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Biphasic synovial sarcoma – A ten year experience with molecular profile and clinical outcome

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Abstract

Context: Synovial sarcoma is one of the commonly encountered spindle cell sarcomas of soft tissue. However, Biphasic synovial sarcoma (BSS) is a rare subtype of synovial sarcoma with limited literature on clinical profile, molecular characteristics and survival outcome.
Aims: We propose to describe the immuno – morphology, clinical features, molecular profile and outcome of patients with BSS.
Settings and Design: This retrospective study included 13 cases of BSS, 3.2% of all synovial sarcomas diagnosed over 10 years in our institute. The clinico-pathological features were studied in detail and immunohistochemistry for TLE-1, EMA, CD34, CD99 and S100 was done. Real time PCR and DNA sequencing for the common translocations (SYT-SSX1/ SYT-SSX2) were performed.
Statistical analysis used: Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp).
Results: BSS was most commonly seen in young, the most common site being soft tissue of extremities (92.3%). 53.8% of patients presented at Enneking stage IIB. The FNCLCC grade varied between 2(46.2%) and 3(53.8%). All cases were positive for EMA and TLE-1; negative for CD34 and S100. Ten of the eleven (90.9%) patients tested had SYT-SSX1 translocation. Over a period of 8 to 46 months, 53.8% cases were alive and well with no evidence of disease; three had (30%) recurred, one (10%) had lung metastasis and one (10%) died.
Conclusions: BSS is most common in extremities. The immunohistochemical profile matches that of monophasic synovial sarcoma. FNCLCC grade is 2 to 3; however the grade does not correlate with clinical outcome. Most cases show SYT-SSX1 translocation. 53.8% cases were alive and well after a mean follow up of 20 months.
Keywords: Biphasic, follow-up, immunoprofile, SYT-SSX1, synovial sarcoma.
Key Messages: Biphasic synovial sarcoma has the same immunoprofile as the monophasic subtype. All patients who tested positive had SYT-SSX1 translocation. More than 50% of patients were alive and well after 20 months.

Introduction

Synovial sarcoma is a mesenchymal tumour with variable degree of epithelial differentiation and accounts for around 6% of all soft tissue sarcomas [1]. It is classified by the WHO as malignant neoplasm of uncertain origin [2]. Morphologically, there are two variants of synovial sarcoma based on the presence or absence of epithelial differentiation – the monophasic and the biphasic subtypes [2]. Biphasic synovial sarcoma has two distinct components - epithelial and mesenchymal/spindle cell. The epithelial component takes the form of glandular structures or nests of cuboidal to columnar cells. The spindle cell component is arranged in sheets and interlacing fascicles of fairly uniform cells. Malignant peripheral nerve sheath tumour, which is often a close clinical and histological differential, can also rarely exhibit this biphasic pattern.

Although much literature has been published on monophasic tumours, as biphasic synovial sarcoma is a rarer entity with a relative lack of published data, the clinical profile, prognostication and the survival outcome for this group have not been clearly defined.

Immunohistochemically, these tumours are positive for CD99, EMA and TLE-1, the latter although non-specific, is highly useful [3]. EMA is an epithelial marker, expressed more widely than the keratins and is used in the diagnosis of biphasic synovial sarcoma [4]. Confirmatory diagnosis is based on the detection of specific t(X;18) translocation, where the SS18 gene (also called SYT) on chromosome 18 fuses with the SSX gene (SSX1/SSX2/SSX4) on chromosome X, by break-apart FISH (fluorescence in situ hybridisation) or RT-PCR (reverse-transcriptase polymerase chain reaction). The most common translocation is the SYT-SSX1 fusion followed by the SYT-SSX2 fusion. The biphasic variant of synovial sarcoma usually harbours SYT-SSX1 fusion, while the monophasic tumours can have either of the two translocations. Very rarely, these tumours can have SYT-SSX4 translocation [5]. The overall prognosis of synovial sarcoma is variable and factors including tumour stage at diagnosis, size, histological subtype, histological grade etc have been shown to be of major prognostic importance [2,6-8]. The biphasic subtype of synovial sarcoma is a rare entity with only a limited number of cases described in literature. We have diagnosed 13 cases of biphasic synovial sarcoma over a period of 10 years (January 2007 – December 2016) in our institution(3.2% of all cases of SS), and this study proposes to document the

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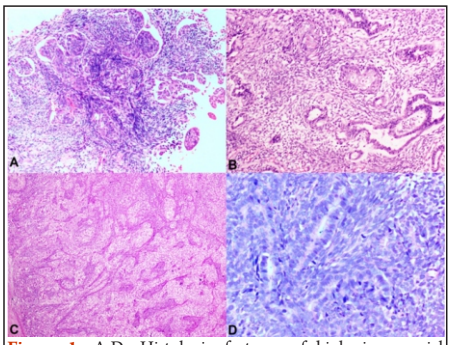

Figure 1: A-D: Histologic features of biphasic synovial sarcoma, (H&E stain) A, Biphasic tumour with epithelial and spindle components, trucut biopsy, 100X. B, Epithelial and spindle components, resection, 200X. C, Epithelial component arranged in cords and interwoven trabeculae, 100X. D, Glandular areas with mitosis, 200X.

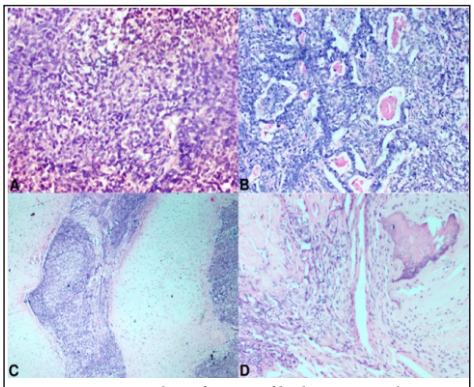

Figure 2: A-D: Histologic features of biphasic synovial sarcoma, (H&E stain) A, Round cell areas, 200X. B, PASD positive intraluminal secretions, 100X. C, Extensive cartilaginous metaplasia, 40X. D, Extensive osseous metaplasia, 20X.

molecular characteristics, clinical features, immunohistological profile and outcome of patients with biphasic synovial sarcoma, for a better understanding of these tumours.

Subjects and Methods

A total of 472 cases of synovial sarcoma were diagnosed in the Department of Pathology from 01/01/2007 to 31/12/2016. Of these, 13 (i.e., 3.2%) cases were diagnosed to be of the biphasic subtype. The slides and blocks and clinical profile of these 13 cases were retrieved from the archives. Restaining of the H&E sections and immunohistochemistry for additional markers were done wherever required.

Clinical and Pathological features

Demographic information, presenting complaints and clinical follow up were obtained from the electronic records. Slides of all the cases were reviewed by two pathologists in corroboration with the immunohistochemical markers. Microscopic diagnosis of biphasic synovial sarcoma was made on H&E slides if the tumour exhibited spindle and epithelial components. The following parameters were then analyzed in detail – architectural pattern (fascicles, sheets and whorls - spindle component; nests, cords, islands, glandular, papillary and alveolar – epithelial component); nuclear pleomorphism (mild, moderate or marked); stromal characteristics (hemangiopericytoma like vascular pattern, ropy collagen, calcification, hyalinization, myxoid change, presence or absence of mast cells); mitotic activity per 10 high power fields (/10 hpf) and necrosis. The tumour was graded according to the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system taking the following parameters into account: tumour differentiation, mitotic activity and necrosis [6-9]. For the resected tumours, the gross appearance of the tumour and size were noted. The distance of the tumour from the surgical resection margin was measured microscopically and documented as R1 (margin involved/ ≤0.1cm) and R0 (>0.1cm) [10].

Immunohistochemistry

Immunohistochemistry (IHC) for TLE-1(clone: M/101, Santa Cruz Biotechnology, USA), EMA (clone: E29, DAKO, Denmark), CD34 (clone: Q-bend10, DAKO, Denmark), CD99 (clone: 12E7, DAKO, Denmark) and S100 (polyclonal, DAKO, Denmark) was done on all cases using the automated stainer Ventana benchmark XT. All tumours were evaluated as positive or negative for the IHC markers.

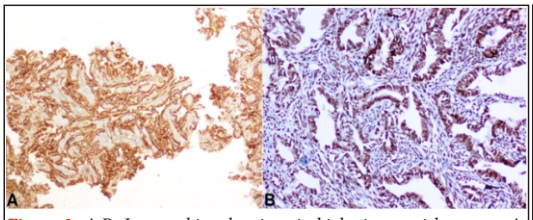

Figure 3: A-B: Immunohistochemistry in biphasic synovial sarcoma A, EMA staining, 100X. B, TLE-1 staining, 200X.

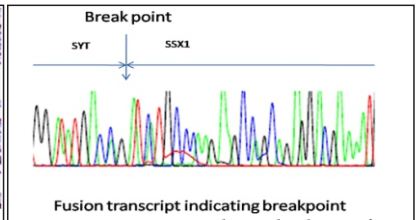

Figure 4: Fusion transcript indicating breakpoint of SYT-SSX1

Real-time PCR and sequencing

All cases underwent additional molecular testing by PCR for detection of the common translocations (SYT-SSX1/ SYT-SSX2). The PCR did not include probes for SYT-SSX4 translocation. Total RNA (Recoverall Total Nucleic Acid Isolation kit - Ambion, USA) was extracted using 3-4 5µ sections from the FFPE blocks. Briefly, the tissue was digested for 3-4 hours in proteinase containing buffer, in a rocking water bath and eventually extracted using the spin columns. Total RNA in the extract was estimated using the nanodrop (Nanodrop technologies, USA) and quality was assessed using a 1% agarose gel, looking for intact 18S and 28S ribosomal bands. Extracted RNA was converted to cDNA using high capacity cDNA conversion kit (Applied Biosystems, USA). The reverse transcription was performed as follows: 160C for 30 min, 420C for 30 min, 850C for 5 min to yield cDNA in a 15µl reaction volume. After the cDNA conversion, PCR was performed using the following GAPDH primers to confirm the cDNA was amplifiable: GAPDH FTTGCCATCAATGACCCCTTCAGAPD H RCGCCCCACTTGATTTTGGA. Real time PCR was performed using SYT-SSX1 and SYT-SSX2 probe mixes cat no. Hs03024820_ft and Hs03024398_ft respectively. The amplification was carried out in the 7500 real-time PCR machine. The samples that were positive for translocation were then sequenced to demonstrate breakpoint [11].The following primers were used for the sequencing: SYT consensus F5'AGACCAACACAGCCTGGACCA 3', SSX 1 R5'GGTGCAGTTGTTTCCCATCG3', SSX 2 R 5'GGGCACAGCTCTTTCCCATCA 3'. All reactions were carried in 25 µl volume. The following thermal cycling profile was used: 950C for 8 min, 950C for 30 secs, optimized anneal for 30 secs, 720C for 1 min and final extension of 720C for 10 min. The PCR product was detected using a 1.5% agarose gel. Sequencing was performed on an automated DNA sequencer (ABI PRISM 310 genetic analyzer) using the ABI PRISM Big Dye Terminator Cycle Sequencing

Table 1: Clinical features of 13 cases of Biphasic synovial sarcoma.

Case	Age	Sex	Presentation	Pain	Site	Enneking stage
1*	49	M	Swelling	No	Hypopharynx	NA
2	22	M	Swelling	No	Ankle	IIB
3	70	F	Swelling	NA	Thigh	NA
4	16	M	Swelling	Yes	Foot	IIB
5	22	M	Swelling	NA	Foot	IIB
6	47	F	Swelling	Yes	Thigh	IIB
7*	40	M	Swelling	Yes	Knee	NA
8	50	F	Swelling	Yes	Knee	IIB
9	22	F	Swelling	NA	Calf	IIA
10	18	F	Swelling	No	Thigh	IIB
11	50	M	Swelling	NA	Thigh	IIA
12	16	M	Swelling	NA	Tibia	IIB
13	22	F	Swelling	Yes	Thigh	II B

Table 2: Gross features and clinical follow up of 13 cases of biphasic synovial sarcoma

Case	Gross size (in cms)	Biopsy / Resection	Margin status	Chemo-therapy	Radiation	Recurrence	Status at last follow up and duration
1	4.5	R	R1	NA	NA	NA	LFU
2	4.5	R	R0	No	60Gy/30 Fr	Yes	Alive with NED, 46 months
3	NA	B	-	No	No	No	LFU
4	5	R	R0	Yes	66Gy/ 33 Fr	No	Alive with NED,27months
5	NA	B	-	Yes	No	No	Alive with NED,25months
6	10	B+R	R1	No	No	No	Died, 3 months
7	7.8	R	R1	NA	NA	NA	LFU
8	NA	B	-	No	No	No	Alive with NED, 11 months
9	7.4	R	R1	No	66Gy/ 33 Fr	No	Alive with NED, 10 months
10	24	B+R	R1	No	66Gy/ 33 Fr	Yes	Alive with NED, 9 months
11	14.5	B+R	R1	No	66Gy/ 33 Fr	Yes	Alive with lung metastasis, 8 months
12	7	B+R	R1	Yes	On RT	No	On treatment
13	17	B+R	R0	No	60Gy/30 Fr	No	On treatment

Ready Reaction Kit (Applied Bio-systems, Foster City, California, USA).

Statistical Methods

Statistical analysis was carried out using the Statistical Package for Social Services (SPSS) software Version 21.0 (Armonk, NY: IBM Corp). For continuous data, the descriptive statistics such as mean, SD, median, IQR and range were presented. For categorical data, the number and percentage were presented.

Results

Thirteen cases of biphasic synovial sarcoma were diagnosed in a 10 year period from January 2007 to December 2016. This included three small biopsies, five resections and five cases with both small biopsy and resection. Two cases (no 1 & 7) were referred from an outside hospital and the follow up details are not available while PCR was performed on all but one case (no 7) that did not have adequate tissue(Table1) Mean age (range) of biphasic synovial sarcoma in our population was 33(16-70) years with a male to female ratio of 1:1 (n=13). All patients presented with swelling; pain was present in only 5/13 (38.5%) patients. 12/13 cases (92.3%) were tumours in the soft tissue, of which 11 cases occurred in extremities and one was in the hypopharynx. One patient, a 16 year old male had multiple lesions in the tibia and was diagnosed to have intra-osseous biphasic synovial sarcoma. Thigh was the most common site of involvement, seen in 5/13 (38.5%) cases. Enneking staging was available in 10/13 patients. The imaging details were not available for 3 cases (2 cases referred from another centre and case no 3 had no investigations or follow up at our hospital). More than half of our patients (53.8%, n=7) belonged to Enneking stage IIB (Table 1). Grossly the tumours ranged in size from 4.5 to 24cm with an average size of 10.2cm (n=10). Of the 10 patients who underwent resection, surgical resection margin was involved by tumour in 7(70%) cases and negative in 3 (30%) cases. Following surgery, radiotherapy was delivered post operatively(n=7) within 6 weeks from the date of surgery by conventional technique (either by opposed lateral portals or AP-PA), to a dose of 60 to 66Gy in 30 to 33 fractions, 2Gy per day and 5 days a week over 6 to 6.5 weeks. Adjuvant chemotherapy was given for three patients, of which one patient received Doxorubicin 25mg/m2, Mesna 600mg/m2 and Ifosfamide 1800mg/m2and the other received 4 cycles of Doxorubicin. The third patient was treated at another centre and details are not available. Follow up was done once in 3 to 4 months in the first year and once in 6 months thereafter. Chest x-ray or CT thorax was done during follow up visits along with local examination and imaging of the primary tumour site as required and status at last follow up recorded (Table 2). Microscopically, the epithelial component was arranged in nests, cords, tubules and glandular structures (Fig 1C) composed of polygonal cells with mild (3 cases) to moderate (10 cases) pleomorphism of the nuclei. Two cases (case 6 & 12) had well defined glandular structures with intra-luminal eosinophilic secretions (Fig 2A), which were periodic acid Schiff (PAS) positive and resistant to diastase. Average mitosis/10hpf was 10 and necrosis was seen in 9 tumours, of which 7 (77.7%) had <50% and 2 (22.3%) had >50% necrosis. Thus, 6/13 (46.2%) tumours belonged to FNCLCC grade 2, while 7/13 (53.8%) belonged to grade 3 (Table 3). Nuclear pleomorphism in the spindle cells was mild in 11 cases (84.6%) and moderate in only 2 cases (16.4%). The stromal changes seen in our study included myxoid/ oedematous

change in 7/13 (53.8%) cases and collagen bundles were seen in one case. Calcification with cartilaginous and osseous metaplasia (Fig 2B) was seen in one case. Hemangiopericytoma like vascular pattern was seen in 6 (46.2%) cases, bundles of collagen in one case (case 11) and aggregates of mast cells in one case (case 2). The results of immunohistochemistry are summarised in table 4. Eleven of the 13 cases included in the study were tested by PCR. One sample did not have adequate tissue and in another, the cDNA was not amplifiable. Ten (90.9%) of the 11 samples tested were positive for SYT-SSX1 translocation by PCR and they were also confirmed by demonstrating the breakpoint by sequencing (Fig 3). Three patients (cases 2, 5 & 11) had undergone surgery elsewhere before presenting to our hospital and hence were diagnosed as recurrent tumours. Follow up ranged from 8 to 46 months with a mean follow up of 20 months. At follow up, 6/13 (46.2%) cases were alive and well with no evidence of disease while one patient died and three cases (cases 1, 3 & 7) were lost to follow up. Two patients have been recently started on chemotherapy and doing well; however they are not included in the analysis of survival. Three of our patients had local recurrence and one patient developed metastasis in the lung and is currently on palliation chemotherapy.

Table 3: FNLCC grading

Case	FNCLCC grading			
	Mitosis/ 10 hpf (Score)	Necrosis (Score)	Total score	Histologic grade
1	5 (1)	<50% (1)	5	2
2[11]	3 (1)	>50% (2)	6	3
3	0 (1)	No (0)	4	2
4	8 (1)	No (0)	4	2
5	0-9 (1)	<50% (1)	5	2
6	28 (3)	<50% (1)	7	3
7	15 (2)	<50% (1)	6	3
8	0-9 (1)	No (0)	4	2
9	10 (2)	<50% (1)	6	3
10	9 (1)	>50% (2)	6	3
11	5 (1)	<50% (1)	5	2
12	>20 (3)	No (0)	6	3
13	22 (3)	<50% (1)	7	3

Table 4: Immunohistochemistry in 13 cases of biphasic synovial sarcoma

Case	TLE-1	EMA	CD34	CD99	S100
1	Focal weak +	+	-	+	-
2	+	+	-	+	Focal +
3	+	+	-	-	-
4	+	+	-	+	-
5	+	+	-	+	-
6	+	+	-	+	-
7	+	+	-	+	-
8	+	+	-	+	Focal +
9	+	+	-	+	-
10	+	+	-	-	-
11	+	+	-	+	-
12	+	+	-	-	-
13	+	+	-	+	-

Discussion

Synovial sarcoma is a rare mesenchymal tumour occurring in young adults in the age group of 15-40 years [5]. The line of differentiation of this tumour is not known with certainty and is classified under tumours of uncertain differentiation. [2] The name synovial sarcoma is a misnomer since this tumour does not arise from or differentiate towards synovial membrane. Synovial sarcoma has four different microscopic subtypes – the biphasic, monophasic fibrous, monophasic epithelial and poorly differentiated. Biphasic synovial sarcoma (BSS) is very rare with only a few cases reported in literature. In this study, we have described the clinical, microscopic, immunohistochemical features and the molecular translocation in 13 cases of biphasic synovial sarcoma. In our institution, BSS accounts for 3.2% of all cases of SS over a period of 10 years.

Literature and isolated data on biphasic synovial sarcoma is very limited and hence our study could be compared only with the few available retrospective multi-institutional studies which include all the histological subtypes. Synovial sarcomas arise in close proximity to articular surfaces, the most common site being the soft tissue around knee joint and thigh [4]. Other common sites include head and neck, trunk and mediastinum [5,12]. In our study, 92% of tumours occurred in soft tissue of the thigh, while one was a hypopharyngeal mass and another was multifocal intra-osseous BSS of tibia. Although uncommon, biphasic synovial sarcoma has been documented in hypopharynx, oral cavity, heart, prostate, stomach and abdominal wall [13-18]. Many patients present with pain as a distinctive symptom [4], however, all cases in our study presented with swelling/ mass lesion and pain was present in only 38.5% of our cases. Multifocal intra-osseous BSS is also rare, the closest differential being adamantinoma in the tibia. Both entities can be positive for epithelial markers; however, our case was also strongly positive for TLE-1, favouring a diagnosis of BSS over adamantinoma. Further investigation by PCR analysis also revealed translocation for SYT-SSX1, thus confirming the diagnosis. Microscopically, biphasic synovial sarcoma is classically composed of epithelial and spindle cell components (Fig 1A&B). Epithelial component was identifiable on the H&E sections as nests, cords and tubules lined by cuboidal or columnar cells with well defined cell borders in all cases, while two cases in our study had well formed glandular structures with bright eosinophilic PASD positive intraluminal secretion. The spindle cell component was arranged in sheets of plump cells with elongated nuclei and scant cytoplasm. Nuclear pleomorphism in the spindle cell component was mild (84.6%) as compared to moderate pleomorphism observed in the epithelial component in majority (75%) of our cases. Mitosis occur in both epithelial and spindle cells, but very high mitotic counts are usually seen in poorly differentiated areas [5]. In our series, the mitotic count ranged from 0 – 28/10hpf with an average mitosis of 10/10hpf and mitotic figures were seen in the spindle cell areas also. Poorly differentiated synovial sarcoma accounts for 5-10% cases, commonly seen in the elderly and is associated with an adverse outcome. One case in our series of BSS, a 22 year old female had foci of poorly differentiated areas (Fig 1D) also, composed of small round cells displaying scant cytoplasm and hyperchromatic nuclei with mitosis upto 22/10hpf and she is currently on treatment. The stromal changes seen in our study included myxoid/ oedematous change in 58% cases and collagen bundles were seen in one case. Although calcification with or without ossification is described in 20% cases [5], this feature was seen in only one case in this study. The presence of stromal mast cells is another prominent feature, however only one case in this study showed mast cells in the stroma. The tumours have a varied vascularity with branching thin

walled haemangiopericytoma like vessels. This feature was seen in 46% tumours in our series of BSS. Some studies regard the grade as the most important parameter, others consider all synovial sarcomas as high grade and do not differentiate between grade 2 and grade 3 tumours [8,11]. However, there is no clear data on the significance of histologic grade as a prognostic indicator. In our study, the histologic grade was variable between 2 and 3. Six of the 10 patients with follow up data in our study, were FNCLCC grade 3 and 4 turned out to be grade 2. Of the 6 patients with FNCLCC grade 3, two patients recurred and one patient died while 3 patients are doing well with no evidence of disease. However, one of the four patients with grade 2 tumour has also recurred and has metastasized to the lung, while three other patients with garde 2 are doing well with no evidence of disease. In the previous studies, patients with histologic grade 3 have been found to have decreased overall survival, recurrence, distant metastasis with a significantly poor prognosis [8]. Our study has not shown definite correlation. However, our numbers are too small for a significant statistical analysis. The immunoprofile of synovial sarcoma (both monophasic and biphasic) is characteristic that they stain for epithelial antigens as well as for other markers like CD99, Bcl2 and TLE-1. Immunostaining for EMA is more sensitive and specific than cytokeratins and is a valuable diagnostic marker in monophasic synovial sarcoma [4-5]. In our study, all BSS also showed scattered to diffuse positivity for EMA (Fig 2C). Although S-100 protein can be positive in 30% of synovial sarcomas [19], this feature was seen only focally in two tumours in our study. In cases that are positive for S-100 protein, EMA can sometimes be helpful in distinction from MPNST [4]. EMA/CK7 staining for synovial sarcoma and S100/nestin stains for MPNST are considered specific [20]. HMGA2 and H3K27ME3 are also relatively recent markers with a high specificity for MPNST [21,22]. As previously described, CD99 positivity was seen in (75%) of cases in this study and this does not help in distinction from Ewing sarcoma [23,24]. However, CD99 positivity poses a diagnostic difficulty only in poorly differentiated SS; the classical biphasic pattern will help in the diagnosis of BSS. Bcl2 is another marker which is expressed in synovial sarcomas, however it is very non-specific. CD34 positivity in synovial sarcoma is extremely rare (negative in all our cases) and thus CD34 can be used to differentiate synovial sarcoma from solitary fibrous tumour [4]. TLE-1 (Transducin-Like Enhancer of split) is a relatively recently introduced immunohistochemical marker, reported in approximately 97% of cases with moderate to strong positivity, although it is non-specific [3]. The consistent strong and diffuse expression of TLE-1 in synovial sarcoma (positive in all our cases in both the epithelial and glandular components) (Fig 2D) and the very low to absent expression in malignant peripheral nerve sheath tumour is very valuable in the diagnosis. Although a specific immunopanel has not been described for BSS in literature, this study highlights the utility of the same immunopanel recommended for monophasic SS; positive for EMA and TLE-1; negative for CD34 and S-100. Molecular diagnosis is considered the gold standard in diagnosis of SS. In our study, PCR could be done on 11/13 cases of BSS, of which 10 cases showed the characteristic t(X,18) translocation. All these showed SYT-SSX1 translocation as opposed to the monophasic variant which can show SYT-SSX2 or SSX1translocations, as described previously [4,5]. Though speculative, the case that was negative for the translocation could have been due to an altered breakpoint that might not be picked up by the primers used or could have partnered with altogether a new region making it impossible to pick up using the current set of primers. There was no association between the type of translocation and survival of the patients in our study similar to other studies [11]. In summary, we report 13 cases of biphasic SS, 11 of them occurring in the extremities and 1 in the hypopharynx. Most of these cases belonged to Enneking stage IIB. The statistical correlation between the grade of tumor and patient outcome did not provide any tangible results perhaps due to small number of cases included. From this study, we infer that the same immunopanel used to diagnose monophasic SS is effective in the diagnosis of biphasic SS. There was no association between the type of translocation and survival of the patients in our study. After a mean follow up of 20 months, 53.8% cases in our series were alive and well with no evidence of disease. This study is one of the few from South East Asia, detailing the clinical profile, imunohistochemistry, molecular diagnosis and disease outcome of biphasic synovial sarcoma. Because of the small numbers, statistical analysis to assess prognostic factors like size, site, stage at presentation and age could not be performed. More studies with larger number of patients are required to better understand the biology of these biphasic tumours.

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