Original Research Paper

Volume - 11 | Issue - 01 | January - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pathology

RARE MALIGNANT SOFT TISSUE TUMOURS OF THE EXTREMITIES: 5 RETROSPECTIVE CASE SERIES FROM TERTIARY CARE CENTRE OF NORTHEAST INDIA.

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ABSTRACT

Introduction: Soft tissue tumours constitute a large and heterogeneous group of neoplasms. Clinically they range from benign, self-limited lesions to intermediate grade to highly aggressive. Most of soft tissue tumours are benign but only few of them are malignant in nature. These tumours can develop at any site in the body.Sixty percent of the malignant soft tissue tumours occur in extremities making this the commonest site.

Materials and methods: This is a retrospective study where we studied the histo-morphological patterns, features and immunohistochemistry of 5 rare malignant soft tissue tumours that occurred in the extremities and diagnosed in department of Pathology GMCH over a period of 8 years (Jan 2012 to December 2019). Among these cases, 3 were rare soft tissue tumours that presented in the extremities while the other 2 cases were relatively common soft tissue malignancies but occurring rarely in the extremities.

Results: Out of the 5 cases of malignant soft tissue tumours 4 cases were observed in males and only 1 case in female. The age ranged from 35 to 55 years. 3 cases were tumours of uncertain differentiation i.e. Alveolar soft part sarcoma, clear cell sarcoma and myoepithelioma.2 cases i.e. Clear cell sarcoma and Malignant Myoepithelioma occurred in the buttocks. 2 other cases i.e. A case of primary leiomyosarcoma of femoral vein and Alveolar soft part sarcoma occurred in thigh and a case of De-differentiated Liposarcoma occurred in thumb. The diagnosis of all the above cases were on histopathology and confirmed by immunohistochemistry.

Conclusion: Because malignant soft tissue tumours are rare, can recur, it cannot be overemphasised that patients require a multidisciplinary approach involving pathology for accurate diagnosis which will determine therapy, follow-up and prognosis.

KEYWORDS : leiomyosarcoma, pleomorphic, dedifferentiated, myoepithelioma

INTRODUCTION

Malignant soft tissue tumours are rare tumours of mesenchymal origin representing 1% of all malignant tumours[1]. Common subtypes in the extremities are liposarcoma and undifferentiated pleomorphic sarcoma.[2]Sixty percent of the malignant soft tissue tumours occur in extremities making this the commonest site. Other locations are trunk (19%), retroperitoneum (10%) and head and neck (9%).[3]Factors such as patient age, tumour size, location, clinical stage, histologic subtype and grade determine the specific approach to management and patient outcome.

Leiomyosarcomas arising from the vessel walls also known as vascular leiomyosarcomas represent only 2% of all leiomyosarcomas.[4,5] They are usually of venous origin. We present a case of leiomyosarcoma of femoral vein arising in right thigh of a 35 year old man.

Alveolar soft part sarcoma is a rare malignant soft tissue sarcoma accounting for 0.2-1% of all soft tissue sarcomas. The tumour occurs primarily in adolescents and young adults between 15-35 years of age [6,7]. In adults, it is seen predominantly in the lower extremities, especially the anterior portion of thigh. We present a case of Alveolar soft part sarcoma arising in thigh of a 35 year old lady.

Dedifferentiated liposarcoma a rare subtype of Liposarcoma primarily occurs in retroperitoneal location (more than 80 % of cases). <01% occur in subcutaneous site[8] We present a case of Dedifferentiated liposarcoma arising in thumb in 55 year old man.

Clear cell sarcoma (CCS) is a rare malignant soft tissue tumour also known as malignant melanoma of soft part representing about 1% of soft tissue tumours and primarily involves tendons and aponeuroses especially in lower extremities[9]. The incidence risk is over the age of 40 years.[10,11]. This tumour is slightly more common in women than in men[12]. We present a case of Clear cell sarcoma arising in right thigh in 38 year old man.

Soft tissue myoepithelioma is a rare soft tissue tumour, with a wide histologic spectrum[13] Men and women are equally affected across all age groups and lesions arise most frequently on the limbs and limb girdles(75% of the cases)[14]. We present a case of myoepithelioma arising in right thigh in 50 year old man.

MATERIALS AND METHODS

The study was a retrospective hospital based study conducted in the Department of Pathology, Gauhati Medical College, Assam. 5 cases of rare malignant soft tissue tumours of extremities with available formalin fixed, paraffin embedded tissue were selected from surgical pathology records between January 2012 and December 2019. The tumours were classified as upper extremity if it was beyond shoulder joint and lower extremity if it was beyond hip joint. Nature of the specimen were surgically excised tumours (4 cases) and an amputated thumb (1 case). Out of these, 4 were primary tumours and 1 was a recurrent tumour. The patient characteristics (age and sex), tumour characteristics (site, size, histologic subtype, necrosis, and mitotic activity) were analysed in these cases. Tissues were received in 10% formalin, processed routinely with haematoxylin and eosin staining and diagnosis based on the histopathologic examination. Immunohistochemistry was performed for confirmation of diagnosis of all the 5 cases.

RESULTS

5 cases of rare malignant soft tissue tumours of extremities were reported during the 8-year study period. The age range of the patients was 35-55 years. Out of the 5 cases ,4 cases occurred in males and a single case was observed in female.

Regarding the site, the lower extremity was involved in 4 cases and upper extremity in 1 cases. In the case of lower extremity, 2 cases occurred in the buttock and 2 in thigh. In the case of upper extremity, we had a single case in thumb presenting as a recurrent mass (Table 1). The tumour size ranged from 2.5 cm to 7 cm. (Table 1).

Table 1: Complete data of 5 cases:

Serial no.	Age (years)	Sex	Site	Specimen	IHC	Diagnosis
1	35	Male	Thigh	Tumour excision	SMA, Vimentin	Primary leiomyosarcoma of femoral vein

2	35	Female	Thigh	Tumour excision	TFE3	Alveolar soft part sarcoma
3	55	Male	Thumb	Amputated thumb	MDM2, S100	Dedifferentiated liposarcoma
4	38	Male	Buttock	Tumour excision	S-100, HMB 45	Clear cell sarcoma
5	50	Male	Buttock	Tumour excision	Calponin	Malignant myoepithelioma

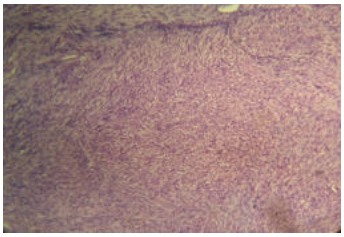
DISCUSSION

Leiomyosarcomas of vascular origin are a rare group of tumours. Fewer than 30 cases of leiomyosarcomas originating from the femoral vein have been reported in the English literature[15] After a thorough literature search, we found that cases of vena-caval leiomyosarcomas have been reported from India but our case happens to be the first primary leiomyosarcoma of femoral vein being reported from India. [16]

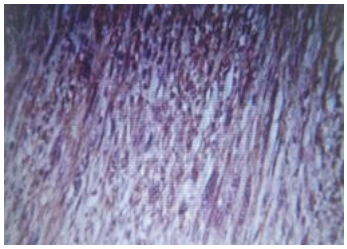
The diagnosis is based on radiological and pathological features; gold standard being histopathology supplemented by immunohistochemistry for smooth muscle actin (SMA).

Leiomyosarcomas of vascular origin have a relatively poorer prognosis. [17] The poorer prognosis of venous leiomyosarcomas compared to those of soft tissue could be because these tumours generally have direct access to the venous system, involving the lumina, and tend to have early blood-borne metastases.

A 35-year-old man presented with a painless swelling on the upper part of the right thigh. Magnetic Resonance Imaging (MRI) showed the mass to be attached to the femoral vein. Gross examination of the specimen revealed a polypoidal firm mass measuring (7x5x2) cm^3, with a lobulated outer surface. A cut section showed greyish white mass with whorled appearance and slit like spaces at places. Microscopy showed long interlacing fascicles of spindle cells having hyperchromatic, moderately pleomorphic nuclei with rounded ends (cigar shaped) and bright eosinophilic cytoplasm (Figure 1). Areas of necrosis, numerous typical and atypical mitotic figures (15-20 per 10 high power fields) along with a few scattered tumour giant cells were also seen. The neoplastic spindle cells were positive for Smooth Muscle Actin (SMA) (Figure 2) and vimentin. The final diagnosis based on MRI, histomorphology and immunohistochemistry was Grade 3 leiomyosarcoma of the femoral vein.



Photomicrograph showing long interlacing fascicles of spindle cells (H and E, 400x)



Photomicrograph showing smooth muscle actin positivity in the neoplastic spindle cells (400x)

Alveolar soft part sarcoma (ASPS) is a rare, distinctive sarcoma, typically occurring in young patients. The prognosis is poor and is often characterized by late metastases and an extended clinical course[18] Common in female patients [19] Because of the relative lack of symptoms, it is easily overlooked; in a number of cases, metastasis to the lung or brain is the first manifestation of the disease [20] Morphologically it consists of circumscribed nests of large, round to oval eosinophilic cells, often showing central dys-cohesion and hence an alveolar architecture. The nests are surrounded by fibrous septa that often contain prominent vessels. Vascular invasion is a constant, striking finding that explains the tendency of the tumour to develop metastasis at an early stage of the disease. Cytogenetic studies of this tumour have identified a specific alteration, der(17)t(X;17) (p1 1.2q25). This unbalanced translocation results in the fusion of the TFE3 gene on Xp11.2 to ASPSCR1 on 17q25. [21,22] The resulting fusion gene encodes for a fusion protein that localizes to the nucleus and functions as an aberrant transcription factor. Detection of this protein through immunohistochemistry helps to confirm diagnosis.

We present a 35 year old lady with a slow growing mass in the medial aspect of her right thigh .MR imaging showed presence of an intramuscular soft tissue mass with multiple hypointense internal fibrous septae and prominent vessels. On Gross examination, it was a solid, greyish white, fleshy tumour mass measuring 4.5×4.3×3 cm^3, the cut surface of which was variegated in appearance showing whitish areas with scattered areas of necrosis and haemorrhage [Figure 3]. Microscopic examination showed tumour cells arranged in alveolar and nested pattern [Figure 4]. The tumour cells are round to oval with abundant eosinophilic and granular cytoplasm, round to oval nucleus with vesicular chromatin and prominent nucleoli. Diagnosis of Alveolar soft part sarcoma was made and confirmed by immunohistochemistry, as the tumour cells showed nuclear positivity for transcription factor E3(TFE3) [Figure 5].

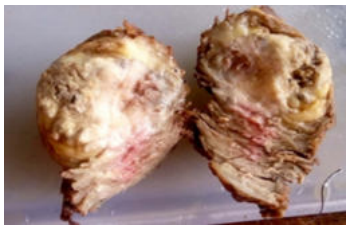


Fig:3 Cut surface of the tumour mass from the Right thigh showing fleshy, greyish-white, variegated appearance, along with some areas of necrosis along with attached muscle.

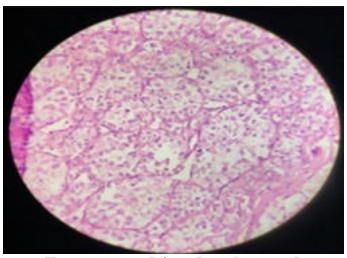


Fig:4 Tumour cells arranged in alveolar and nested pattern; the nests being surrounded by thin walled vessels. (H & E,40X)

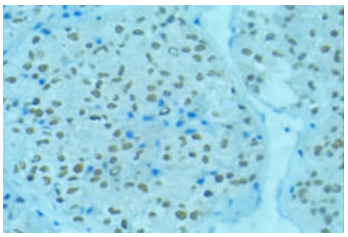


Fig:5 Strong diffuse positive nuclear expression of Transcription Factor E3(TFE3) by the tumour cells.

Liposarcoma is one of the most common soft tissue sarcomas of adult life, the relative incidence among other sarcomas ranging from 9.8% to 16%.[23] Its principal histologic subtypes are entirely separate disease entities with different morphology, genetics, and natural history.

Dedifferentiated liposarcoma: Dedifferentiation or histologic progression to a higher grade, less well differentiated neoplasm was first described by Dahlin. [24,25,26]

Dedifferentiated liposarcoma reaches a peak during the early 7th decade. The retroperitoneal location is a favoured site of this subtype. <01% occur in subcutaneous site. [23] An extensive review of literature shows that dedifferentiated liposarcoma of the thumb is very rare with only one reported case of de - novo subungual right thumb liposarcoma with brain metastasis.[27] Dedifferentiated areas may be high grade or low grade and are generally non lipogenic. Dedifferentiated liposarcoma, despite its high-grade morphology, exhibits a less

aggressive clinical course than other subtypes of high-grade pleomorphic sarcoma.[26,28,29]

We present a case of 55 years old man with recurrent thumb mass. Grossly, specimen consisted of amputated thumb (Figure 6). Cut section was fleshy, whitish - yellow with destruction of underlying bone. Microscopic examination showed features of WDLS juxtaposed to areas of a high grade pleomorphic undifferentiated sarcoma (Figure 7). Immunohistochemistry for S - 100 was positive in well-differentiated areas and MDM2 was positive in dedifferentiated areas (Figure 8).

Fig:6 Specimen of amputated thumb showing fleshy, whitish - yellow cut surface (Dedifferentiated LS case)

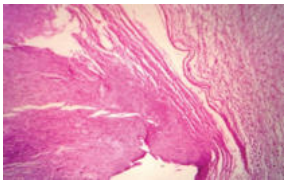


Fig 7:Low power view of dedifferentiated liposarcoma showing the pleomorphic undifferentiated component in the left side and the WDLS component in the right

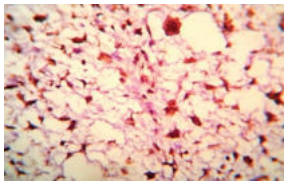


Fig 8:High power view of IHC showing nuclear positivity of MDM2 in the case of dedifferentiated liposarcoma

Clear cell sarcoma

Clear Cell Sarcoma (CCS) of soft tissue is an exceedingly rare tumour that originates from neural crest cells. They are seen between 20-40 years of age [30] and are relatively more common in women than in men[31] .They commonly arise from tendinous sheaths ,aponeuroses and majority occur in the lower limbs particularly around ankles. [32] True incidence remains unknown. They share histological and immunochemical characteristics with Malignant Melanoma.[33]

Histologically, CCS displays compact nests and fascicles of uniform to minimally pleomorphic tumour cells which are delineated by dense fibrous septa. Mitotic activity is often low, while scattered multinucleated giant cells are seen in half of cases[34]. The tumour cells are immune-positive for the common melanocytic markers, namely *HMB-45*, microphthalmia transcription factor (*MITF*), *S-100* protein, and *Melan-A* [35]. A reciprocal translocation t (12;22) (q13; q12) resulting in a *EWSR1/ATF1* chimeric transcript was also seen in 90% cases as a cytogenetic hallmark of CCS ([36,37])

We present a case of a 38 year old man with a swelling over right thigh. MRI showed soft tissue mass with hyperintense T1 and T2 weighted images. Grossly it was a circumscribed mass measuring 3.5x3x2.8 cm^3. Cut surface was solid greyish white with few areas of necrosis. Microscopically nested growth pattern with mixture of spindle and epithelioid cells with clear cytoplasm was noted. (figure 9). Scattered areas showed cytoplasmic melanin pigment. Immunohistochemistry showing S100 ,HMB45 positivity confirmed the diagnosis. (figure 10,11.)

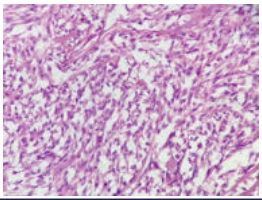


Fig 9: tumour cells arranged in alveolar pattern with clear cytoplasm (40x)

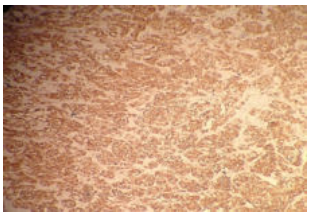


Fig 10:tumour cells positive for HMB45

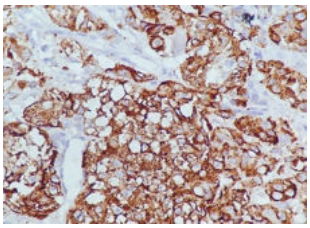


Fig 11: tumour cells positive for S100.

MYOEPITHELIOMA

Myoepithelioma of soft tissue is a rare mixed tumour that derives from deeply located adnexal structures. It occurs in the dermis, subcutis, or deep soft tissue. [38,39,40,41].

This tumour peaks in the third to fifth decades with equal distribution in gender, and is most common in the extremities and limb girdles [39,42]

Microscopically, its architecture consists of lobulated, multinodular, reticular, solid or mixed patterns without or with very limited epithelial differentiation. The neoplastic myoepithelial cells can display a wide range of morphologic features, such as spindle-shaped, ovoid, plasmocytoid, epithelioid or clear cells. The stroma is also variable and it may appear hyalinized, myxoid or show different forms of mesenchymal metaplasia [38,42,43,44].

Immunohistochemical studies using epithelial markers (cytokeratins, epithelial membrane antigen) and S100 protein with variable expression of GFAP, P63 and myogenic markers calponin, smooth muscle actin, desmin, h-caldesmon) are required to confirm the diagnosis.[34,37].

We present a case of 50 year old man with a swelling over right thigh for 2 years. On Gross examination, tumour was solid, grey white in colour measuring (3×2.5×2.3) cm^3 the cut surface of which was partly whitish and partly mucinous with scattered areas of haemorrhage [Figure12]. Microscopic examination showed lobulated architecture composed of solid sheets and trabeculae of cells. Cells are admixture of columnar, epithelioid spindle and clear cell type. Focal areas show moderate pleomorphism, presence of bizzare tumour cells. Areas of haemorrhage and fibrosis were noted. Immunohistochemistry for Calponin was positive.(fig 13)

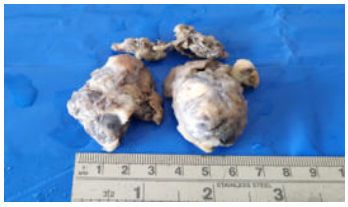


Fig 12: gross examination of the tumour masses

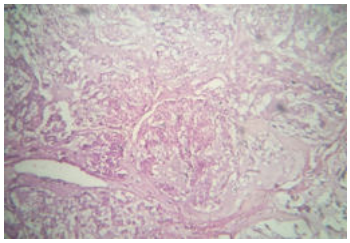


Fig 13: lobulated architecture composed of trabeculae of tumour cells.

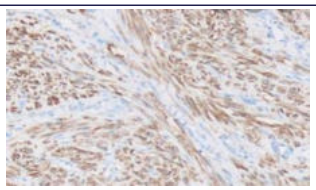


Fig 16: tumour cells are positive for Calponin

CONCLUSION

As every type of soft tissue tumour has a particular biological behaviour and response profile to systemic therapy, histological diagnosis is a crucial and critical criterion when selecting appropriate therapy.

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