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Case Series

Pathology Section

Diagnostic Challenges of Soft Tissue Sarcomas with Special Emphasis on Immunohistochemical Profile- A Case Series

VANDANA MAROO[1], SANGHAMITRA MUKHERJEE[2], GOPINATH BARUI[3], MANISHA MAHATA[4]

ABSTRACT

Soft tissue tumours arise from the mesenchymal tissues of different origin like adipocytic, smooth muscles, skeletal muscle, fibroblastic/myofibroblastic, fibrohistiocytic, pericytic, vascular, osteo-cartilagineous or even unknown. Its diagnosis depends on the age of the patient and site of presentation but sometimes they may present at unusual sites. Some of the tumours have overlapping histomorphological features which results in a list of differential diagnosis. Therefore, immunohistochemistry and molecular genetics play an important role for definite diagnosis. French Federation of Cancer Centres Sarcoma Group System (FNCLCC) based on necrosis, tumour grading and tumour differentiation is commonly used for grading of the sarcomas to assess the treatment response and prognosis of the patient. Hereby, authors present a series of nine cases of soft issue tumours, comprising five cases of synovial sarcomas and one each of dedifferentiated liposarcoma, rhabdomyosarcoma, epithelioid angiosarcoma and Well Differentiated Liposarcoma (WDLS). Few cases are located at unusual anatomical sites; hence, they should be kept in mind as differential diagnosis. Immunohistochemistry has played an important role for confirmation of diagnosis of synovial sarcomas and angiosarcoma.

Keywords: Dedifferentiated liposarcoma, Epithelioid angiosarcoma, Rhabdomyosarcoma, Synovial sarcoma, Well differentiated liposarcoma

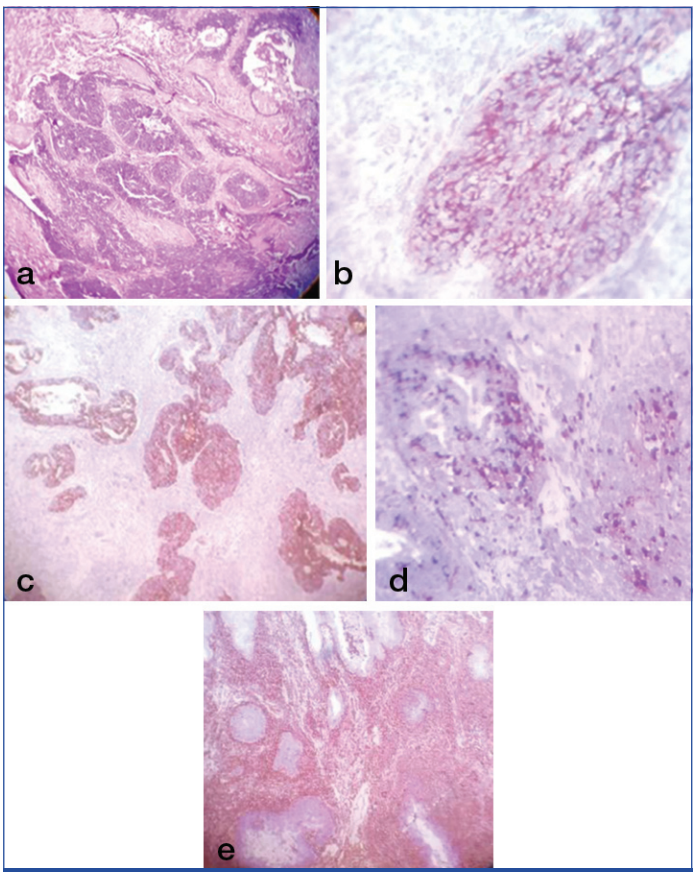
INTRODUCTION

Soft tissue tumours originate from mesenchymal cells with different differentiation like adipocytic, fibroblastic/myofibroblastic, fibrohistiocytic, pericytic, vascular, osteo-cartilagineous, skeletal and smooth muscles [1]. World Health Organisation (WHO) Classification of bones and soft tissue tumours, 2020 further classifies them as benign, intermediate (locally aggressive and rarely metastasising) and malignant [1]. Hence, soft tissue tumours are a huge spectrum where clinico-radiological correlation is required along with histology, immunohistochemistry and cytogenetics for a definite diagnosis [2]. Here, we present a series of diversified soft tissue tumours encountered in a tertiary healthcare centre of Eastern India.

CASE SERIES

Case 1

A 55-year-old female presented to the Department of General Surgery with an infra-axillary (9×7) cm intermittently painful swelling for four months. Her medical history was insignificant. Magnetic Resonance Imaging (MRI) thorax revealed a {80 (anterioposterior) x56(mediolateral)x64(superioinferior)}mm well defined, heterointense lesion in the subcutaneous plane of infra-axillary region. Biopsy showed a combination of epithelial and spindle cell elements-epithelial component represented by well-formed glandular structures surrounded by a basement membrane while the spindle cells arranged in fascicles and whorling pattern. Individual cell had scant cytoplasm, ovoid nuclei, vesicular chromatin and inconspicuous nucleoli. The intervening areas of necrosis and approximately 8 mitotis/10 High Power Field (HPF) classified it as a FNCLCC Grade 2 sarcoma [Table/Fig-1a]. The epithelial and sarcomatous component were immunopositive for Epithelial Membrane Antigen (EMA) [Table/Fig-1b], Pan-Cytokeratin clone AE1/AE3 [Table/Fig-1c], Transducin-Like Enhancer of split 1 (TLE1) [Table/Fig-1d] and Vimentin [Table/Fig-1e], CD99 respectively. The histomorphology was in favour of biphasic synovial sarcoma. The patient was treated with chemotherapy and followed-up for four months. There was no recurrence noted.

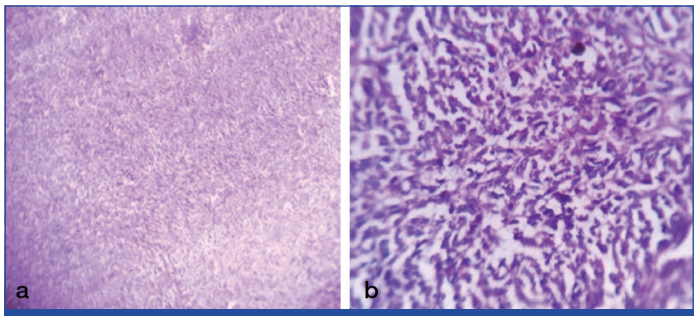


[Table/Fig-1]: a) Biphasic synovial sarcoma. (H&E stain, 40X); b) Biphasic synovial sarcoma, (membranous EMA, 100X); c) Biphasic synovial sarcoma, (cytoplasmic AE1/AE3, 40X); d) Biphasic synovial sarcoma, (nuclear TLE1, 100X); e) Biphasic synovial sarcoma, (cytoplasmic vimentin, 40X).

Case 2

A 20-year-old female presented to the Department of Gynaecology with a (5x4) cm painful swelling in the inguinolabial region. Computed Tomography (CT) scan of pelvis showed a well circumscribed (60×53×31) mm lesion with few calcific foci. Microscopically,

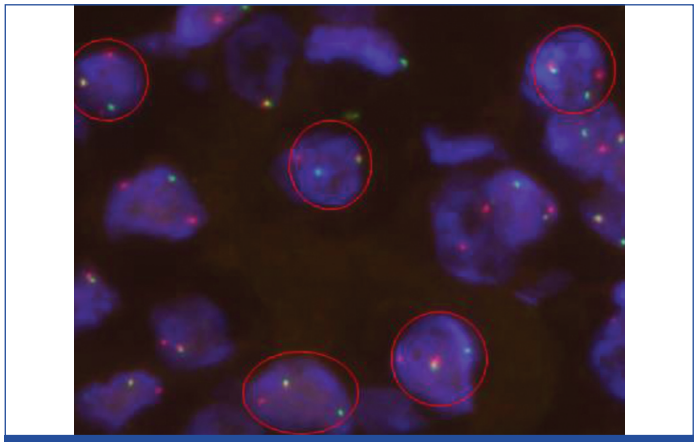
uniform spindle cells with scant cytoplasm and dense chromatin arranged in short, tightly packed fascicles were noted. A hemangiopericytomatous pattern and very low mitotic count was noted. Necrosis was absent. It was a FNCLCC Grade 2 sarcoma [Table/Fig-2a,b]. They were CD99, vimentin and EMA positive while CD34, S100 and Smooth Muscle Antibody (SMA) negative. Therefore, diagnosis of monophasic synovial sarcoma was offered. She was treated with ifosfamide and doxorubicin. However, follow-up could not be done as the family was non compliant.



[Table/Fig-2]: a) Monophasic synovial sarcoma, (H&E stain, 40X); b) Monophasic synovial sarcoma, (H&E stain, 400X).

Case 3

A 34-year-old male presented to the Department of General Surgery with an 8 cm gradually increasing swelling over left thigh for five months. Radiologically, it was a soft tissue heterogenous mass with calcific foci. Incisional biopsy showed a spindle cell lesion with few necrotic areas. The tumour cells gave cytoplasmic positivity for EMA and CK while nuclear for TLE1; giving a favourable diagnosis of monophasic synovial sarcoma; later, confirmed by Fluorescent In-Situ Hybridisation (FISH) for t(X:18) [Table/Fig-3]. The patient lost to follow-up after wide local excision.



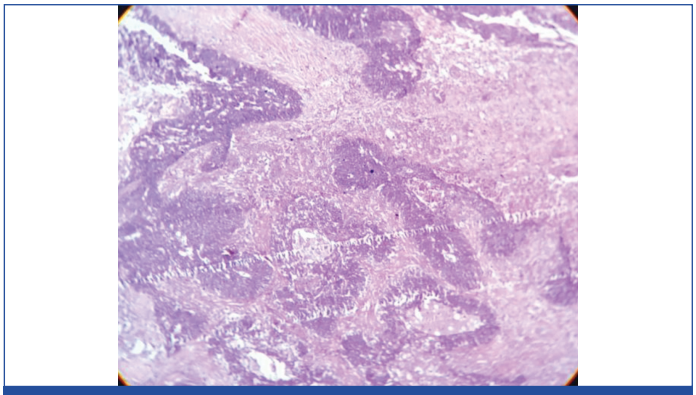
[Table/Fig-3]: Positive FISH for SS18 gene rearrangement.

Case 4

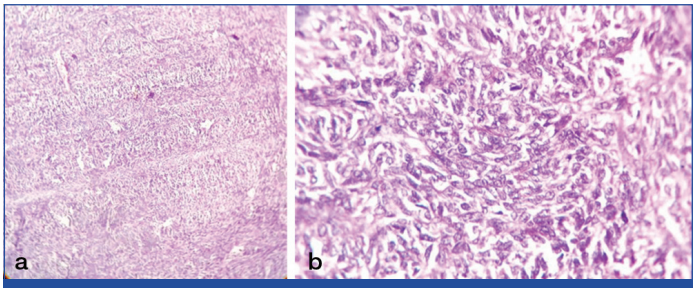
A 43-year-old female came to the Department of General Surgery with a 3 cm nodular lump in right leg; associated with intermittent pain. CT scan of leg revealed a well circumscribed heterogenous lesion of soft tissue origin. It was histologically and immunohistochemically similar to the case 1 stated above [Table/Fig-4]. So, it was diagnosed as biphasic synovial sarcoma. Wide local excision was done and the patient was doing well till two months.

Case 5

A 29-year-old male presented to the Department of General Surgery complained of a 4 cm rapidly increasing painful swelling in right arm. Tru-cut biopsy cores revealed similar histological and immunohistochemical features as that of case 2 stated above [Table/Fig-5a,b]. The diagnosis of monophasic synovial sarcoma was later confirmed by the fusion study for SYT-SSX-1 gene. Neoadjuvant chemotherapy was given initially; however, he was non compliant and follow-up was lost.



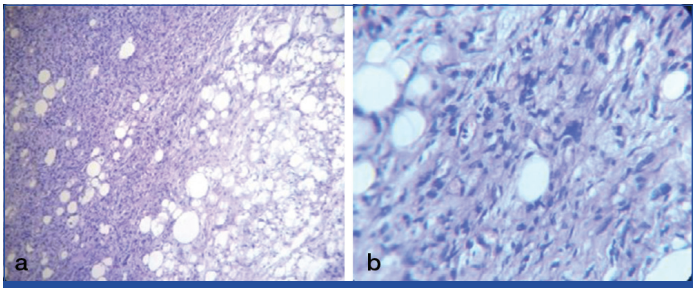
[Table/Fig-4]: Biphasic synovial sarcoma, (H&E stain,40X).



[Table/Fig-5]: a) Monophasic synovial sarcoma, (H&E stain, 40X); b) Monophasic synovial sarcoma, (H&E stain, 400X).

Case 6

A 40-year-old female presented to the Department of General Surgery with abdominal discomfort, weight loss and anorexia for 5 months. Radiological examination showed a (8×7×7) cm retroperitoneal mass with two components differing in signal intensity. Grossly, there were wide necro-haemorrhagic areas and sections from different areas of the mass were submitted. Histology revealed areas of WDLS with abrupt transition to the non lipogenic sarcomatous areas [Table/Fig-6a,b]. The diagnosis of dedifferentiated liposarcoma was given. Surgical excision was done. However, a close follow-up showed a local recurrence after six months.



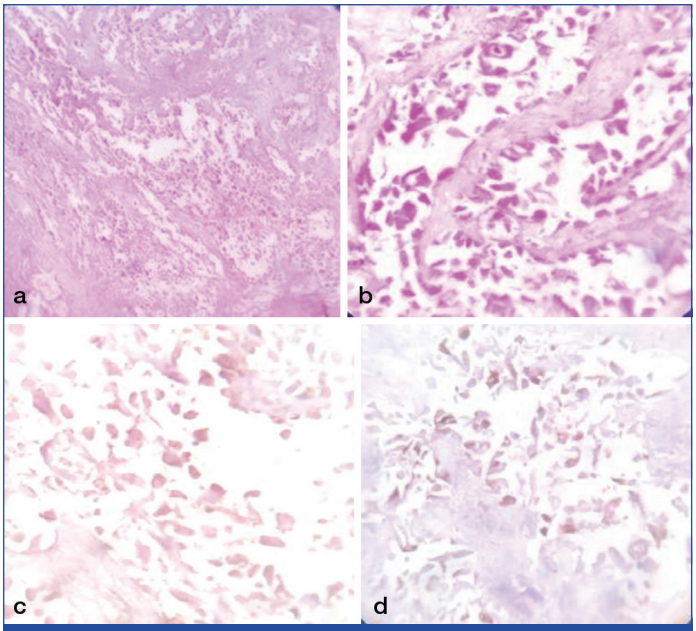
[Table/Fig-6]: a) Dedifferentiated Liposarcoma, (H&E stain, 40X); b) Dedifferentiated Liposarcoma, (H&E stain, 400X).

Case 7

A 51-year-old lady presented to the Department of General Surgery with abdominal discomfort. There was no significant history of radiation exposure. Radiology showed a diffuse (5×3) cm mass in spleen. Biopsy demonstrated large epithelioid cells predominantly in nests and sheets [Table/Fig-7a]. Individual cell had abundant eosinophilic cytoplasm, large vesicular nuclei and prominent macronucleoli. Irregular vascular spaces lined by protuberant epithelioid cells were noted [Table/Fig-7b]. Necrosis and high mitotic count was present. They were CD34 [Table/Fig-7c] and EMA [Table/Fig-7d] immunopositive. Hence, the diagnosis of epithelioid angiosarcoma of spleen was given. No local recurrence or metastasis has been noted after receiving chemotherapy till the date of case reporting after a follow-up for four months.

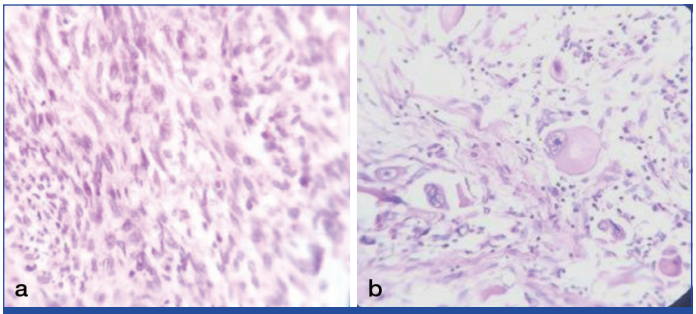
Case 8

A 14-year-old male came to the Department of General Surgery with a gradually increasing scrotal mass for 8 months. CT scan revealed an enlarged testicular tumour measuring (13×10.5×8.5) cm. The



[Table/Fig-7]: a) Epithelioid Angiosarcoma, (H&E, 40X); b) Epithelioid Angiosarcoma, (H&E, 400X); c) Epithelioid Angiosarcoma, (Nuclear CD34, 400X); d) Epithelioid Angiosarcoma, (Membranous EMA, 400X).

specimen of testis with spermatic cord was received after orchiectomy. Cut section showed a solid-whitish growth measuring (14×11×9) cm with a small area of normal looking testicular area. Histology showed atypical spindle cells admixed with large round ovoid cells resembling rhabdomyoblasts [Table/Fig-8a,b]. Tadpole cells and those with cross striations were also noted. A mitotic rate of >19/10HPF, focal (<50%) necrosis and a differentiation score of 2; FNCLCC grade 3 was assigned. The cells were MyoD1 positive and a histomorphological diagnosis favouring embryonal rhabdomyosarcoma was given. On close follow-up of the case for five months, it was found that he had been doing well after receiving chemotherapy.



[Table/Fig-8]: a) Embryonal Rhabdomyosarcoma (H&E stain, 100X); b) Embryonal Rhabdomyosarcoma (H&E, 400X).

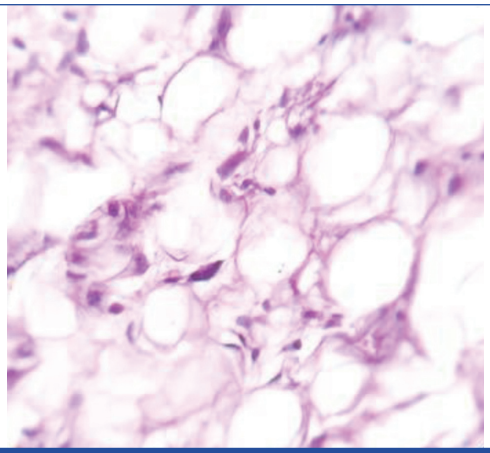
Case 9

A 55-year-old male presented to the Department of General Surgery with a painful scrotal swelling for six months. Radiologically, it was a paratesticular mass with homogenous intensity. Grossly, it was a (10×8×6) cm greyish brown to yellow tissue piece. Histopathological sections showed variable sized adipocytes with scattered atypical lipoblasts and stromal cells [Table/Fig-9]. Necrosis and mitotic activity was absent. Hence, histopathological diagnosis of WDLS was delivered. Wide local excision was performed and follow-up of the case could not be done.

[Table/Fig-10] summarises the diversified soft tissue sarcomas with respect to their age of the patient, anatomical site and immunohistochemistry.

DISCUSSION

Soft tissue sarcomas are a group of rare heterogeneous tumours which arises in the connective tissues embryologically derived from the mesenchyme [3]. Sarcomas constitute <1% of all neoplasms, which often results in a delay in diagnosis [4]. The adverse prognostic



[Table/Fig-9]: Atypical Lipomatous Tumour (H&E stain, 400X).

Case No.	Age/Sex	Anatomical site	Immunohistochemistry	Diagnosis
1.	55 years/ Female	Infra axillary region	Epithelial Membrane Antigen (EMA), Pan-Cytokeratin clone AE1/ AE3, Transducin-Like Enhancer of split 1 (TLE1),Vimentin, Cluster of differentiation 99 (CD99)	Biphasic synovial sarcoma
2.	20 years/ Female	Inguino labial region	• CD99, Vimentin and EMA positive • CD34, S100 and Smooth Muscle Antibody (SMA) negative	Monophasic synovial sarcoma
3.	34 years/ Male	Left thigh	EMA, CK, TLE1	Monophasic synovial sarcoma
4.	43 years/ Female	Right leg	EMA, AE1/AE3, TLE1,Vimentin, CD99	Biphasic synovial sarcoma
5.	29 years/ Male	Right arm	• CD99, Vimentin and EMA positive • CD34, S100 and SMA negative	Monophasic synovial sarcoma
6.	40 years/ Female	Retroperitoneum	-	Dedifferentiated liposarcoma
7.	51 years/ Female	Spleen	CD34, EMA	Epithelioid angiosarcoma
8.	14 years/ Male	Testicular mass	Myoblast determination protein 1 (MyoD1)	Embryonal rhabdomyosarcoma
9.	55 years/ Male	Scrotal mass	-	Well differentiated liposarcoma

[Table/Fig-10]: Summary of the cases with respect to age, sex, anatomical site, immunohistochemistry and diagnosis.

factors for STS include increasing age, size, high grade, metastasis at diagnosis, high levels of tumour necrosis, local recurrence at diagnosis (following unplanned excision), positive surgical margin and deep to muscular fascia [5].

Synovial sarcoma: It is a malignant soft tissue tumour of uncertain differentiation. Its relative frequency is age-dependent, being 1.6% in more than 50 years and 15% in the age group of 10-18 years [6]. It can virtually be found anywhere in the body, predominantly in the extremities [7]. A study by Ferrari A et al., of 271 patients showed that the median age at presentation was 32 years with 232 cases involving the extremities, followed by trunk, head and neck, abdominopelvic region and mediastinum [8]. In our study, the age of the patients ranged from 20-55 years; median being 34 years. Three of them were present in the extremities while two cases were located at rare sites like inguinolabial and infra-axillary region. Although the histomorphology is characteristic, the differentials should be considered before giving a definite diagnosis [9,10]. Monophasic subtype should be distinguished from malignant peripheral nerve sheath tumour, fibrosarcoma and solitary fibrous tumour using S100 and CD34 respectively. Biphasic mesothelioma

or ectopic hamartomatous thymoma could be considered in the Biphasic subtype [7]. Synovial Sarcoma shows positivity with TLE1, CD99, SMA, Vimentin, CK and EMA and fusion study for SYT-SSX-1 gene [1]. Hence, immunohistochemistry and molecular studies play an important role in the definite diagnosis of synovial sarcoma.

Dedifferentiated liposarcoma (DL): It is the tumour with a non lipogenic component within an atypical lipomatous tumour. It accounts for 18% of liposarcomas. According to the FNCLCC grading system, dedifferentiated liposarcoma is assigned 3 points for differentiation, resulting in an intermediate grade at the minimum. DLs located in the retroperitoneum have the worst prognosis. Local recurrence has occurred in at least 40% of cases. However, almost all retroperitoneal cases seem to recur locally if patients are followed for 10-20 years [1].

Angiosarcomas: They are highly aggressive malignant vascular tumours constituting less than 1% of all sarcomas [11]. The most common locations are the skin, soft tissue, breast, bone, liver and spleen [7]. Some soft tissue angiosarcomas arise from major vessels, such as the inferior vena cava or aorta. It is difficult to identify the endothelial nature of the lesion as they have an undifferentiated appearance with a solid growth pattern. The different histologic growth patterns include papillary, spindled and epithelioid morphologies. The common etiologies for angiosarcomas include previously irradiated field, in arteriovenous fistulas or arising within pre-existing benign tumours, such as haemangioma, neurofibroma or leiomyoma. The histomorphology of EA may show diagnostic challenges with other lesions like epithelioid haemangioma, Epithelioid Haemangioendothelioma (EHE), metastatic carcinoma, metastatic melanoma, lymphoma, epithelioid sarcoma and other sarcomas with epithelioid features. More than 50% patients die of this within one year [12].

Rhabdomyosarcomas: They are malignant skeletal muscle tumours and histologically are of three types-embryonal, alveolar and pleomorphic. Embryonal variant constitute approximately 60% [13]. The genitourinary tract is the second most common site for rhabdomyosarcoma, following head and neck [14]. In the Intergroup Rhabdomyosarcoma Study (IRS) series, 24% cases arose in this region. The tumours most commonly arise in a paratesticular location occurring predominantly in adolescents. Histologically, most tumours present in this location are of the embryonal subtype, spindle cell variant [15,16]. It has an excellent prognosis, with a 5-year overall survival rate of about 90%, when confined disease is treated with combined surgery, radiation and chemotherapy and less than 30%, when metastatic [17].

Atypical lipomatous tumour and WDLS: They are used synonymously. They belong to the Intermediate (locally aggressive) category of adipocytic tumours in the WHO classification of soft tissue and bone, 2020. However, the latter is used for lesions arising in anatomical sites like retroperitoneum, spermatic cord and mediastinum, which have greater potential for disease progression. They account for 30%-40% of all liposarcomas [18]. Three main histologic patterns are recognised: lipoma-like, sclerosing and inflammatory (lymphocyte-rich). WDLS is a grade 1 sarcoma in the FNCLCC classification. Recurrences are common because of the difficulty of radical excision. It does not metastasise unless it dedifferentiates [19]. Hence, this diagnosis should alert the surgeons to the well-known problem of local recurrence and these tumours should be fully excised [20].

CONCLUSION(S)

Soft tissue tumours may be of diverse origin. Their diagnosis is an amalgam of clinico-radiological, histomorphological, immunohistochemical and molecular correlation. Proper diagnosis is helpful in predicting the prognosis of the patient. Complete excision is required as few of them have increased risk of recurrence.

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PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Pathology, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
2. Assistant Professor, Department of Pathology, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
3. Associate Professor, Department of Pathology, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India.
4. Assistant Professor, Department of Pathology, College of Medicine and Sagore Dutta Hospital, Kolkata, West Bengal, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Manisha Mahata,
Flat-2A, Vasundhara Niwas, P-27, Motijheel Avenue, Dumdum,
Kolkata-700074, West Bengal, India.
E-mail: drmanisha252@gmail.com

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