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Role of fine needle aspiration cytology and adjunctive techniques in the diagnosis of musculoskeletal tumors: An institutional experience

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Abstract
The role of fine needle aspiration cytology in diagnosing recurrent and metastatic sarcomas has been well dealt with, however; its utility in rendering a primary diagnosis of sarcoma still remains a topic of debate. The present study evaluates the scope of FNAC along with adjunctive techniques including cell blocking and immunocytochemistry in diagnosing and subtyping of soft tissue tumors. A total of 71 patients presented with musculoskeletal lesions underwent fine needle aspiration. Cell blocks were contributory in exact subtyping in 41/56 (73.2%) cases. Round cell tumors were the most easily subtyped tumors with 19/20(95%) subtyped accurately. Similarly, 8/17(47.1%) of pleomorphic tumors, 9/19(47.3%) of spindle cell tumors, 1/1(100%) of myxoid tumors, 0/1(0%) epithelioid tumors, 0/2(0%) of lipomatous tumors, 1/2(50%) of mixed tumors and 3/9(33.3%) of other tumors could be accurately subtyped using ancillary techniques. Histopathological correlation was available in 51 cases.

Keywords: Musculoskeletal tumors, Fine needle aspiration cytology, Cell blocks, Immunocytochemistry

Introduction
Fine needle aspiration cytology has many advantages that make it a first line investigation in the primary evaluation of tumours of breast, thyroid and lymph nodes. The primary diagnosis of sarcomas by FNAC, however; remains controversial and relatively underused. This may be attributed to the fact that most pathologists lack extensive experience with the cytopathology features of sarcomas, since in comparison with other forms of cancer, soft tissue sarcomas are rare, constituting less than 1% of all malignant neoplasms [1]. Secondly, these tumors are often heterogenous and show a bewildering array of cyto morphological and histomorphological pictures, which makes the pathologist all the more reluctant in rendering a specific diagnosis [2]. Despite these difficulties, FNA cytology is being used as a diagnostic modality for initial diagnoses, as well as for recurrences and metastases of soft tissue and bone lesions in numerous medical centers due to its simplicity, low morbidity, cost-effectiveness, and ability to issue rapid diagnoses that can facilitate clinical decision making [3-8]. The present study focuses on the utility of fine needle aspiration cytology along with adjunctive techniques including cell blocking and immunocytochemistry in diagnosing and subtyping of musculoskeletal lesions.

Material and methods
71 unaided aspirates from musculoskeletal neoplasms were evaluated over a period of one year. FNA smears were stained with conventional Papanicolaou (Pap), May Grunwald Giemsa (MGG) and Hematoxylin and Eosin (H&E). Residual material in the hub of the needle and material obtained from another fresh needle pass was used to prepare a cell block using fixed sediment method. On primary cytological evaluation, all cases were placed into 8 cytomorphological categories, namely spindle cell, round cell, pleomorphic, myxoid, epithelioid/polygonal cell, lipomatous, mixed cell and other tumors [9]. Immunocytochemistry (ICC) was done on cell block sections and on cytosmears, as and when necessary and exact sub type was offered in the clinical context, with ICC as an adjunct. Histo-cytological correlation was done in cases where adequate histopathological

follow up was available. Cell blocks were made by Fixed sediment technique. The aspirate was first ejected in a test tube containing a mixture of 100% alcohol and distilled water in a ratio of 1:1. The test tube was centrifuged at 1500rpm for 6 minutes leading to formation of a pellet. The residual alcohol was decanted and the pellet was fixed using 100% alcohol and formalin (40%) in a ratio of 9:1. After a 45 min. stand, the mixture was centrifuged at 1000 rpm for 6 minutes. The fixed pellet was dislodged and processed as a histological specimen.

Immunocytochemistry on cell block sections were done. The sections were first deparaffinized in xylene and rehydrated through graded alcohols (100%, 90%, 70%, 50%, 30%) followed by distilled water for 5 minutes in each. Deparaffinized sections were placed in a pressure cooker in TRIS-EDTA (TRIS-1.21gm, EDTA 0.37 gm, Tween 20 - 500µl) buffer (ph 9.0) for antigen retrieval (120 °C for 15 min at full pressure). It was followed by 3 gentle washes in TRIS for 5 min each. Sections were treated with 3% H_2O_2 for 10 min to block endogenous peroxidase activity. It was followed by 3 gentle washes in TRIS buffered saline- TBS (ph 7.4) for 5 min each. Slides were wiped off excess buffer & incubated for 90 minutes with primary antibody at 4° C in a moist chamber. Slides were rinsed with TRIS buffer (ph 7.6) thrice. Excess buffer was wiped off and sections were covered with link antibody (Secondary) for 30 min at room temperature. Enzyme conjugate (Streptavidin horse radish peroxidase) was applied for 30 min followed by 3 washes in TBS for 5 min each. Concentrated Diaminobenzine solution (DAB) was diluted with substrate buffer (500µl of substrate buffer + 2 drops of DAB). Sections were counterstained using 10% hematoxylin and washed in distilled water for 5 minutes followed by mounting of sections by DPX. Presence of brown coloured end product at the site of target antigen was indicative of positive reactivity. Statistical analysis was carried out using SPSS (version 14) software.

Results

During the year 2015-16, total 276 patients were referred to our department with complaints of musculoskeletal lesions for fine needle aspiration cytology. Majority (205/276) of these lesions comprised of clinically obvious, superficial benign lipomatous lesions which were excluded from the study, remaining 71 cases were evaluated in the present study. Out of a total of 71 aspirates, 55(77.5%) were categorised as malignant, 11(15.5%) as benign, 4(5.6%) as equivocal and one case was deemed as inadequate on fine needle aspiration. Among the 55 cases cytologically classified as malignant, 1 was reported as Nodular Fasciitis on histology. This was the only case of a false positive diagnosis in our series while there were no false negatives. Thus, taking into account the false positive diagnosis as well the final histologic diagnosis of the equivocal/inadequate cases, a total of 57/71(80.3%) came out to be malignant while the remainder 14/71(19.7%) turned out to be benign either on histopathology and or on cell block/cytology (where a histopathological follow up was not available). Cell blocks were made in 61 cases, 56/61(91.8%) were found to be adequate. The adequacy of cell blocks was found to be a reflection of the cellularity of corresponding FNAC smears. On comparison, it was found that cell blocks were adequate in 100%, 95% and 75% of cases which were hypercellular, cellular and paucicellular on cytology (excluding cases where cell block was not made). This came out as an advantage in cases of paucicellular smears where a diagnosis which was rendered with difficulty on the basis of smears was facilitated by enhanced cellularity in cell blocks, comprising of a total of 9/12(75%) cases.

In benign cases, utility of cell block was adjudged to be contributory in accurate subtyping in 53.8%, contributory in excluding a diagnosis in 15.4% and non-contributory in 30.7% whereas in malignant cases this proportion was 70.8%, 18.8% and 10.4% respectively for the corresponding outcomes. Statistically, this difference was significant (p=0.001).In terms of adequacy of cell blocks, they were found to be adequate in 100% of round cell tumors, 83.3% of pleomorphic tumors, 92.8% of spindle cell tumors, 100% of myxoid tumors, none in epithelioid tumors, 100% of lipomatous tumors, 50% of mixed tumors and 100% of other tumors. Overall, cell blocks were contributory in exact subtyping in 41/56(73.2%) cases, excluding the inadequate samples. [Table1]. Round cell tumors were the most easily subtyped tumors with 19/20(95%) subtyped accurately by the use of ancillary techniques. Out of 71cases, histopathology of 51 cases was available. Taking FNAC diagnosis as the test technique against HPE diagnosis as the gold standard, out of 51 cases, 43 were identified as true positive, none false negative, 1 false positive and 7 true negative. Correspondingly, FNAC was shown to have a sensitivity and specificity of 100% and 87.5%. The positive and negative predictive values were 97.7% and 100.0% respectively. The accuracy of the method was 98.0%.

Table 1: Distribution of Cases according to Utility of Cell Block in Subtyping among Various Morphological Categories

Morphological category	Total no. of cases	no. of cell blocks made	cell block adequate	cell block inadequate	cB contributory in accurate subtyping	CB contributory in ruling out a diagnosis	CB non contributory
ROUND CELL TUMORS	20	20	20	0	19	1	0
PLEOMORPHIC TUMORS	17	12	10	2	8	2	2
SPINDLE CELL TUMORS	19	14	13	1	9	4	1
MYXOID TUMORS	1	1	1	0	1	0	0
EPITHELIOID TUMORS	1	1	0	1	0	0	1
LIPOMATOUS TUMORS	2	2	2	0	0	0	2
MIXED TUMORS	2	2	1	1	1	0	1
OTHERS	9	9	9	0	3	4	2
tOTAL	71	61	56	5	41	11	9

Table 2: Spectrum of tumors presenting with predominant Round Cell Morphology (n=20)

Case No.	Age	Sex	Site	Diagnosis on FNA	Diagnosis after ancillary techniques	Diagnosis on HPE	Concordance between FNA and Dx after ancillary techniques	Concordance between FNA and HPE	Concordance between subtype offered on FNA and HPE
1	14	male	Chest wall	SRCT	DSRCT	DSRCT	1	1	1
3	7	female	scalp	Metastasis-NB	Metastasis-Neuroblastoma	Abd mass-Neuroblastoma	1	1	1
5	14	male	cervical	SRCT	EWS/PNET	EWS/PNET	1	1	1
6	16	female	Right elbow	EWS/PNET	EWS/PNET	EWS/PNET	1	1	1
13	24	female	scapular	SRCT	EWS/PNET	EWS/PNET	1	1	1
14	4	male	cheek	SRCT	Histiocytic SA	RTT	1	1	1
16	4	male	cheek	SRCT	Lymphoma	Lymphoma	1	1	1
17	10	female	occiput	SRCT	EWS/PNET	EWS/PNET	1	1	1
18	30	male	Right arm	EWS/PNET	EWS/PNET	EWS/PNET	1	1	1
24	10	male	Knee joint	EWS/PNET	EWS/PNET	EWS/PNET	1	1	1
27	18	female	Scalp	Metastasis-EWS	Metastasis-EWS	Metastasis-EWS	1	1	1
31	11	male	thigh	SRCT	EWS/PNET	EWS/PNET	1	1	1
35	11	male	Left leg	EWS/PNET	EWS/PNET	EWS/PNET	1	1	1
36	7	male	Thigh	EWS/PNET	EWS/PNET	EWS/PNET	1	1	1
37	6	male	shoulder	SRCT	EWS/PNET	EWS/PNET	1	1	1
43	3	male	arm	Metastasis-SRCT	Metastasis-WT	Metastasis-WT	1	1	1
46	40	male	Chest wall	Chondroblastoma	Chondroblastoma	N/A	1	3	3
52	7	female	Abdominal mass	SRCT	Neuroblastoma	Neuroblastoma	1	1	1
53	15	male	Gluteal	SRCT	EWS/PNET	N/A	1	3	3
59	10	female	Left leg	EWS/PNET	EWS/PNET	N/A	1	3	3

Key: Concordance: 1: Concordant; 2: Not specified; 3: Couldn't be ascertained; 4: Discordant. [SRCT: small round cell tumor, DSRCT: desmoblastic small round cell tumor,NB: neuroblastoma, WT: wilms tumor, EWS: sewings sarcoma, PNET: peripheral Neuroectodermal tumor.]

Table 3: Spectrum of Spindle Cell Tumors encountered in the study (n=19)*

Case No.	Age	Sex	Site	Diagnosis on FNA	Diagnosis after ancillary techniques	Diagnosis on HPE	Concordance between FNA and Dx after ancillary techniques	Concordance between FNA and HPE	Concordance between subtype offered on FNA and HPE
4	42	M	Upper arm	Spindle cell sarcoma	Synovial sarcoma	Synovial sarcoma	1	1	1
8	32	F	Parotid region	Benign spindle cell lesion(SCL)	Benign spindle cell lesion	Myofibroblastic tumor	1	1	1
10	28	M	Rt cervical	Benign SCL	schwannoma	Schwannoma	1	1	1
11	35	F	Thigh	Malignant SCL	Malignant SCL	Fibrosarcoma	1	1	2
15	75	M	shoulder	SCL	N/A	Fibrosarcoma	3	2	3
20	42	M	Lower leg	Malignant SCL	Fibrosarcoma	Fibrosarcoma	1	1	1
22	21	M	Cervical	Benign SCL	Cellular schwannoma	Schwannoma	1	1	1
25	48	M	Chest wall	Benign to borderline spindle cell lesion	Solitary fibrous tumor	Solitary fibrous tumor	2	2	1
26	27	M	Arm	Malignant SCL	Synovial sarcoma	Synovial sarcoma	1	1	1
38	14	M	Trunk	Benign SCL	Neurofibroma	Neurofibroma	1	1	1
40	42	M	Thigh	Malignant SCL	Malignant SCL	Fibrosarcoma	1	1	2
44	28	F	Rt arm	Malignant SCL	Malignant SCL	N/A	1	3	3
49	50	F	Trunk	Benign SCL	BenignSCL	N/A	1	3	3
50	57	M	Trunk	Benign SCL	Schwannoma	N/A	1	3	3
55	53	M	Rt inguinal	Malignant SCL	N/A	Leiomyosarcoma	3	1	3
61	10	M	Lt leg	Malignant SCL	N/A	N/A	3	3	3
68	22	F	Cervical	Benign SCL	schwannoma	schwannoma	1	1	1
69	2	M	Rt middle finger	Benign SCL	N/A	Fibroma	3	1	3
70	57	M	Ankle	Malignant SCL	Malignant SCL	N/A	1	3	3

Key: Concordance: 1: Concordant; 2: Not specified; 3: Couldn't

Discussion

The age of patients presenting with soft tissue masses varied widely between 2 months to 75 years with a mean of 31.90 years with round cell tumors predominating in the first two decades of life while pleomorphic tumors showing a preponderance in patients over 50 years of age. In terms of site of occurrence, malignant lesions were most commonly located on the trunk(35.1%), followed by the lower extremity(28.1%) in our study, however many other studies [10-12] state that lower extremity is the most common site for sarcomas.

With respect to adequacy of FNAC smears, we observed a low inadequacy rate in FNA sampling with only 1 in 71(1.4%) cases being inadequate. Palmer *et al*. [13] have defined adequacy in soft tissue FNAB as the presence of at least 5 clusters of 10 unobscured cells on the majority of slides. A basic cytological approach towards making a STT diagnosis begins with the familiarity with normal structures, along with myxoid or metachromatic stromal fragments and a variety of dyscohesive cells like spindly, round, pleomorphic, polygonal that are indicators of a STT, on aspirates [14]. These observations are further integrated with clinical and radiological findings and the aspirates are sorted out as benign, malignant or unsure. Role of radiological correlation in approaching the soft tissue diagnosis has been discussed in many studies [15, 16]. Based on this approach we grouped the lesions under 8 morphological categories which included:

1. Small round cell/Ovoid;
2. Pleomorphic;
3. Spindle cell;
4. Myxoid;
5. Epithelioid/Polygonal cell;
6. Lipomatous
7. Mixed category: This included lesions where more than one cell type was identified, none predominating the other. viii) Others: Tumors which could not be classified into the above 7 heads (including metastatic epithelial malignancies, plasmacytoma and osteoclastoma in the present series).

Morphological subtyping in cytology subsequently confirmed on histology, is an integral part of diagnosis and management of soft tissue tumors and the therapy for sarcoma is driven by tumor location and stage, the latter incorporating the tumor grade.

Some authors have advocated that establishing a specific histologic subtype is unnecessary and not a prerequisite for adequate therapy. Nevertheless, Kilpatrick *et al*. (2001) [17] have brought out several problems with this conclusion. First, the accurate histologic grading requires accurate histologic subtyping. Established grading systems including the FNCLCC and the NCI systems utilize histological subtypes for grading. Once a subtype has been established, the grade of the tumor is readily apparent in most cases. Secondly, specific therapeutic protocols exist for different subtypes of tumors. Subtyping of soft tissue lesions remains a time tested technique, as proven by many studies. Subtyping is of prime importance in case of round cell sarcomas, the treatment of which varies widely among subgroups [Table 2 and figure1]. For pleomorphic sarcomas, subtyping is usually not warranted; since all are regarded as high grade for purpose of treatment. The myxoid sarcomas often are easily subtyped on the basis of cytomorphologic and clinical features alone with the smears having a myxoid granular film in the background which tended to be diffuse (involving virtually the entire slide) in cases of myxofibrosarcoma but more localized (discrete aggregates) in cases of myxoid liposarcoma and myxoid chondrosarcoma [17]. Spindle cell sarcomas pose great diagnostic difficulties because distinguishing benign proliferations from low grade sarcomas as well as pseudosarcomatous lesions from true sarcomas remains challenging. Accurate subtyping based on immunocytochemistry is however possible. [Table 3 and figure 2].

In the present study; overall cell blocks were contributory in exact subtyping in 41/56(73.2%) cases, excluding the inadequate samples. If the cases where cell blocks have proved contributory in excluding a diagnosis are also included, this figure would rise to 92.8% (52/56). Round cell tumors were the most easily subtyped tumors with 19/20(95%) subtyped accurately by the use of ancillary techniques. Cell blocks provided material for immunocytochemistry and proved extremely useful in subtyping of tumors. In our practice, a single needle pass after the routine FNA procedure was found to yield sufficient material for immunocytochemistry. This was also useful in terms of archival storage. Cell blocks were specifically helpful in cases where the smears were paucicellular on FNA and hence a cytological diagnosis which was rendered with difficulty was supported by cell block sections. In a few cases, such as that of osteosarcoma and neuroblastoma, the cell block provided a better background than the conventional smears, the focal presence of which in the latter may have been missed.

Immunocytochemistry on smears was used in 5 cases, but was helpful in accurate subtyping in only 2 cases which were diagnosed as metastatic melanoma and undifferentiated pleomorphic sarcoma respectively. The third case where immunocytochemistry on smear was done, was given a false positive diagnosis of pleomorphic sarcoma which turned out to be nodular fasciitis on histopathology. In the remaining 2 cases, a final subtype could not be reached.

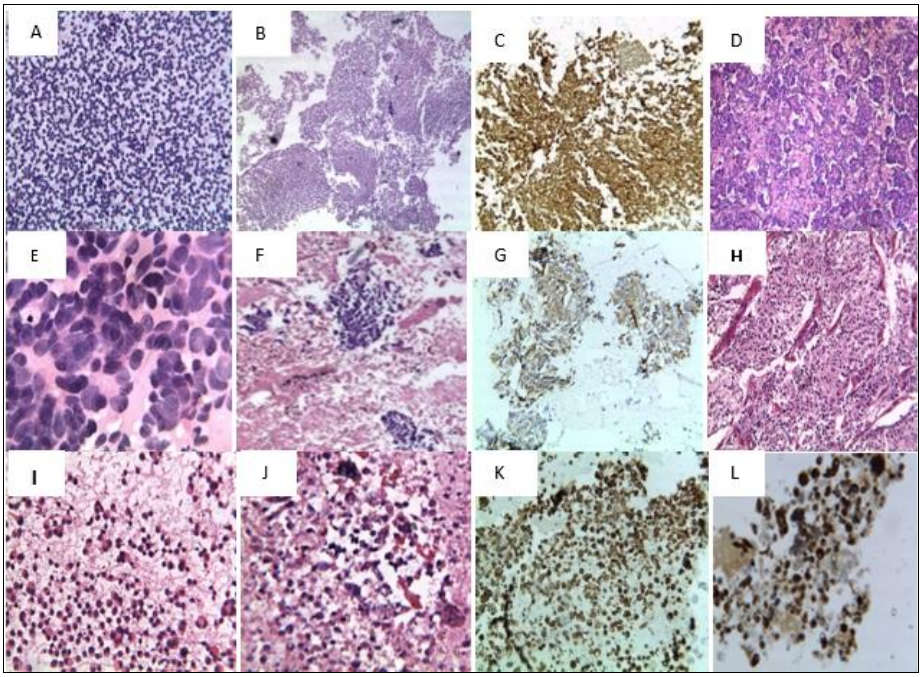

Fig 1: Morphology of small round cell tumors on FNAC and Cell Block.

Ewings sarcoma:(A) and (B) are FNAC and cell block sections showing sheets of small blue round cells, (C) IHC on cell block showing membranous positivity for CD99,(D) histology section showing rosette formation. Neuroblastoma: (E) and (F)are smears and cell block showing sheets of round primitive cells with fine nuclear chromatin,(G) neuron specific enolase (NSE) positivity,(H)section shows hommer wright rossetts. Rhabdomyosarcoma: (I) cellular smear with round cells, including plasmacytoid and binucleate forms,(J)cell block with singly scattered round cells and an isolated strap cell/ rhabdomyoblast.(K) desmin positive,(L)strong myogenin positive cells.

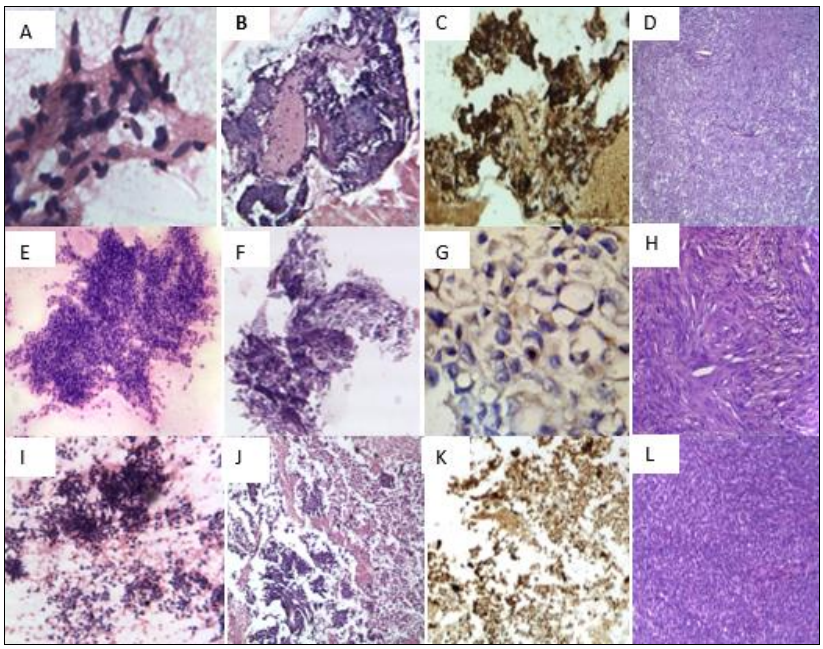

Fig 2: Morphology of spindle cell mesenchymal tumors on FNAC and Cell Block.

Schwanoma: (A) smear shows clusters of spindle cells in myxoid background,(B)cell block is cellular showing antoni 'A' areas,(C)cells show strong S100 expression,(D)histology section shows sheets of spindle cells exhibiting hyper and hypo cellular areas with palisaded nuclei. Leiomyosarcoma: (E) smears are hyper cellular showing overcrowding of spindle cells,(F)cell block section,(G)SMA is positive in the spindle cells,(H) biopsy section show sheets and fascicles of bizarre spindle cells. Synovial sarcoma: (I) Smears show spindle to oval cells, (J) cell block section show cluster of spindle cells in haemorrhagic background,(K)cells are strong positive for EMA,(L)biopsy show fascicles and sheets of spindle cells.

There have been studies highlighting application of the ancillary techniques in exact subtyping of these tumors. [18, 19] Overall 43/71 (60.6%) could be accurately subtyped using ancillary techniques in our study. While Costa *et al* [20] achieved 20.9% rates in terms of exact sub typing of sarcomas, we, like Yang *et al*. [21] observed an overall higher rate. In their review, Kilpatrick *et al*. [17] have presented a range of 21–74% of exact sub typing of sarcomas, based on

various studies. The rates of subtyping observed in the present study lies within this documented range.

In this study FNAC was shown to have a sensitivity and specificity of 100% and 87.5%. The positive and negative predictive values were 97.7% and 100.0% respectively. These were comparable with the findings of 100% sensitivity and 87% specificity in a study done by Rekhi *et al*. [22] In our study, 1/71 (1.4%) case was reported as false positive while there were no false negatives. A study on 517 STT aspirates by Akerman *et al*. [23] revealed a 2.9% false positive rate, however few other studies [11, 17] yielded single false negative case and none false positive case.

We also found few Diagnostic difficulties in the present study. One of the greatest pitfalls of FNAC was encountered in diagnosing aspirates from large lipomatous lesions. In the present series, 2 such cases of were seen in male patients above 50 years of age with lesions >15 cm in maximum dimension. The cell blocks were also inconclusive. These cases were subsequently reported as liposarcoma and benign lipomatous lesion on histopathology. Kilpatrick *et al*, in their series observed that the diagnosis of well-differentiated liposarcoma is not easily determined by FNAB analysis with the presence of diagnostic lipoblasts being a helpful but unfortunately rare cytologic feature.

In the present series, only a single case of a false positive diagnosis was encountered. This was a lesion located on the back of a 52 year old female. The diagnosis on smears was given as sarcoma owing to the pleomorphic nature of cells and nucleolar prominence. However, the lesion turned out to be nodular fasciitis on subsequent histopathology. Jakowski *et al*. [24] reported that nodular fasciitis was a problematic benign lesion that was misdiagnosed as sarcoma on cytology in 2 of 4 patients in their series. This pseudosarcomatous lesion is a well-known pitfall in aspiration cytology of soft tissue masses that has been previously reported by Plaza *et al*. [25] Another area of diagnostic difficulty was in cases of fibrosarcoma which is actually a diagnosis of exclusion and requires well defined architectural features which were not provided by smears or cell blocks. Thus, in the present series FNAC was found to be a fairly sensitive and specific technique in diagnosing soft tissue tumors with its advantages alongwith cell blocking and immunocytochemistry being obviously more than its limitations. The study was limited to aspirates of superficial, palpable lesions and did not include deep seated lesions which may be more challenging to sample.

Conclusion

Less invasive, inexpensive and done on an outpatient basis in comparison to conventional trucut or core biopsies, FNAC has lesser complications and in combination with cell blocking and application of immuno cyto Chemical techniques, it is useful in determining the subtype of the tumor.

Competing interests

The author(s) declare that they have no competing interests.

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