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Clinicopathological and Immunohistochemical Study of Synovial Sarcoma: A Series of 42 Cases from Single Institution

Deepthi B[1*], Uppin SG[2], Challa S[2], Uppin MS[2], Paul TR[2], Prayaga AK[1]
[1]Department of pathology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India
[2]Department of Pathology, Nizam's Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, India

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***Corresponding author**
Deepthi B

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Abstract: Synovial sarcoma is a translocation associated sarcoma characterized by SS18 – SSX1/2 fusion. It is one of the common adult soft tissue sarcomas predominantly affecting lower extremities. In resource poor settings, exact characterization by molecular methods may not be feasible always. In our study we attempted to study the clinical profile, histomorphology and immunoprofile of cases diagnosed as synovial sarcomas. Forty two cases diagnosed as synovial sarcomas based of presentation, histomorphology and immunopanel were analysed .The median age of presentation was 26 years with male to female ratio of 1.5:1. Majority of the sarcomas were of monophasic type (83%) with predominant hemangiopericytomatous pattern (67%) followed by fascicular pattern (48%). Tumor size was greater in adults older than 20 years when compared to younger age group. Tumors with large areas of calcification were seen with significantly low mitotic index.
Keywords: Synovial sarcoma, monophasic type, HPC pattern, calcifications.

INTRODUCTION

Synovial sarcoma is a mesenchymal tumour which exhibits a variable degree of epithelial differentiation. At molecular level synovial sarcomas show a characteristic t(X;18)(p11;q11) translocation resulting in the fusion of SS18 with either SSX1 or SSX2, with very rare tumors having fusions involving SSX4 [1-9]. It is the fourth most common among adult soft tissue sarcoma and accounts for 5-10% of all soft tissue sarcomas [10-12]. Lower extremities are the most common sites affected, although any site is vulnerable [10, 11].

Histologically synovial sarcomas are divided into monophasic (epithelial and spindle) synovial sarcoma [MSS], biphasic synovial sarcoma [BSS] and poorly differentiated synovial sarcoma (PDSS) [10, 13, 14]. The diagnosis of BSS is pretty straight forward owing to its distinct histomorphology. The monophasic (spindle) and the poorly differentiated SS pose diagnostic difficulties as they closely mimic other spindle cell sarcomas and round cell tumours respectively. The significance of exact characterisation of these tumours lies in the fact that these tumours show modest response to conventional cytotoxic chemotherapy when compared to other soft tissue sarcomas. Though translocation studies done by FISH, RTPCR or cytogenetics are considered gold standard in confirming the diagnosis; these facilities pose financial and technical constraints especially in resource poor settings like our country. Hence histomorphology combined with carefully selected immnopanel will help in arriving at diagnosis. With this background we have attempted to analyze retrospectively the clinical, histopathological and Immunohistochemical profile of those cases diagnosed as synovial sarcoms in our institute, which is a tertiary care university hospital in southern India.

MATERIALS AND METHODS

It is a retrospective study of five years duration from 2007 – 2012 at Nizams Institute of Medical Sciences, Hyderabad. All the cases diagnosed as synovial sarcoma were retrieved and reviewed during the study period which included 9 biopsies, 25 wide local excisions and 8 amputation specimens (4 above knee, 3 below knee and 1 Symes amputation). Basic demographic and clinical details were recorded from the pathology files that included age, sex, clinical presentation, tumour site and size. For all cases, each microscopic slide(H&E) was reviewed and the following histologic features were studied: type - monophasic or biphasic or poorly differentiated; pattern - hemangiopericytomous, fascicular, palisdaing; and other histopathological variables such as number of mitosis, presence or absence of necrosis, ossification, calcification, myxoid change, hyalinization and presence of rhabdoid morphology. Tumours were typed as biphasic SS when they showed epithelial and spindle cell components, in varying proportions. The epithelial

cells displayed ovoid nuclei and abundant cytoplasm with gland formation and lumina (containing epithelial mucin) or papillary structures with one or (rarely) more layers of uniform cells. The monophasic spindle type were charecterised by spindled tumour cells which were uniform and relatively small, with ovoid, pale-staining nuclei, inconspicuous nucleoli and scant cytoplasm. Poorly differentiated areas were characterized by the sheet-like growth pattern of round cells with vesicular nuclei, prominent nucleoli, scant cytoplasm and increased mitotic activity. Mitotic counts were determined by evaluating the most cellular section of the neoplasm and calculating the average counts from five sets of 10 HPFs, using an Olympus CX21*i* microscope with a 40× objective and 10× ocular ($0.25mm^2$). Necrotic and haemorrhagic areas as well as overtly paucicellular areas were avoided for mitosis counting purposes

The IHC slides for the available cases were also reviewed. The IHC panel was different for each case and it incorporated several markers in various combinations which included Bcl2, Pan CK, EMA, Vimentin , SMA, CD99, LCA, Desmin, CD34 ,S100 and HMB45. IHC was done using a semiautomated immunostainer (*i 6000 Biogenex*) by immunoperoxidase method using Superenhancer Polymer- HRP detection system. Antigen-antibody complex visualized by using DAB 3'-3'-diaminobenzidine tetrahydrochloride as chromogen. All the primary antibodies were purchased from Biogenex.

Statistical analysis

The categorical variables were expressed as percentages, continuous variables as mean± standand deviation. The categorical data was analysed using chi square test, nominal data using Student t test, non parametric data using Mann-whitney U test and the correlation was done using Pearson correlation coefficent. The data was entered and anlysed using SPSS 17 statistical software.

Table-1: Demography, clinical profile and the tumour charcterstics of patients with synovial sarcoma

Total patients (n)	42
Age in mean±SD; median (range)	28.65±12.24 ; 26 (4-50)
M:F	25:17
SIZE in mean±SD; median (range)	8.321±6.5 ; 6 (1cm to 25cm)
SITE	
Lower extremities	26 (62%)
Upper extremities	7 (16.6%)
Back	5 (11.9%)
Lung	1 (2.3%)
Mediastinum	2 (4.7%)
Retroperitoneum	1 (2.3%)
Type	
Monophasic	35 (83.3%)
Biphasic	5 (11.9%)
Poorly diffentiated	2 (4.7%)
Recurrence	4 patients
Metastses	1 patient (lung)

Table-2: Tumour histological characteristics

Tumour patterns	**Positive (n=42)**	**Percentage**
Hemangiopericytomatous	28	67%
Fascicles	20	48%
Hyalinization	15	36%
Necrosis	14	33.33%
Calcification	8	19.04%
Myxoid changes	4	9.5%
Palisading	2	5%
Ossification	1	2.3%

RESULTS

Fifty cases of synovial sarcomas were diagnosed during the study period. The complete clinical, demographic and microscopic slides for review were available only in 42 cases. The clinical data of the 42 cases are summarized in Table-1. The age of the patients ranged from 4 to 50 years with a mean of 28.65±12.24 years and a median of 26 years. There were 25 males and 17 female with M:F ratio of 1.5: 1. Most of the patients presented with swelling and pain. Majority of the tumours 62% (26/42) were located in lower extremities. The tumours were predominantly of

monophasic type in 35 patients (83.3%), followed by biphasic in 5 (11.9%) and 2 were poorly differentiated (4.7%) (Table-1). The tumour patterns most commonly noted were as follows: hemangiopericytomas in 28 patients (67%), fascicular pattern in 20 (48%). Hyalinization was seen in 15 (36%), necrosis in 14 (33.33%), calcification in 8 (19.04%) Table-2.

The most commonly sought IHC marker, Bcl2 was done in 31 cases out of the 42 cases and it was found to be positive in almost all performed cases (100%). Vimentin was done in 4 cases and was also found to be positive in the performed cases. CK was done in 30 cases and it was intensely positive within the epithelial islands. In few cases focal singly scattered to very tiny clusters of epithelial elements entrapped amongst the sheets of spindle cells were discernible only after peforming IHC with CK, hence exact characterisation of BSS was achieved, which could be easily missed if only routine H&E sections are studied. EMA was positive within the epithelial islands in 66% of cases, hence in our study EMA was a better marker for epithelial elements when compared to CK positivity (33%). IHC results are summarised in Table-3.Recurence was noted in 4 patients and lung metastasis was seen in one patient.

Table-3: Immunohistochemistry (IHC) results of patient with synovial sarcoma

IHC marker	Done (n)	No. of Positive cases	% Positivity
BCL2	31	31	100%
Vimentin	4	4	100%
EMA	9	6	66%
CK	30	10	33%
S 100	14	4	29%
CD 99	6	-	0%
CD 34	5	-	0%
Desmin	3	-	0%
HMB 5	3	-	0%
SMA	2	-	0%

Several multivariate analyses have shown age of the patient to be an important prognostic predictor. So we have attempted to compare the various clinic opathological features of patients with synovial sarcoma with age group less than 20 years and greater than 20 years age group. On analysis, there was no significant difference in site of the involvment , type of the tumour, tumour charcterstics or immunohistochemical positivity between these two subgroups, however tumour size of <5cm was signficantly more common in age group less than 20 year (p = 0.03) Table-4.

Table-4: Comparison of site, size, type, and tumour characteristics and IHC positivity with age group <20 years and >20 years

	<20 years(n= 17)	> 20 years (n = 25)	p value
Site			
Lower limb	10	15	0.93
Upper limb	5	1	0.062
Back	1	3	0.89
Supraclavicular	0	2	0.65
Lung	0	3	0.38
Mediastinum	1	0	0.84
Retropertioneum	0	1	0.40
Tumour size			
<5 cm	9	4	0.03
5-10 cm	4	11	0.30
10 -20cm	1	8	0.10
>20 cm	2	2	0.68
Type			
Monophasic	14	19	0.91
Bi phasic	2	3	0.98
Poorly differentiated	1	3	0.89
Tumour characterstics			
Hemangiopericytomtous	9	19	0.22
Necrosis	4	11	0.30
Ossification	0	1	0.38

Calcification	3	3	0.95
Myxoid changes	1	2	0.80
Hyaline	5	7	0.92
Rhabdoid	0	0	0.98
Fascicles	4	10	0.33
Pailsading	1	0	0.40
Mitosis	12.11±14.6 (7)	10.24±9.85 (6)	
Immunohistochemistry			
Bcl2	14 (14)	16(16)	1.0
CK	4(12)	5 (18)	1.0
S 100	1 (5)	3(9)	1.0
CD 99	3(4)	5(7)	1.0
Vimentin	2(3)	2(2)	1.0

In this study we have also attempted to find if there was any association of tumour size with mitotic activity. However there was no correlation of tumour size with mitoses (r=0.12, p=0.52). However on further analysis of various histopathological variables with mitoses, tumours with low mitotic index was significantly associated with presence of calcification (p = 0.001) Table-5.

Table-5: Correlation of mitotic index with presence or absence of other tumour characterstics

	Positive **n** **Mitotic index in Mean±SD)**	**Negative** **n** **Mitotic index in Mean±SD)**	**p value**
HPC pattern	28 10.21±9.79	14 12.57±15.37	0.61
Necrosis	15 14.53±16.60	27 9.04±16.60	0.243
Calcification	6 4±1.80	36 12.17±12.47	0.001
Myxoid	3 10.00±10.58	39 11.08±12.12	0.882
Hyaline	12 7.17±6.79	30 12.53±13.19	0.09
Fasciclar pattern	14 11.14±9.662	28 10.93±13.03	0.95

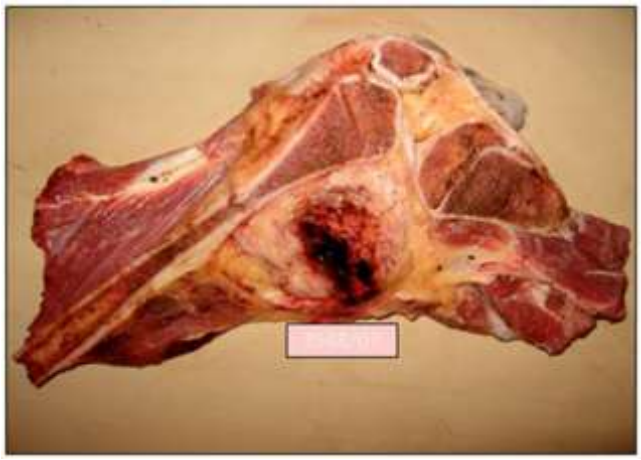

Fig-1: Gross photograph of a case of synovial sarcoma in the lower thigh and popliteal region. The tumour is relatively well circumscribed, fleshy, gray -tan with areas of hemorrhage and necrosis at the centre .

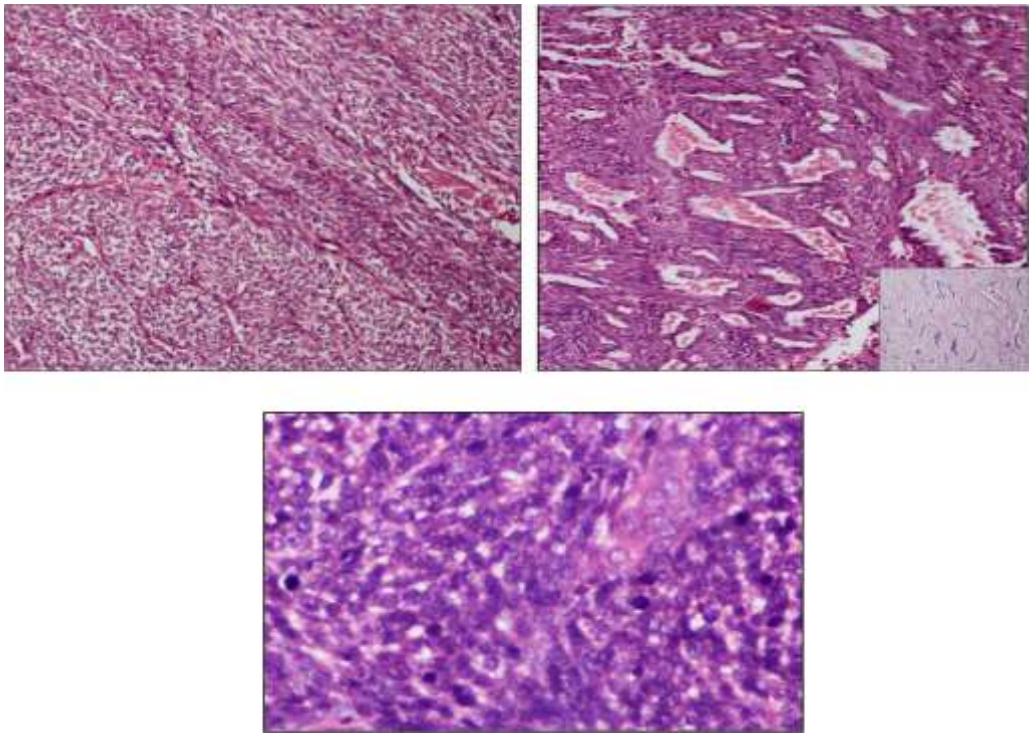

Fig-2: Photomicrographs of histological types of synovial sarcoma: A, Monophasic synovial sarcoma showing spindle cells arranged in well defined fascicles. B, Biphasic synovial sarcoma showing apposition of glandular elements with malignant spindle cells, inset APAS positivity within the glandular elements. C, Poorly differentiated synovial sarcoma showing sheets of cells with round cell morphology and high mitotic activity.

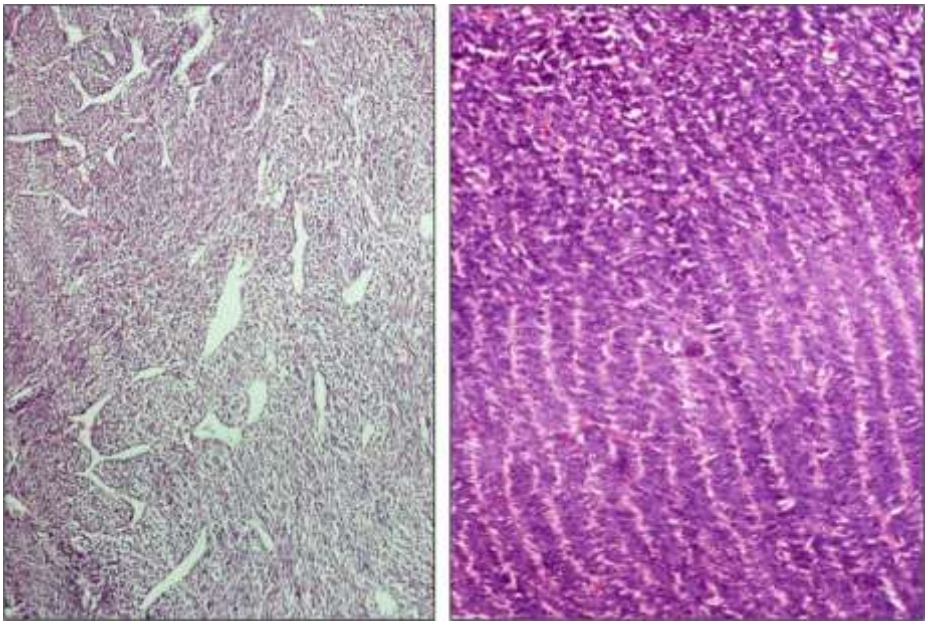

Fig-3: Photomicrographs of monophasic synovial sarcoma showing A,Hemangiopericytomatous pattern. B, palisading pattern

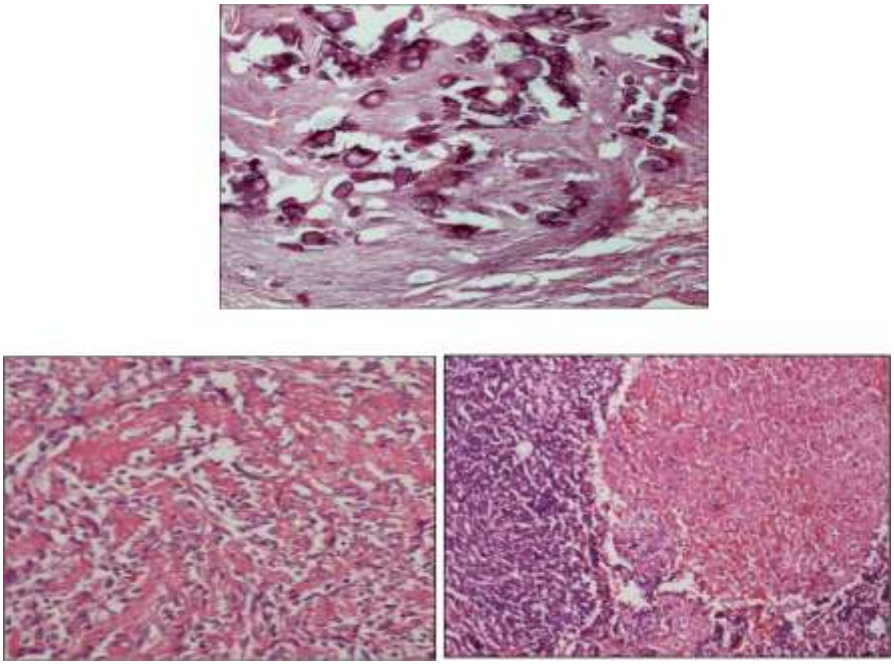

Fig-4: Photomicrographs showing areas of A, Calcification B, Hyalinisation , C, Necrosis

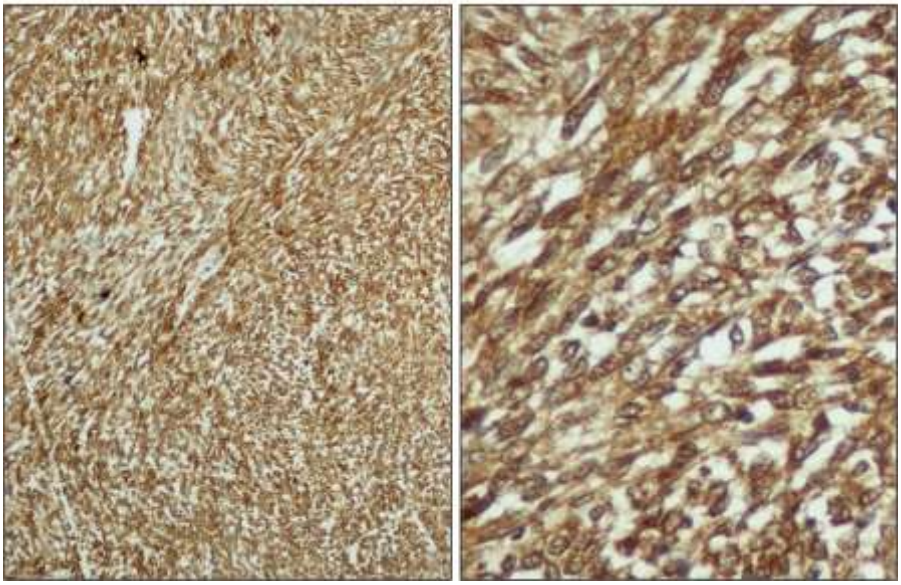

Fig-5: Photomicrographs showing immunohistochemical positivity to Bcl2

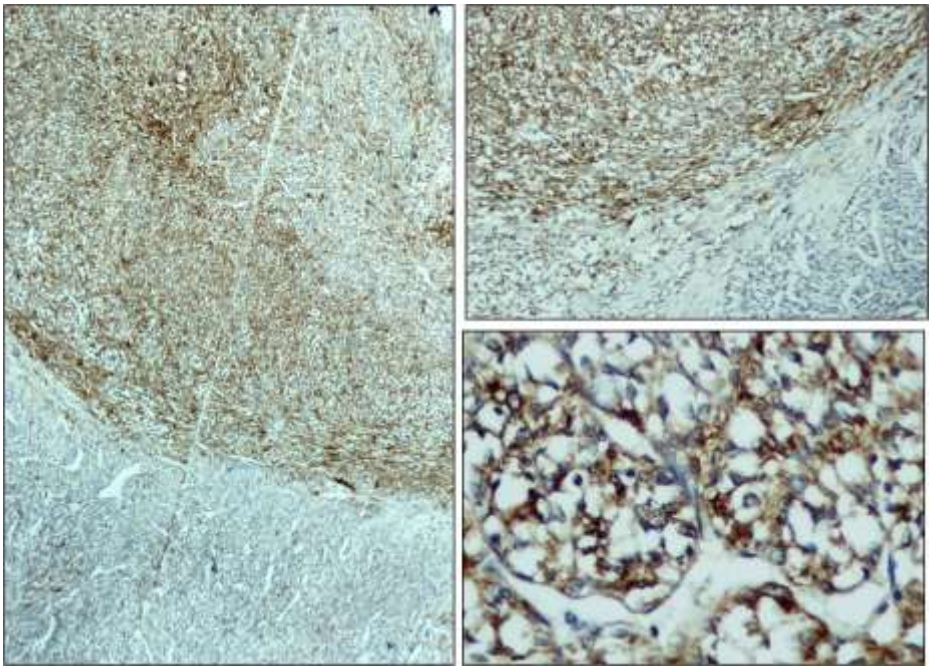

Fig-6: Photomicrographs showing immunohistochemical positivity of epithelial islands to Pan CK in a case of biphasic synovial sarcoma

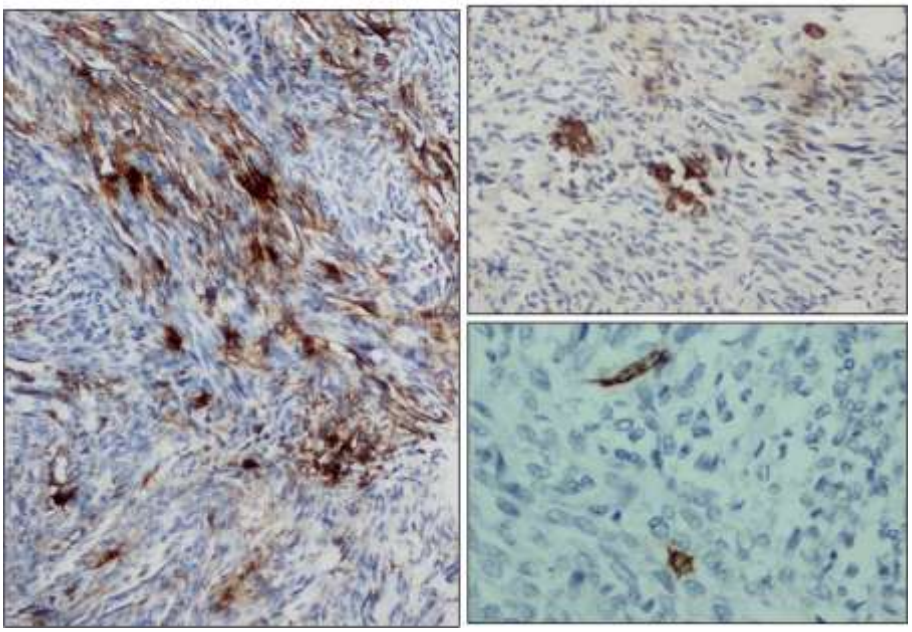

Fig-7: Photomicrographs showing immunohistochemical positivity to EMA

DISCUSSION

Synovial sarcoma is a distinct soft tissue tumour that shows evidence of both mesenchymal and epithelial differentiation, at the light microscopic, immunohistochemical, or ultrastructural level. It has become increasingly important to make a definitive diagnosis of synovial sarcoma because more effective chemotherapeutic agents such as ifosfamide have become available to treat patients with these tumours. Numerous studies have attempted to evaluate both clinical and pathologic features that might be useful in identifying those patients with synovial sarcoma who are more likely to follow an aggressive clinical course. Several prognostic factors, such as age, size, surgical margins, histologic grade, histologic subtype, p53 overexpression, Ki-67 proliferative index, and SYT-SSX fusion type, have been identified [15-19]. However, the relative prognostic value of each of these factors remains controversial. Only large tumor size has been consistently associated with a poor prognosis.

Synovial sarcoma is most prevalent in adolescents and young adults of 15-40 years of age. In this study we found that the majority of patients are of

more than 20 years age group with median age of 26 years. Males (25) were more commonly affected than females (17). In the series by Cadman *et al.*, [20] the median age at the time of operation was 31.3 years, with 83.6% of the patients being between 10 and 50 years. Lewis *et al.*, [16] who had studied various prognostic factors in 112 primary localised synovial sarcomas also found similar results with median age of patients was 35 years. Our patients presented at a relatively young age when compared with the western studies. However when compared with the similar Indian study done by Rekhi *et al*, [21] the median age was almost similar(25 years). The most common site was lower extremity followed by upper extremity which is in concordance with several other studies. However thoracic and retroperitoneal location was also noted in few patients.

The diagnosis of biphasic synovial sarcomas pose no difficulty as they exhibit both spindle and glandular components. But the monophasic fibrous and epithelial types of synovial sarcoma can be easily confused. Monophasic synovial sarcoma can be difficult to distinguish from its histological mimics which include other spindle cell sarcomas such as malignant peripheral nerve sheath tumours, cellular schwannoma, solitary fibrous tumour, fibrosarcoma and leiomyosarcoma. Poorly differentiated synovial sarcomas closely mimic other round cell tumours which include Ewings/ PNET, myxoid chondrosarcoma and various other tumours with predominant round cell and undifferentiated morphology. The specific diagnosis and subtyping of synovial sarcomas is further complicated in small biopsy samples in which epithelial elements may be spase or may not be sampled. Hence histomorphology must be coupled with carefully selected IHC panel to arrive at a specific diagnosis and to rule out histological mimics. Monophasic histology was the most common type (83.3%) in our study followed by biphasic (11.9%) and the rest were poorly differentiated. Hemangiopericytomas pattern was the most common pattern noted in 67% of patients followed by fascicular pattern. Palmerini *et al*., [22] has found more number of patients with monophasic histology similar to our study (60% vs 83.3%). Though there are array of markers for synovial sarcomas, no single marker is considered specific for its diagnosis. A combination of markers which can delineate mesenchymal and epithelial differentiation are used. In our study the most sensitive IHC marker was BCL2 which was positive in almost all the performed cases. In our study EMA was more sensitive (66%) in staining the focal tiny clusters or singly scattered epithelial elements when compared to CK (33%). In the study conducted by Jagdis *et al*., [23] Bcl2 and cytokeratin was positive in 96.8% and 70.6% respectively.

There are always financial and technical constraints in using several IHC markers and further confirmation with translocation studies in Indian settings. The search for a single specific marker for synovial sarcomas are on the rise and one such marker unravelled through gene expression profiling studies is TLE1. There are various studies highlighting its utility as a fairly sensitive and specific when compared to other commonly used markers.

Several large studies of synovial sarcoma have found that increasing age, particularly age of at least 15 years, is predictive of a more aggressive clinical course. In the study done by Lewis et al in which multiple prognostic factors were studied, they were unable to show any statistical differences affecting outcome between patients 25 years of age or younger and those older than 25 years in recurrence or survival. However in our study low tumour size was significantly associated in less than 20 year age group and the presence of mitosis was significantly lower in the presence of calcification.

Other factors significantly associated with worse prognosis in multivariable analysis includes large tumour size (>5 cm) and monophasic histology [24-28]. However in our study tumour size did not correlate with mitotic index which is also considered as an important prognostic indicator. So large tumour size and mitotic activity could be regarded as twoindependant prognostic variables. Adults had higher tumour size than younger cohort of age So it can be extrapolated that such cases may have more recurrences due to incomplete surgical resection owing to their large size, thereby poor prognosis in older age group due to the well known aggressive behaviour of recurrent tumours. In our study recurrence was noted in 4 patients, all are adults (>20 years).

Our study concludes that Synovial sarcomas are most commonly seen in adults and majority affect lower extremities and are of monophasic type. The interesting observation is that of younger age of onset among adults compared to western study. Adults have high tumour size so is the prognosis and BCL2 is the consistent IHC marker. The presence of calcfication may be associated with good prognosis.

The potential drawbacks of the study includes retrospective data, small sample size for appropriate comparison among the groups, IHC panel was not consistent and all markers were not done in all cases. Translocation studies not performed in any of the case.

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