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Needle preceding the scalpel in soft-tissue sarcomas – A case series

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ABSTRACT

Soft-tissue sarcomas (STSs) are rare neoplasms that can be initially evaluated by fine-needle aspiration cytology (FNAC). Although they are difficult to subtype, these sarcomas can be graded and classified based on cytomorphology. FNAC, with clinical and radiological correlation, can be effectively used in the diagnosis of STSs. Application of ancillary techniques is essential to arrive at the final diagnosis. The aim of the study was to determine the efficacy of FNAC in the initial diagnosis of STSs. Three patients who presented with soft-tissue masses were initially evaluated by ultrasound and/or magnetic resonance imaging and FNAC. Following which, all the three cases were operated on and studied on histopathology and immunohistochemistry to arrive at a final diagnosis. All the three cases were diagnosed as malignant on FNAC even when radiology findings differed or was not confirmatory in one case. FNAC diagnosis was appropriate in case of grading of tumors and classification based on morphology in all the three cases. FNAC of soft-tissue tumors (STTs) is a quick, reliable, and cost-effective mode of initial investigation for STTs. Although it is difficult to subtype the diagnosis, in majority of the cases, a diagnosis of benign or malignant and grade of the tumor can be assessed.

Key words: Soft-tissue sarcomas; Fine needle aspiration cytology; Immunohistochemistry

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INTRODUCTION

Soft-tissue sarcomas (STSs) are heterogeneous group of malignancies and diagnostically challenging and require a multidisciplinary approach in diagnosis, treatment, and patient management and prognosis. These tumors pose significant challenge due to morphological overlap and biologic heterogeneity.[1,2]

Fine-needle aspiration cytology (FNAC) of soft-tissue lesions is now an accepted mode of evaluation though literature search yields studies contradicting its use. However, studies have proved that FNAC is fairly specific and sensitive in soft-tissue tumor (STT) diagnosis of primary, recurrent, and metastatic lesions. It is now considered as an initial diagnostic modality for STTs as it has high sensitivity and specificity for determining malignancy. The advantage of this procedure being rapid and early diagnosis and more access to mass through multiple aspirates. The STSs can be graded, however, subtyping is difficult in these lesions but attempts have been made in some studies with variable results.[2-4]

With the improvised localization of STTs with radiological techniques, the amount of aspirate that can be achieved through FNAC, especially deep-seated lesions, has made it one of the preferred choice in evaluation as against the limited sampling issues in the past studies which was the reason for not choosing FNAC in initial diagnosis.[3]

FNAC has a role in determining if the tumor is benign or malignant. The cytomorphological diagnosis and grading the tumor has an effect on deciding the future course of action.[5]

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Aims and objectives

The aim of the present study was to determine the efficacy in diagnosing STSs on FNAC, to compare the grading and morphological diagnosis on FNAC with histopathology and to confirm the diagnosis by immunohistochemistry.

MATERIALS AND METHODS

The present study is conducted at a rural tertiary care teaching hospital. Three patients of varying age groups presented with STTs in the lower extremity. After the clinical evaluation, radiological investigations were performed and were diagnosed as soft-tissue neoplasms. FNAC was performed on all the three cases. The cytology slides were stained with hematoxylin and eosin (H and E), Pap stain, and Leishman stains. All the three cases were diagnosed as STSs with probabilities as mentioned below in the detailed discussion of the cases. Following, FNAC, the masses were operated on and sent for histopathological study. Diagnoses as mentioned below were offered and immunohistochemistry was suggested and performed. IHC yielded a specific subtyping in all the three cases.

RESULTS

We present the case details of all the three cases with the investigations, treatment, and follow-up of the patients. Institutional ethical clearance was obtained for the study.

Case 1

A 54-year-old female presented with swelling on the medial aspect of the left thigh above the knee joint. On color Doppler study of lower limb, a large lobulated soft-tissue mass in the fascial plane of medial aspect of thigh. Mild internal vascularity and calcification were noted. The mass was compressing and displacing the great saphenous vein. A possibility of a tumor of neurogenic/vascular origin was suggested. Following the Doppler, MRI of the left thigh was performed. Well defined multilobulated significantly enhancing T1 iso intense, T2/STIR heterogeneous hyperintense lesion in the subcutaneous plane of mid-third of the medial thigh suggestive of benign soft-tissue neoplasm, peripheral nerve sheath tumor was reported on. A FNAC was performed and the smears were highly with pleomorphic round to spindly cells and tumor giant cells (Figure 1).

A diagnosis of high-grade spindle cell sarcoma was made. The patient was operated upon by wide resection and sent to lab for HPE. On gross examination, a skin covered mass measuring 12×10×8 cm was received. The overlying skin measured 12×8 cm, C/s: through the skin shows a grey-white nodular tumor in the subcutaneous plane measuring 3.8×3.2×2 cm. C/s: was grey-white, nodular, and homogenous with no areas of hemorrhage and necrosis. All the surgical margins appeared free from tumor involvement. The tumor was 1 cm away from the nearest medial margin. On microscopy, the mass was nodular with tumor cells in whorls and sheets. The cells were elongated spindle cells with blunted nuclei, hyperchromatic nucleus, and tumor giant cells (Figure 2).

A diagnosis of pleomorphic sarcoma and a differential diagnosis of malignant peripheral nerve sheath tumor *(MPNST)* was made. The histologic grade was 2, and the stage was pT1a pNx. Immunohistochemistry was suggested for subtyping the tumor. SMA +, S100 –, Vimentin +, CD34 –, H Caldesmon –, Desmin –, Calponin –, Ki67 + (High index) were applied to the tumor and a final diagnosis of pleomorphic leiomyosarcoma *(LMS)* was arrived at. Postoperatively, the patient was treated by intensity –

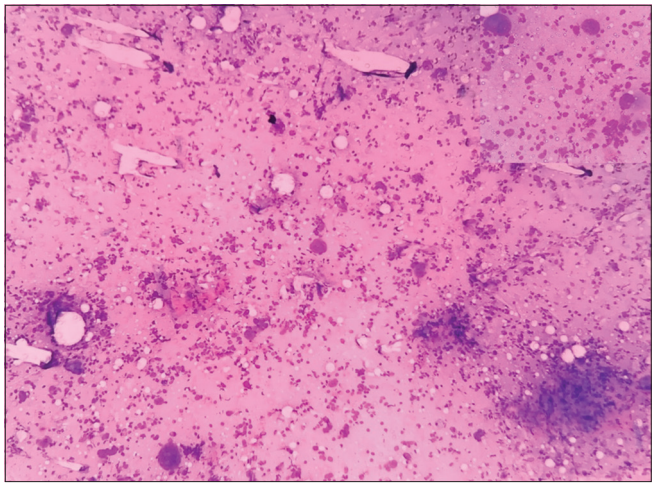

Figure 1: Cellular smear, highly pleomorphic spindle cells with irregular nuclei and tumor giant cells (inset) (FNAC, Leishman stain, ×10)

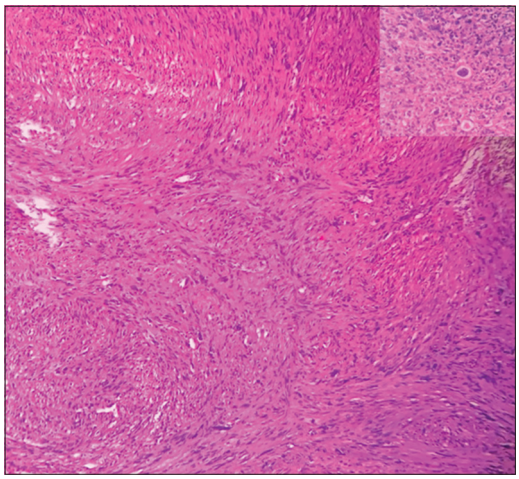

Figure 2: Nodular tumor with tumor cells arranged in whorls and sheets, tumor cells are pleomorphic(inset) with hyperchromatic nuclei and tumor giant cells (H and E, ×10)

modulated radiation therapy (IMRT). The patient is followed up for the past 1 ½ years and is well with no recurrences.

Case 2

An 18-year-old female presented with a swelling on the medial aspect of the knee joint, gradually increasing in size for past 4 months. An FNAC of the lesion was performed. Aspirate was highly cellular composed of a mixture of tissue fragments and dispersed small to medium sized cells. The nuclei were round to oval, fine granular with bland chromatin and small and inconspicuous nucleoli. Vague acinar patterns and abnormal mitoses were noted (Figure 3).

A diagnosis of spindle cell sarcoma probably monophasic synovial sarcoma (SS) was made based on cytological findings, age of the patient and location of the lesion. Function – sparing complete excision was done and the mass was sent for HPE. Sections showed epithelioid cells with variably sized rounded nuclei. The tumor showed hemangiopericytomatous vasculature (Figure 4).

A diagnosis of SS was made and IHC was suggested. CK – focally +, vimentin +, CD34 –, Bcl2 – Strong and diffuse +, CD99 – weak and cytoplasmic +, EMA +. IHC confirmed the diagnosis of poorly differentiated SS. Following this, the patient was given IMRT and the patient is doing well after 3 years without any recurrences.

Case 3

A 28-year-old female presented with a recurrent nodular ulceroproliferative exophytic mass on the anterior aspect of the right leg, below the knee joint measuring 14×14×6 cm. The patient had a mass in the same region 2 years ago which was operated on. However, no reports of the previous procedure were available with the patient. A FNA was performed. The smears were highly cellular showed variably sized round cells. Smaller, darker cells, and larger cells with scant cytoplasm and prominent nucleoli were noted. In the view of round and few spindle cells, a diagnosis of small round cell tumor, probably SS was made (Figure 5).

Following, FNAC a core biopsy was received which showed small round cells with hyperchromatic nuclei and scant eosinophilic cytoplasm with occasional rosette formation was seen around the blood vessels. Hence, a diagnosis of Ewing's sarcoma (ES)/Primitive neuroectodermal tumor (PNET) was offered. A pre-operative chemotherapy followed by above knee amputation was performed and the limb was received for histopathology. On histopathology, tumor cells arranged in sheets separated by delicate fibrous strands and thin-walled blood vessels was seen. The tumor cells were small, round with dark nuclei, some showing prominent nucleoli, and with scant cytoplasm. Extensive Areas of necrosis was seen (Figure 6).

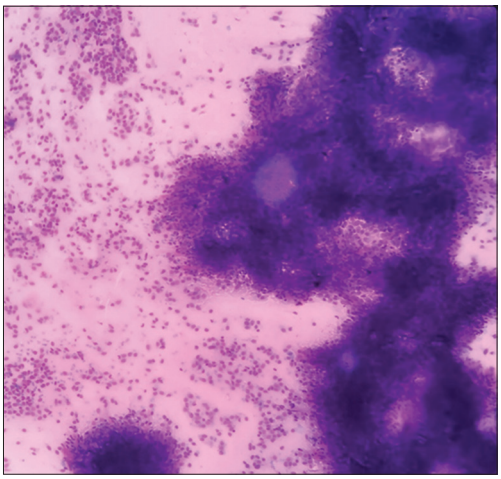

Figure 3: Highly cellular with typical appearance of mixture of tissue fragments and dispersed cells (FNAC, Leishman stain, ×10)

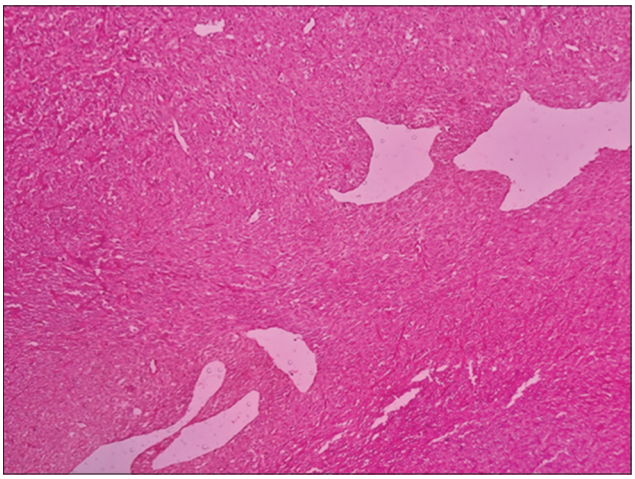

Figure 4: Epithelioid cells with hemangiopericytic vasculature (H and E, ×10)

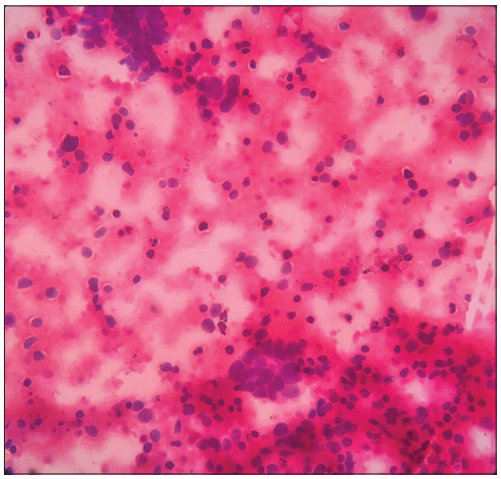

Figure 5: Mixture of cells with larger pale-staining nuclei and cells with smaller and darker nuclei with occasional rosettes (FNAC, Leishman stain, ×20)

A diagnosis of small round cell sarcoma (SRCS) and probably ES/alveolar rhabdomyosarcoma (RMS) was

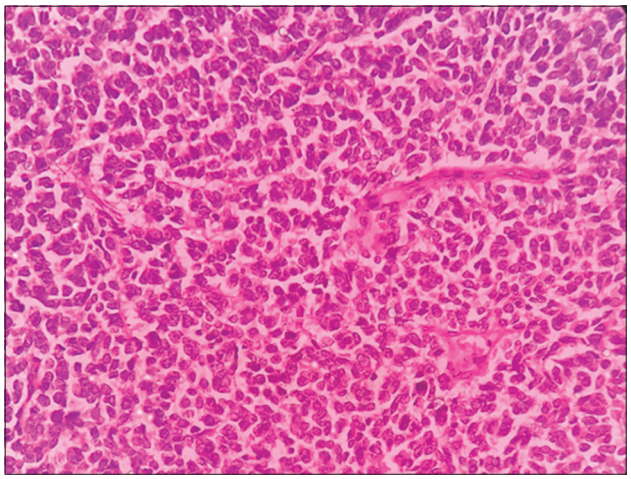

Figure 6: Small round tumor cells with dark nuclei arranged in sheets separated by delicate fibrous septa (H and E, ×40)

made and panel of IHC for small round cell tumors was suggested. On cytochemistry, PAS was positive. On IHC, CD99, synaptophysin, and chromogranin were positive, vimentin – weak and variably positive, SMA, S-100, desmin, myogenin, CD34, EMA, LCA, pan CK, and CK20 were negative. Ki67 showed a high index of positivity. A diagnosis most consistent with ES/PNET was confirmed. However, we lost the patient for follow-up during the COVID pandemic.

As discussed in the above three cases, we had two cases of high-grade spindle cell sarcomas (pleomorphic LMS and SS) and one case of round cell cytomorphology (ES/PNET). All three cases were high grade tumors. The patient and her care takers were appropriately counseled regarding the nature of the sarcoma, treatment options and prognosis. The surgeries and future treatment strategies were planned without any ambiguity.

DISCUSSION

FNAC is definitely a valid screening tool with a high sensitivity and specificity in establishing presence of malignancy and in determining the mesenchymal nature of the lesion.[6]

The cytologic aspirations from STTs are placed into six categories based on the cytomorphology, namely, spindle cells, round cells, pleomorphic, myxoid, epithelioid/polygonal, and lipomatous types. Grading on cytology has a higher concordance for Grade II and III tumors (high grade) than for Grade I tumors (low grade). In some centers, the treatment is planned based on FNAC interpretation, the low-grade tumors are excised whereas in high-grade sarcomas, pre-operative radiotherapy or chemotherapy are used to reduce or to better define the extent of surgery. The pleomorphic and round cell sarcomas are always high grade, the pure myxoid tumors are low grade and the polygonal and spindle cell types pose difficulty in grading. On FNAC, subtyping of round cell tumors and pleomorphic tumors has a fairly good correlation with histopathology diagnosis whereas the chances of subtyping are low with spindle cell tumors. Immunocytochemistry subtyping in round cell tumors is important as it helps in the management of these cases.[2,5-7]

Accurate grading is more important than histologic subtypes to plan treatment strategies and to determine prognosis. In the hands of expert cytopathologist, the sensitivity in diagnosis of STTs is 90%. Sarcomas have a predilection for extremities followed by central trunk.[8]

In the present study, the cases of spindle cell sarcomas (pleomorphic LMS and SS) and SRCS (ES/alveolar RMS) were all high-grade tumors.

Spindle cell sarcomas account for 1–2% of all sarcomas and include SS, fibrosarcoma, LMS, MPNST, and angiosarcoma. Cytology is an established tool in diagnosing these tumors. Subtyping these tumors on cytology is difficult but they can be graded which has prognostic significance and an indicator for metastatic risk.[4,6]

Histological classification of these sarcomas also has limitations due to overlapping features and poor differentiation in some sarcomas. Ancillary techniques used in adjunct with the above investigations are essential for subtyping on these tumors. Some sarcomas may evade exact subtyping even on IHC due to negativity of specific lineage.[2]

LMS are smooth muscle tumors and account for 5–10% of all STSs. The common age group is in adults in the range of 31–89 years, peaking in 7th decade with increased frequency in males (60.7%). They arise more commonly in the lower extremities, retroperitoneum, abdomen/pelvis, and trunk. Some of the LMS arise in the large blood vessels especially, inferior vena cava, its major branches, and in the large vessels of the lower limbs. Most commonly located in the intramuscular or subcutaneous planes.[1,2,9-11]

Pleomorphic LMSs account for around 8% of all LMS. FNACs of LMSs show an admixture of dispersed cells or stripped nuclei in fascicles. The cells are spindly with elongated and blunt ends, nuclei are segmented to fusiform. Large tissue fragments are commonly seen in LMS. Pleomorphic variants show bizarre giant cells. Based on these findings, a LMS can be suggested. It is impossible to differentiate between pleomorphic sarcomas on FNAC.

However, this does not hinder the management of most high-grade tumors. However, the diagnosis should be confirmed by ancillary techniques.[7,9,10,12]

These are poorly differentiated with a pleomorphic appearance and show classic LMS features which may be <5% of the tumor tissue or have a history of LMS. The typical and pleomorphic areas may have a clear demarcation or may show no transition.[11]

SS is a mesenchymal spindle cell tumor. The common age group of occurrences of the tumor is 15–40 years with a male preponderance. The age range in wider in many studies varying from 10 to 65 years. The tumor arises close to the tendon sheaths, bursae and joint capsules and is commonly seen in foot, forearm, knee, ankle, elbow, and leg. Site of occurrence is an important clue to the diagnosis. They tend to remain dormant for a long time before behaving aggressively at a later stage. The presence of irregular and small flecks of calcification is an important clue on radiology.[6,7,12,13]

Conventional biphasic tumors are easily diagnosed on cytology than the monophasic and poorly differentiated ones. Although FNAC is reliable, for recognizing and subtyping, a multidisciplinary approach is needed.[6]

These tumors can be reliably subtyped based on cytology smears with a clinical correlation. The smears are highly cellular with three dimensional clusters composed of oval to spindle cells with bipolar cytoplasmic processes, uniform vesicular nuclei, and micronuclei. Monomorphic cells and vascular channels are seen in these tumors.[4]

A pre-operative diagnosis of SS should be made in such a manner that it does not compromise the radical surgical treatment.[6]

SRCSs are high grade sarcomas and include ES family of tumors, desmoplastic round cell tumor, poorly differentiated SS, alveolar RMS, mesenchymal chondrosarcoma, and small cell osteosarcoma. Other small cell malignant tumors such as lymphomas, blastemal tumors, and small cell carcinomas should be considered as differentials for SRCSs.[14]

ES includes undifferentiated SRCS of bone and soft tissue including round cell sarcomas with EWSR1-non-ETS fusions, CIC-rear-ranger sarcomas, and sarcomas with BCOR genetic alterations. The peripheral PNET was used when ES displayed neuroectodermal differentiation. Both ES and PNET harbor the same translocation t (11,22) q (24;12) resulting in EWS/FLI1 fusion. As both tumors share the same molecular profile, the term PNET is not used now.[14,15]

ES family of tumors are highly aggressive tumors common in the first and second decade of life. However, studies have reported them in elderly age group also. Lower extremities are the commonest sites of occurrence, followed by pelvis, chest wall, upper extremities, spine, hands and feet, and skull.[16-18]

FNA of such lesions display variable population of cells. The nuclei show significant pleomorphism with smaller and darker nuclei as well as larger, paler nuclei. The cytoplasm may be abundant, may have vacuolations and densities creating rhabdoid-like features. Apart from these features, architectural patterns as pseudo rosettes, papillae, tigroid or myxoid background, cartilaginous, fibrillary or osteoid matrix, and eosinophilic connective tissue associated with desmoplasia may present in between the cells or in the background of the smears. These features narrow down the differentials for SRCSs and aid in selecting appropriate ancillary tests.[12]

On cytohistological correlation, though the subtyping is difficult, the grading of the tumors have better correlation especially for the high grade sarcomas. Ancillary techniques are essential for subtyping these tumors as the management of various SRCSs varies.[8]

CONCLUSION

FNAC of STTs is a quick, reliable, and cost-effective mode of initial investigation for STTs. Although it is difficult to subtype the diagnosis, in majority of the cases, a diagnosis of benign or malignant and grade of the tumor can be assessed. A cytomorphological diagnosis can be offered in majority of the cases. It helps in planning the next mode of treatment, especially with regard to pre-operative options and surgical procedures. FNAC, when used in adjunct with radiological findings, histopathology and IHC is essential for all STSs.

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REFERENCES

1. Choi JH and Ro JY. The 2020 WHO classification of tumors of soft tissue: Selected changes and new entities. Adv Anat Pathol. 2021;28(1):44-58.
https://doi.org/10.1097/PAP.0000000000000284
2. Rekhi B, Gorad BD, Kakade AC and Chinoy R. Scope of FNAC in the diagnosis of soft tissue tumors--a study from a tertiary cancer referral center in India. Cytojournal. 2007;4:20.
https://doi.org/10.1186/1742-6413-4-20

3. Robles-Tenorio A and Solis-Ledesma G. Undifferentiated pleomorphic sarcoma. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570612 [Last accessed on 2022 Apr 14].
4. Chilari G, Uppin MH and Prayaga AK. Cytology of spindle cell sarcomas-an institutional experience. Indian J Pathol Oncol. 2019;6(4):512-519.
   https://doi.org/10.18231/j.ijpo.2019.100
5. Contreras CM and Heslin MJ. Soft tissue sarcoma. In: Townsend CM, Evers BM, Beauchamp RD and Mattox KL, editors. Sabiston Textbook of Surgery: The Biological Basis of Modern Surgical Practice. Philadelphia, PA: Elsevier Saunders; 2004. p. 741.
6. Kaushik A, Khanna G, Rajni, Yadav YK. Subtyping and grading of synovial sarcomas: A cyto-histopathologic correlation study. Ann Pathol Lab Med. 2015;2(2):82-86.
7. Geisinger KR and Abdul-Karim FW. Fine-needle aspiration biopsy of soft tissue tumours. In: Goldblum JR, Folpe AL and Weiss SW, editors. Enzinger and Weiss's Soft Tissue Tumours. 6th ed. Philadelphia, PA. Elsevier Saunders; 2014. p. 111-126
8. Chauhan S, Sahu N, Sahu MC, Hansa J, Das K and Dash AK. A correlative study on spindle cell sarcoma with cyto-histological grading by conventional method in an Indian tertiary care teaching hospital. Asian J Pharm Clin Res. 2017;10(6):267-272.
   https://doi.org/10.22159/ajpcr.2017.v10i6.17896
9. Gupta S, Husain N, Kumar A and Sunder S. Adult primary pleomorphic leiomyosarcoma of forearm with axillary lymph node metastasis: A case report and literature review. J Cancer Res Ther. 2012;8(3):448-450.
   https://doi.org/10.4103/0973-1482.103532
10. Oda Y, Miyajima K, Kawaguchi K, Tamiya S, Oshiro Y, Hachitanda Y, et al. Pleomorphic leiomyosarcoma: Clinicopathologic and immunohistochemical study with special emphasis on its distinction from ordinary leiomyosarcoma and malignant fibrous histiocytoma. Am J Surg Pathol. 2001;25(8):1030-1038.
    https://doi.org/10.1097/00000478-200108000-00007
11. World Health Organization. Classification of Tumours Editorial Board. Soft Tissue and Bone Tumours. WHO Classification of Tumours Series, 5th ed., Vol. 3. Lyon, France: International Agency for Research on Cancer; 2020.
12. Domanski HA, Akerman M, Rissler P and Gustafson P. Fine-needle aspiration of soft tissue leiomyosarcoma: An analysis of the most common cytologic findings and the value of ancillary techniques. Diagn Cytopathol. 2006;34(9):597-604.
    https://doi.org/10.1002/dc.20499
13. Kilpatrick SE, Teot LA, Stanley MW, Ward WG, Savage PD and Geisinger KR. Fine-needle aspiration biopsy of synovial sarcoma. A cytomorphologic analysis of primary, recurrent, and metastatic tumors. Am J Clin Pathol. 1996;106(6):769-775.
    https://doi.org/10.1093/ajcp/106.6.769
14. Domanski HA. The small round cell sarcomas complexities and desmoplastic presentation. Acta Cytol. 2022;66(4):279-294.
    https://doi.org/10.1159/000524260
15. Chuthapisith S, Prasert W, Warnnissorn M, Pradniwat K, Srimuninnimit V and Angsusinha T. Ewing's sarcoma and primitive neuroectodermal tumour (ES/PNET) presenting as a breast mass. Oncol Lett. 2012;4(1):67-70.
    https://doi.org/10.3892/ol.2012.698
16. Yadav A, Jahan A, Yadav SK, Pruthi SK, Singh S and Sarin N. A case report of small round cell tumor of palm: A difficult code to decipher on cytology. Int J Surg Case Rep. 2021;89:106659.
    https://doi.org/10.1016/j.ijscr.2021.106659
17. Trikalinos NA, Chrisinger JS and Van Tine BA. Common pitfalls in Ewing sarcoma and desmoplastic small round cell tumor diagnosis seen in a study of 115 cases. Med Sci (Basel). 2021;9(4):62.
    https://doi.org/10.3390/medsci9040062
18. Yang J, Wei H, Lin Y, Lin N, Wu S and Yu X. Challenges of diagnosing primary Ewing's sarcoma in the small intestine of the elderly: A case report. Front Oncol. 2021;11:565196.
    https://doi.org/10.3389/fonc.2021.565196

Authors' Contributions:
VR- Concept, design, design of study, analysis, and interpretation; **RMV-** Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation, and submission of article; **NB-** Design, clinical protocol, manuscript preparation, editing, and manuscript revision; and KR- Review manuscript: coordination and manuscript revision.

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