignant cases on FNAC and Cell block

Sr. no	Malignancy	FNAC	Cell block
1	NHL	4 (9.09%)	4 (9.09%)
2	HL	1 (2.27 %)	1 (2.27 %)
3	Metastasis	39(88.63%)	41 (89.13%)
	i.SCC	18 (46.15 %)	26 (63.41%)
	ii..Adenocarcinoma	9 (23.07%)	10 (24.39%)
	iii.Epithelial	8 (20.51%)	
	iv.Melanoma	1 (2.56%)	1 (2.43%)
	v. Small cell carcinoma lung	1 (2.56%)	1 (2.43%)
	vi. PTC	1 (2.56%)	1 (2.43%)
	vii.GCT	1 (2.56%)	-
	viii. Embryonal cell carcinoma	-	1 (2.43%)
	ix. Adenosquamous	-	1 (2.43%)
	Total	**44 (100%)**	**46 (100%)**

All the data obtained from FNAC and cell block was correlated and calculated for sensitivity and specificity as shown in table 4 which showed cell block is having 100% of sensitivity and negative predictive value, thus increasing diagnostic accuracy from 89.01 % in FNAC to 98.9% in cell block.

Table 4: Statistical correlation of FNAC and cell block.

Statistical indices	FNAC	Cell block
Sensitivity	84.78%	100%
Specificity	93.33%	97.78%
Positive predictive value	92.86%	97.87%
Negative predictive value	85.71%	100%
Diagnostic accuracy	89.01%	98.9%

Discussion

The pathologist's diagnostic armament including new techniques, special stains and specimen processing has expanded dramatically over past few years. FNAC has been established as an investigation of choice in the diagnosis of superficial masses. Though FNA is reliable and preferable in the diagnosis of metastasis in lymph node, its role in diagnosis and sub-classification of primary lymphoid disease is still controversial and usually is followed by open biopsy. Excision biopsy is considered as gold standard for these cases. [7],[8],[9] Surgical lymph node biopsy is not devoid of complication, though injuries of such structures are rare, they can have serious consequences. Open biopsy from LN harboring metastatic SCC is a grave error. [10],[11] Therefore FNA remains an optimal initial step for diagnosing LN disease. Modifying the technique by adding the cell block technique can increase the accuracy of FNA while keeping its safety and advantages. In present era histological diagnosis is becoming more popular, especially in malignant neoplasm. Hence age old technique like cell block is now evaluated in almost all material of FNAC aspirates.

In the present study, FNAC and cell block technique were compared in lymphadenopathy and results were evaluated. Specific diagnosis could be given in most cases. The

findings like age, sex and site were coinciding with the other studies. (Table 5)

Table 5: Comparison of age range, sex ratio and site of lymphadenopathy

Study	Age range	Sex ratio	Site
Hirachand S et al [12]	13-84 years	1.09:1	Cervical
Bharathi K et al [13]	15-75 years	1: 1.08	Cervical
Present study	10-85 years	1:1.06	Cervical

In our study, malignant lymphadenopathy outnumbered benign lymphadenopathy. Out of 91 cases, on FNAC 43 (47.25%) cases were diagnosed as benign lesions and 44 (48.35 %) cases were diagnosed as malignant lesions. Total four (4.39 %) cases were grouped under category of inconclusive cases. Of the 43 benign conditions, FNAC diagnosed 7 (7.69) cases of reactive lymphadenitis, 11 (12.08) cases of granulomatous lymphadenitis, 21 (23.07%) cases of tuberculous lymphadenitis, one case of lymph nodal abscess and three (3.29%) cases of necrotizing lymphadenitis. On cell block sections, out of 91 cases, 44 (48.35 %) cases were diagnosed as benign conditions and 46 (50.55%) cases were diagnosed as malignant conditions. Only one case was categorized as inconclusive. Among 44 benign conditions on cell block, eight (8.79 %) cases were of reactive lymphadenitis, 22 (24.17%) were of tuberculous lymphadenitis, one case of lymph nodal abscess and three cases of necrotizing lymphadenitis.

Thus, cell block picked up one more case each of reactive and tubercular lymphadenitis whereas FNAC had one more case of Granulomatous lymphadenitis on its list as compared to cell block sections. Among Granulomatous lymphadenitis, one case was of fungal granuloma. This was possible as cell block provides better architectural pattern of tissue fragments along with an additional benefit of studying multiple paraffin block sections. Sometimes, diagnosis on cell block becomes difficult because of inadequate material available, poor fixation, preparation or staining techniques. One case which remained inconclusive was diagnosed as reactive lymphadenitis on biopsy. Possible reason was inadequate material available for cell block. Hence, an attempt has been made to prepare and analyze both conventional smears and cell block section.

Out of 44 malignant cases diagnosed on FNAC, four (9.09%) cases of nonhodgkins lymphoma and one case of hodgkins lymphoma showed concordance with cell block sections. However, total malignant cases diagnosed on cell block were 46. Difference was evident in metastatic deposits in lymph nodes. There were 39 (88.63%) cases of metastatic deposits out of 44 on FNAC which was less when compared to cell block sections. Cell block diagnosed 41 (69.13%) cases of metastatic deposits out of 46 malignant cases. FNAC diagnosed metastatic deposits from SCC in 18 (46.15%) cases, from adenocarcinoma in 9 (23.07%) cases, one case each from malignant melanoma, small cell carcinoma lung, PTC, GCT ovary. However, eight cases were difficult to type on FNAC which were reported as metastatic deposits of poorly differentiated epithelial malignancy. These cases however were stratified on cell block. Out of these eight cases, six cases were reported as metastasis from SCC primaries and two cases were diagnosed as metastasis from adenocarcinoma primaries. Besides, germ cell tumor ovary was further typed as embryonal carcinoma on cell block.

Two cases of SCC metastasis were misdiagnosed by FNAC. One case totally missed adenocarcinoma component; which was reported as metastatic deposits of adenosquamous malignancy on cell block (Fig. 15). Its suspected primary was from lung. Other case was given

tubercular lymphadenitis as FNAC smears showed caseous necrosis only with few squamous cells and special stain for AFB was positive. However, cell block sections from same lymph node showed malignant squamous cells along with granuloma (Fig. 16). The possible reason could be excessive background hemorrhage, spreading artifacts, overlapping of cells and scanty cellularity.

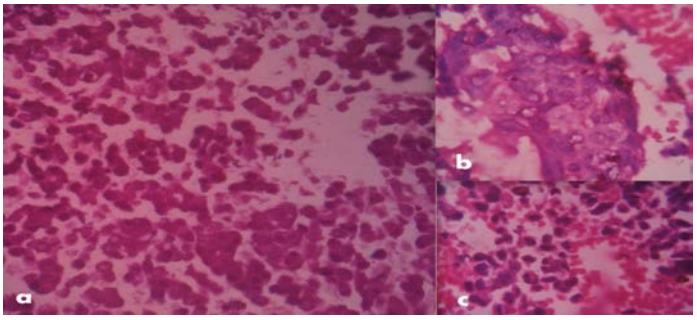

Fig. 15: Metastasis of adenosquamous carcinoma a) FNAC smear showing cells in groups and scattered having moderate cytoplasm, oval nuclei (H&E 400X) b) CB section glandular arrangement of malignant cells s/o adenocarcinoma (H&E 400X) c) CB section showing singly dispersed malignant cells with hyperchromatic nuclei s/o SCC

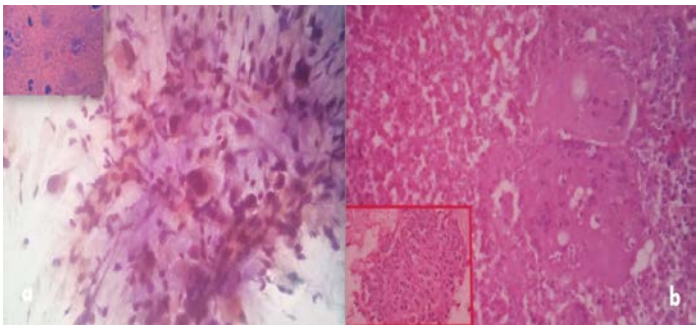

Fig. 16: Metastasis of SCC with tubercular lymphadenitis a) FNAC smear showing granuloma and few squamous cells (Pap 400X). Inset – Tubercle bacilli (ZN 1000X) b) CB section showing necrosis, giant cells & mixed inflammatory infiltrate with foci of SCC metastasis (Inset) (H&E 400X)

As paraffin blocks gives concentrated material in small fields, a more frequent appearance of the architectural pattern help in reaching diagnosis. [14],[15] The serial sections which were made from even a minute amount of cellular material from various types of the sample showed a high cellularity with an excellent morphologic preservation. [16] The diagnosis of carcinoma which is more reliable when it is based on the cell clusters rather than on the individual cells.[17] The glandular forms and mucin can be more reliably seen on CB'S.

A study conducted by Thapar et al [18] opined that cell block technique has the added advantage that multiple sections of the same material can be obtained for special stains and immunohistochemistry with preservation of architectural pattern, excellent nuclear and cytoplasmic details, and individual cell characteristics. Moreover, fragments of tissues can easily be interpreted in a biopsy like fashion.

In this study, sensitivity, specificity and diagnostic accuracy of cell block technique was found more than FNAC in diagnosing lymph node lesions. These findings were in accordance with Dareen Mohamed et al [19] who carried out similar study of FNA and cell block combined with immunohistochemistry as screening tools in 87 patients with peripheral lymphadenopathy.

Table 6: Comparison of sensitivity, specificity and diagnostic accuracy of FNAC and cell block

Study	**Mohamed D et al[19]**	**Wang X et al[20]**	**Present study**
Fine Needle Aspiration Cytology			
Sensitivity	89.19 %	76.47 %	84.78 %
Specificity	64.00 %	67.74 %	93.33 %
Diagnostic accuracy	74.71 %	70.83 %	89.01 %
Cell block			
Sensitivity	100 %	88.00 %	100 %
Specificity	98.00 %	87.00 %	97.78 %
Diagnostic accuracy	98.85 %	88.00 %	98.90 %

Very few studies are done to compare cell block sections with conventional FNAC smears in lymphadenopathy but there are studies conducted in other lesions. Wang X et al [20] carried out the study in lacrimal gland tumors along with immunohistochemistry on CB sections concluded that CB results in greater percentage of accurate tissue diagnosis than cytologic smears. Keyhani- Rofaga et al [2] conducted a study on 85 patients showed that sensitivity of cell blocks varied from 60% to 86% depending on sampling type and size, type of specimens and aspiration technique used. Kern and Haber [3] conducted a study on 393 patients. Cell block and FNAC results were compared. 60.3% cases were confirmed to FNA results and in 26.2 % the cell blocks provided additional information for diagnosis. However, Axe et al [21] concluded that sensitivity of PAP smears (79%) was superior to cell blocks (73%). Wojcik and Selvaggi [22] concluded identical results on both smears and cell blocks in almost 84% of cases. Leung and Bedard [23] found that all cases with adequate material could be diagnosed on a cell block preparation with sensitivity of 86% in 54 out of 63 cases. Nathan N A et al [24] stated that overall sensitivity of PAP smears (87.9%) was slightly superior to cell blocks (85.8%). But when combined with malignant fluids, sensitivity of smears was 90.6% and cell blocks was 89.4%, which reinforces the contribution that cell blocks can make to final diagnosis.

Thus FNAC and cell block when used together provide additional edge to diagnosis and can be considered as sensitive indicators. Besides this, it helps clinicians to start appropriate treatment within time while avoiding excision biopsy. Though rare, this not only reduces complications but also relieves patient's anxiety that can result from repetition of procedure or subjecting them to more invasive procedure and subsequent delay in reports. However, still excision biopsy for assessment of the pattern of expression of immunomarker is necessary in some lymphoma patients who remain challenging to diagnose by FNA with the help of cell block immunohistochemistry.

Conclusion

Although FNAC is safe, quick and minimally invasive technique which can be performed as an outpatient department procedure not requiring anesthesia and readily acceptable by the patient but FNA alone doesn't yield sufficient information for precise diagnosis. Cell block method improves accuracy of FNA, allows the recovery and processing of small fragments of tissue left in needle hub which facilitate the better classification of tumor especially if accompanied with special stains. Cell block for histology and immunohistochemistry provides supportive evidence for the diagnosis. In the present study, it can be concluded that cell block method yielded more cellularity and better architectural pattern which improved the diagnosis of malignancy. Multiple sections could be obtained if required for special stain. Therefore, the cell block technique could be considered as a useful adjunct technique in evaluating lymph node cytology for a final cytodiagnosis, along with the routine conventional FNAC smears method.

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