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Case Series

Pathology Section

Soft Tissue Sarcomas with Enigmatic Clinical Presentation- Unveiled by Histomorphology and Immunohistochemical Picture

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ABSTRACT

Soft Tissue Sarcomas (STS) are aggressive neoplasms of dismal outcome, predominantly occurring in elderly age group. Synovial Sarcomas (SS) show preponderance in adolescents and poorly differentiated histological variants need exhaustive work up employing Immunohistochemistry (IHC) and molecular pathology. Pleomorphic liposarcomas have short preoperative period and hence necessitates early identification despite being rare. Rhabdomyosarcomas are often diagnostic with skeletal muscle differentiation on histology even in the absence of embryonic or alveolar pattern. However, while dealing with small blue round cell tumours of adolescents in the absence of any specific differentiation and pattern, molecular analysis including PAX-FOXO1 fusion, FUS-ETS fusion, EWSR1-non ETS fusion, CIC and BCOR fusion is of paramount importance. In this series, we have compiled a set of four cases with diversified histomorphology, presenting at extremely uncommon sites with varying clinicoradiological profiles yet biologically behaving aggressive almost to a similar extent necessitating adjuvant therapy. An intriguing case of biphasic SS in the axilla, an uncommon site was discussed where narrowing the differentials was an uphill task. Another case of monophasic SS at yet another uncommon site (inguinolabium) with overlapping histology warranted the need to rule out the other probabilities employing IHC. The next case of pleomorphic liposarcoma encountered here needs special mention owing to low incidence and labelling it with certainty required meticulous analysis including extensive sampling and IHC. Another interesting case of pleomorphic rhabdomyosarcoma with striking histology where role of IHC was only supplementary further reinforced the vital role of histopathological examination in the diagnostic work up of sarcomas.

Keywords: Liposarcoma, Pleomorphic, Rhabdomyosarcoma, Synovial sarcoma

INTRODUCTION

The Soft Tissue Sarcomas (STS) are ubiquitous malignant neoplasms and the tumour classification is based on multitude of parameters including cell lineage, morphology, Immunohistochemistry (IHC) and genetic factors terminating into a final diagnosis [1].

Synovial Sarcomas (SS) are an uncommon malignancy of unknown origin accounting to 5-10% of STS, rarely encountered in patients over 50 years [2,3]. The SS18: SSX pathognomonic of the disease is linked to aberrant E-cadherin repression, overexpression of BCL2, and downregulation of MCL1 [4,5]. Tyrosine kinase inhibitor (pazopanib) improves the overall survival rate dramatically [6,7].

Liposarcomas constitute one of the most common STS, however pleomorphic liposarcomatous subtype is extremely rare yet most aggressive [8]. The low incidence leads to underdiagnosis, however identification at an early stage is clinically relevant as haematogenous metastasis (lung) is frequently seen [9]. The identification of pleomorphic lipoblasts establishes the diagnosis over other high grade sarcomas. However, a benign entity, pleomorphic lipoma needs a special mention owing to its well circumscription, located at posterior neck region in middle aged males [10]. The presence of multinucleated floret-like giant cells simulating lipoblasts is a pitfall but the characteristic ropy collagen bundles with immunostaining for CD34 is a distinguishing feature [11]. The genomic complexities of pleomorphic rhabdomyosarcomas, are responsible for the response to chemotherapy similar to adult high grade STS.

In this series, authors have attempted to put forward a set of high grade STS with varying clinical manifestations at uncommon anatomical sites with a multitude of possibilities where the pathognomonic histology and IHC served as inevitable tool of diagnosis and thus ensuring the adequate management guidelines to be adopted [Table/Fig-1].

CASE SERIES

Case 1

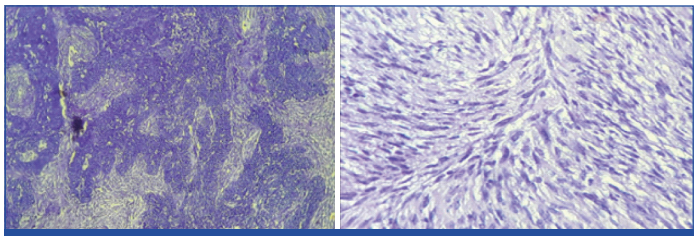
A 57-year-old female presented with an axillary swelling rapidly progressing in size since one month. Computed Tomography (CT) revealed well-defined lobulated mass with punctate calcification and low-intensity signal in the deeper plane of axilla. On tru-cut biopsy,

Case	Age/Gender	Chief complaint	Clinical diagnosis	Histopathological diagnosis	Immunohistochemistry	Follow-up
1	57 years/F	Rapidly progressing painless axillary swelling since 1 month	Soft tissue Space Occupying Lesion (SOL)	Biphasic Synovial Sarcoma, FNCLCC Grade 2	Pancytokeratin (cytoplasmic), CD99 (membranous)and TLE1 (nuclear)	Followed-up for 6 months and no local reccurence or metastasis noted.
2	20 years/F	Painless inguino-labial swelling since 1 month	Soft tissue SOL	Monophasic Synovial Sarcoma, FNCLCC Grade 2	Vimentin (cyotplasmic), CD 99 (membranous) and TLE1 (nuclear)	Followed-up closely for 8 months and no local reccurence or metastasis noted.
3	62 years/F	Rapidly progressing retroperitoneal SOL since 1.5 months	Soft tissue SOL	Pleomorphic liposarcoma, FNCLCC Grade 2	-------	Followed-up for 5 months and no reccurence noted.
4	41 years/M	Painless lump in the periumbilical region since 1 month	Soft tissue SOL	Pleomorphic rhabdomyosarcoma, FNCLCC Grade 3	Desmin (membranous and cytoplasmic), MyoD1 (focal nuclear)	Local relapse noted in 5 months.

[Table/Fig-1]: Depicting case-wise distribution with respect to demography, clinical presentation, histology, Immunohistochemistry (IHC) and behaviour on follow-up.
FNCLCC: Federation nationale des centers de lutte contre le cancer; TLE1: Transducin-like enhancer of split 1

nests of basaloid cells and spindle cells having pleomorphic, atypical nuclei were noted. A provisional diagnosis of adnexal neoplasm was made, followed by excision. However, no previous history of adnexal neoplasm was documented.

On gross examination, a poorly circumscribed Space Occupying Lesion (SOL) was noted in the deeper soft tissue measuring (10×8×6 cm). Cut section revealed solid areas with extensive necrosis. Microscopically, biphasic tumour comprising epithelial elements (glandular structures lined by columnar stratified epithelial cells) and spindle cells arranged in sheets, fascicles and herringbone pattern were seen. Both the components exhibited nuclear overlapping, hyperchromasia, brisk mitosis (6/10 HPF) interrupted with necrosis [Table/Fig-2,3]. The major differentials considered here were malignant mixed tumour of appendageal structures of skin, sarcomatoid basal cell carcinoma and trichoblastic carcinosarcoma. IHC demonstrated moderate nuclear transducin-like enhancer of split 1 (TLE1) by both spindle and epithelial elements, diffuse strong membranous CD 99 by spindle cells and cytoplasmic pancytokeratin expression by epithelial cells rendering the final diagnosis of biphasic SS, Federation Nationale des Centers de Lutte Contre le Cancer (FNCLCC) Grade 2 [Table/Fig-4].



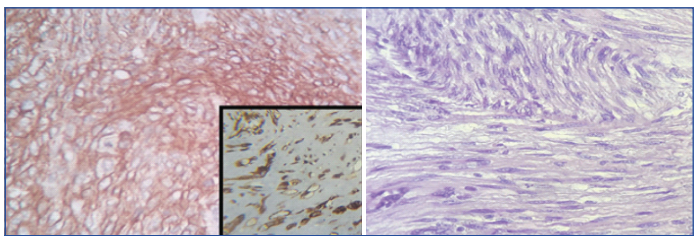
[Table/Fig-2]: Biphasic Synovial Sarcoma (SS), epithelial component, (H&E, 400X); **[Table/Fig-3]:** Biphasic Synovial Sarcoma (SS), herringbone pattern of spindle cells, (H&E, 400X). (Images from left to right)

In accordance with higher age group, anatomical site, size and grade the prognosis is expected to be poor. The patient is being followed-up (six months) after wide surgical resection and administration of cytotoxic chemotherapy with adriamycin and ifosfamide. There has been no local recurrence or metastasis till the date of case reporting.

Case 2

A 20-year-old female presented with inguinolabial swelling since one month. Clinically, the mass was hard and fixed. On CT, it was heterogeneously enhancing situated in the deeper soft tissue plane with varying attenuation (predominantly similar to muscle and lower corresponding to necrohaemorrhagic areas.

On gross examination, a diffuse mass measuring 10 cm in greatest dimension cut surface tan-greyish. Microscopy showed uniform spindle to ovoid cells with scant cytoplasm arranged in fascicles. Individual cells had nucleomegaly, vesicular, pleomorphic nuclei and brisk atypical mitotic figures (6/10 HPF) interspersed with necrosis. At places, herringbone pattern, staghorn vasculature and scant collagenised areas were noted [Table/Fig-5], raising the possibility of malignant solitary fibrous tumour. IHC revealed diffuse strong nuclear TLE1, membranous CD99 and vimentin (cytoplasmic) expression while CD34 being negative [Table/Fig-6]. Final diagnosis of monophasic SS, FNCLCC Grade 2 was made.



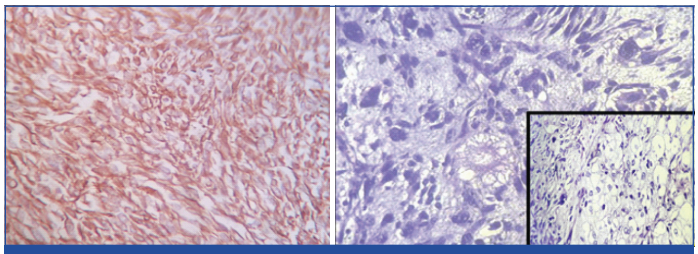
[Table/Fig-4]: Biphasic Synovial Sarcoma (SS), diffuse and membranous positivity CD99 IHC; inset: moderate nuclear positivity for TLE1 (IHC, 400X).
[Table/Fig-5]: Monophasic Synovial Sarcoma (SS), sweeping fascicles of spindle cells, (H&E, 400X). (Images from left to right)

Surgical excision was performed along with adjuvant chemotherapy (doxorubicin and ifosfamide). After a close follow-up, no local recurrence or distant metastasis was documented over a period of eight months.

Case 3

A 62-year-old female presented with a retroperitoneal SOL rapidly progressing since 1.5 months. There was no significant past history. On CT scan, a heterogeneously enhancing deep soft-tissue density isodense to muscle was noted prompting excision.

Grossly, an unencapsulated tumour, spindle cells arranged in fascicles with pronounced nuclear atypia and pleomorphism were seen on microscopy. Numerous multinucleated tumour giant cells, atypical mitosis and pleomorphic lipoblasts with multiple cytoplasmic vacuolations indenting upon nuclei were typical of the tumour admixed with myxofibrosarcomatous areas [Table/Fig-7]. No areas of atypical lipomatous tumour differentiation were noted supporting the diagnosis of pleomorphic liposarcoma, FNCLCC Grade 2.



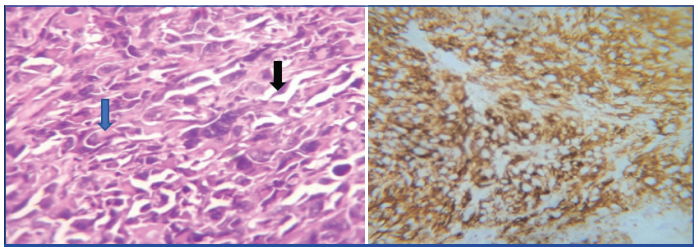
[Table/Fig-6]: Monophasic Synovial Sarcoma (SS), diffuse membranous CD 99 (IHC, 400X); **[Table/Fig-7]:** Pleomorphic liposarcoma, in a background of undifferentiated pleomorphic sarcoma; inset: pleomorphic lipoblasts: (H&E 400X). (Images from left to right)

Along with the wide local excision, neoadjuvant chemotherapy in the form of doxorubicin and ifosfamide were administered. After a close follow-up of the case for five months, no recurrence was noted.

Case 4

A 41-year-old male presented with a lump in the periumbilical region since a month. No significant past history was given. CT scan revealed a fairly marginated heterogeneously enhancing lesion, measuring (8x6x5) cm in the deeper soft tissue plane.

The cut section was fleshy with necrotic foci. Microscopically, an encapsulated tumour comprising pleomorphic bizarre atypical cells and multinucleated forms in sheets interspersed with tadpole cells and rhabdomyoblasts [Table/Fig-8]. To confirm the diagnosis, IHC was done, showed diffuse membranous and cytoplasmic desmin and focal nuclear MyoD1 expression leading to final diagnosis of pleomorphic rhabdomyosarcoma, FNCLCC Grade 3 [Table/Fig-9].



[Table/Fig-8]: Pleomorphic rhabdomyosarcoma, rhabdomyoblasts (blue arrow) and tadpole cells (black arrow), (H&E 400X); **[Table/Fig-9]:** Pleomorphic rhabdomyosarcoma, membranous Desmin (IHC, 400X). (Images from left to right)

Wide surgical resection and chemotherapy with doxorubicin was administered. Patient experienced local relapse in five months, for which the patient was further treated with gemcitabine and docetaxel.

DISCUSSION

The STS are rare group of malignant neoplasms constituting 1% of the total. The low incidence coupled with multiple histological subtypes, widespread anatomical sites, varying clinical presentation, specific molecular biology mount to diversified clinical outcomes.

The ratio of STS to bone sarcoma incidence is 4:1, with slight male preponderance (1.4:1) and the median age being 59 years. The adverse prognostic factors are increasing age, larger size, high grades, local recurrence and metastasis at diagnosis, deeper planes (muscular fascia) and extensive necrosis.

The SS are monomorphic blue spindle cell neoplasms with variable histology ranging from monophasic, biphasic to poorly differentiated subtypes. Classically occurring in adolescents, however the exact frequency of the cases is age dependent (15% in 10-18 years, 1.6% in >50 years) [12]. The most common site being the deeper soft tissue in juxta-articular locations of extremities. Two cases of SS at rare sites (axilla and inguinal region) with fallacious morphology and uncommon age group (57-year-old) have been enlisted. In the first case peripheral palisading pattern shown by basaloid cells makes way for other possibilities. Even after extensive sampling, no foci of benign adnexal neoplasms were noted ruling out malignant neoplasms arising from benign appendegeal tumour of apocrine or eccrine origin. No evidence of follicular mesenchyme excluded trichoblastic carcinosarcoma. Lack of fibromyxoid stroma and sun exposed site eliminates sarcomatoid basal cell carcinoma. TLE1 and CD99 expression pattern were contributory to the final diagnosis of biphasic SS (case 1). This was indeed an unexpected case at this age and location, otherwise the most common site being deep soft tissue of lower extremities [13]. Any other anatomical site apart from extremities is an independent poor prognostic factor as noted here [3,14,15].

A case of monophasic SS (case 2) in inguino-labial area, an extremely uncommon site with only seldom cases reported in literature so far [16]. The closest morphological mimicker was malignant solitary fibrous tumour with alternating areas of low and high cellularity, variably collagenised stroma and focal haemangiopericytomatous vasculature. However, CD34 negativity coexistent with TLE1 and diffuse CD99 acted as strong pointers towards the diagnosis of SS.

Although, well-differentiated liposarcomas contribute to the largest subgroup of adipocytic malignancies (40-45 %) with highest incidence in the fourth-fifth decades of life. Pleomorphic liposarcoma is the least common (<5%) yet most aggressive subtype of liposarcoma [12], making the diagnosis critical. They are unique in the sense that they have no specific immunohistochemical or molecular genetic characteristics for diagnosis unlike other categories where molecular pathology is the key to diagnosis. The mere presence of pleomorphic lipoblasts in the absence of well differentiated liposarcomatous areas sufficed for diagnosis (case 3).

Rhabdomyosarcomas are a group of neoplasms derived from immature striated muscles and the most common sarcomas in head and neck region of young children [17]. Pleomorphic rhabdomyosarcomas however are seen in 6th-7th decades of life and are rare (<2%). A case of pleomorphic rhabdomyosarcoma (case 4) in an adult was reported. Although, complex karyotypes with structural and numerical changes are seen, the genetic profile is not diagnostic and is similar to undifferentiated pleomorphic sarcoma. So, the role of morphology and IHC is of utmost importance.

CONCLUSION(S)

The STS are heterogeneous group with the age group ranging from children to elderly depending on the histological subtypes. The most common site being extremities followed in small numbers by trunk wall and extremities. The grading (FNCLCC) of the tumour is an indicator for distant metastasis while the staging is an important predictor of loco-regional recurrence. Currently the revolutionary change is from one-size-fits-all treatment paradigm towards a histology-specific treatment algorithm attempting at tailoring the type and extent of surgical resection to be performed and the decision regarding administration of multimodality treatment, employing a multi-disciplinary team. The diagnosis is aided by immunohistochemical staining often supplemented with molecular testing to detect translocations and amplifications for a specific diagnosis and in turn for targeted therapy.

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