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# ORIGINAL ARTICLE

## Primary pulmonary synovial sarcoma: A clinicopathological study of 22 cases

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*Abstract*

*Introduction:* Primary pulmonary synovial sarcoma (PPSS) is a rare mesenchymal tumour with characteristic translocation SS18-SSX1/2/rarely 4 fusion transcripts, and presents most often in adolescents and young adults. According to the World Health Organization (WHO) classification, synovial sarcoma is a malignant tumour of uncertain differentiation. Aims: To present a case series of PPSS with clinical, pathological and molecular analysis at a rare primary site. Setting and design: Retrospective study conducted in a tertiary care hospital. *Materials and Methods:* Twenty-two cases of PPSSs were retrieved from electronic database between January 2009 to December 2018. Metastatic tumours from soft tissue primaries were excluded. Immunohistochemistry (IHC) and reverse transcription polymerase chain reaction (RT-PCR) were performed. Statistical analysis was performed using Mann-Whitney non-parametric test. *Results:* Among 22 patients, the male-female ratio was 3.4:1 and the median age was 31.5 years. The tumours were classified as monophasic (90.9%) and biphasic (9.1%) subtypes and graded as grade 2(77.3%) and grade 3(22.7%). IHC demonstrated expression of TLE1 (17/17 cases), Bcl-2 (7/8 cases), focal EMA (16/17 cases), CD99 (10/11 cases), focal pancytokeratin (8/12 cases) and CD56 (14/14 cases). The fusion transcripts included SYT-SSX1(4/11, 36.4%) and SYT-SSX2 (2/11, 18.2%). The remaining five cases were negative for SS18 rearrangement by RT-PCR. Only 8 patients had localised tumour. Surgical excision was performed in 5 patients. The median follow-up period was 6 months and 21 days. *Conclusions:* Monophasic SS was the most common subtype. Small core biopsies pose a diagnostic challenge, in such a scenario, a combination of clinical, histomorphological, immunomarkers and genetic studies help confirm the diagnosis of PPSS.

*Keywords:* mesenchymal tumour, prognosis, pulmonary, synovial sarcoma, SYT-SSX fusion transcript

### INTRODUCTION

Synovial sarcoma (SS) is a rare aggressive mesenchymal tumour accounting for nearly 10% of all soft tissue sarcomas involving predominantly soft tissues near the joints of extremities of young adults with slight male predominance. Primary pulmonary/ pleuropulmonary synovial sarcoma (PPSS) is similar to the soft tissue SS but arises from the lung parenchyma, tracheobronchial tree, pulmonary artery and pleura mainly (genuine PPSS) and comprises 0.1%-0.5% of all lung neoplasms.[1-3] It may also include SSs that arise from the chest wall, heart, mediastinum and hemithorax.[2,3] Primary intrathoracic SSs, as well as Primary pleuropulmonary and mediastinal SSs (PPMSSs), are the other terms used for the same anatomic subset of SSs which loosely encompass the above-mentioned regions.[3-5]

There are two major histological subtypes of SS: monophasic (spindle or epithelial) and biphasic. Both subtypes can show poorly differentiated areas.[6-9] Metastasis from soft tissue sites must be excluded before considering the diagnosis of PPSS. A combination of clinical, histological, immunohistochemical and cytogenetic findings aid in confirming the diagnosis at rare sites.[10]

Most PPSSs harbour the translocation t(X;18) (p11.2; q11.2), noted in 95% of cases. One

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of the SYT (synovial tumour) gene, SYT4 on chromosome 18 gets fused to either SSX1, SSX2 or very rarely SSX4 (synovial sarcoma X), located on the X chromosome. This translocation produces a chimeric transcriptional activator protein.[11]

The prognosis of SS is variable and depends on various factors including tumour stage at diagnosis, size, histological subtype, mitosis and poorly differentiated areas.[11,12]

Primary SSs of the pleuropulmonary region are rare and very few studies have been published, hence the following retrospective study was done to assess its clinicopathological, immunohistochemical and molecular features at rare primary sites.

## MATERIALS AND METHODS

Twenty-two cases of PPSSs were retrieved from the pathology electronic database using keyword searches, at the Department of General Pathology, Tertiary care hospital from January 2009 to December 2018. Among the 22 cases, five were lobectomy/ surgical excision specimens and remaining were image-guided core biopsies.

The study was approved by the institutional review board (IRB No.11596). The clinical details and follow-up information of each patient were obtained from the hospital medical records. All the archived slides (H&E and immunohistochemistry) were reviewed and wherever necessary fresh slides were prepared. The diagnosis of PPSS was considered only in the absence of extrapulmonary/extra-thoracic soft tissue synovial sarcoma at a distant site, absence of synchronous synovial sarcoma at a distant site and positive radiological evidence of tumour in the pulmonary or intrathoracic region.

*Classification and grading of Synovial Sarcoma*
All 22 cases of SS were classified as either monophasic, biphasic or poorly differentiated subtypes. Poorly differentiated areas were defined by the presence of in part or entirely of densely cellular proliferation of primitive round to spindled cells displaying severe nuclear atypia, necrosis and high mitotic activity (> 15/10 HPF) or large epithelioid cells with prominent nucleoli or epithelioid cells with rhabdoid change.[6-9] The French Federation of Cancer Centers Sarcoma Group grading system (FNCLCC) was used to grade synovial sarcoma.[13]

*Immunohistochemistry (IHC)*
The IHC archival slides that were reviewed had been carried out using the Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ, USA). Details of primary antibodies used for IHC were TLE-1 [M-101, Sigma (concentrated)], BCL-2 [124, Dako (concentrated)], Epithelial membrane antigen (EMA) [E29, Dako (concentrated)], CD99 [12E7, Dako (1:50)], CD56 [123C3, Dako (1:50)], Pancytokeratin(Pan-CK) [AE1/ AE3, Dako (concentrated)], CD34 [Q-bend-10, Dako (concentrated)], smooth-muscle actin (SMA) [1A4, Dako (concentrated)], desmin [D33, Dako (concentrated)], vimentin [V9, Dako (concentrated)], myogenin [F5D, Biosb (concentrated)], OCT3/4 [NINK, Dako (1:50)], STAT6 [EP325, PathnSitu (concentrated)], calretinin [DAK-Calret 1, Dako (1:100)], synaptophysin [SP11, Ventana (concentrated)] and h-caldesmon [H/CD, Dako (concentrated)]. Appropriate positive controls were included for each antibody throughout the study. The stain was considered to be positive if the tumour cells showed specific cytoplasmic membrane and/ or nuclear staining for the particular antibody.

*Real time and Reverse transcription polymerase chain reaction (RT-PCR)*
Molecular studies were performed on eleven cases (11/22 cases) by RT-PCR for the detection of the common translocations (SYT-SSX1/ SYT-SSX2). The RT-PCR did not include probes for SYT-SSX4 translocation.

RNA was extracted from deparaffinised formalin-fixed paraffin-embedded (FFPE) tumour samples, using Recover All Total Nucleic Acid Isolation kit - Ambion, USA. Total RNA in the extract was estimated using the Nanodrop (Nanodrop technologies, USA). RNA was converted to cDNA using the High-capacity cDNA reverse transcription kit (Life Technologies, USA). PCR was performed to determine the amplifiability of the cDNA using the following GAPDH primers: GAPDH F 5'TTGCCATCAATGACCCCTTCA 3'GAPDH R 5'CGCCCCACTTGATTTTGGA3'. Real-time PCR was performed using SYT-SSX1 and SYT-SSX2 probe mixes from Applied Biosystems (USA) cat no. Hs03024820_ft and Hs03024398_ft respectively.

The amplification was carried out in the 7500 real-time PCR machine. Further, to demonstrate the breakpoint the PCR was performed and the products were sequenced using the following primers SYT consensus forward 5'AGACCAACACAGCCTGGACCA3',
SSX1 R5'GGTGCAGTTGTTTCCCATCG3',

SSX2 R5'GGGCACAGCTCTTTCCCATCA 3'. All reactions were carried in 25 µl volume. The following thermal cycling profile was used: 95$^0$C for 8 min, 95$^0$C for 30 secs, optimised anneal for 30 secs, 72$^0$C for 1 min and final extension of 72$^0$C for 10 min. The PCR product was detected using a 2% agarose gel. Sequencing was performed on an automated DNA sequencer (ABI 3130 genetic analyzer) using the ABI PRISM Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Bio-systems, Foster City, California, USA). Appropriate positive and negative controls were used.

Clinical details like chemotherapy, radiotherapy, surgery, and basic follow-up details including status of last follow-up were obtained from the electronic medical records. Patients who did not report for follow-up after 3 months of initial diagnosis were considered as lost to follow-up. Patients who succumbed to the disease within 3 months of diagnosis, were included as part of follow-up.

Statistical evaluation was performed by statistical package for the social sciences (SPSS) version 22 (Chicago, IL) for Windows statistics program using Mann-Whitney non-parametric test and descriptive statistics for continuous variables and percentages for categorical variables. Data was expressed as median with minimum and maximum values along with p values. A p value <0.05 was considered statistically significant.

## RESULTS

*Patient demographics*

All the 22 patients were institution in-house cases. The age of the patients ranged from 15 to 72 years with the median age of 31.5 years. More than 75% of patients were males (Males: Females= 3.4:1). Chest pain, cough, dyspnoea, constitutional symptoms and haemoptysis were the common presenting symptoms.

*Tumour characteristics*

PPSS was commonly found in left lung, most commonly in the left lower lobe (Table 1). Though 10 patients had tumour size less than 10cm, 4 of them had other lung lesions. Eleven patients had metastatic disease at presentation and four patients had more than one site of metastasis including rare sites such as skin and adrenal gland. Computed Tomography (CT) scan showed enhancing solid pattern, cystic change with no enhancement or cystic change plus enhancing solid areas (FIG. 1).

**Table 1: Tumour characteristics in the study patients**

| Tumour characteristics | | No of patients |
|---|---|---|
| Location | Both lungs | 1 |
| | Right hemithorax | 1 |
| | Right upper lobe | 3 |
| | Right lower lobe | 2 |
| | Left hemithorax | 3 |
| | Left upper lobe | 3 |
| | Left lower lobe | 8 |
| | Intrathoracic | 1 |
| CT findings | <10 cm | 10 |
| | >10 cm | 12 |
| Metastases at presentation | Lung | 7 |
| | Pleural effusion | 4 |
| | Skin | 1 |
| | Bone | 2 |
| | Adrenal | 1 |
| | Brain | 2 |

cm, centimeter

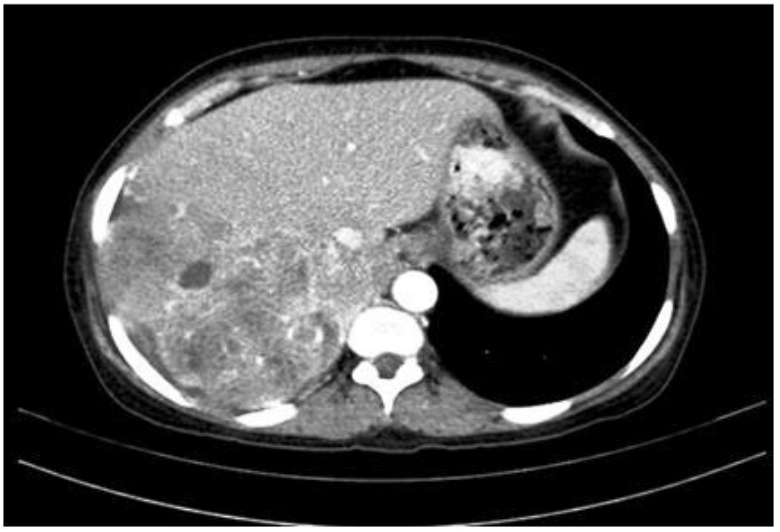

FIG. 1: Computed tomography showing synovial sarcoma involving the right lung with heterogeneous enhancement, having both solid and cystic components and prominent vascular structures within the solid component.

*Histopathological findings*

Twenty out of 22 cases were monophasic SS and the remaining two were biphasic SS (9.1%). All the cases showed classic histomorphologic features such as staghorn, branching hemangiopericytoma-like vessels, hyalinised stroma and stromal mast cells (FIG. 2A). Poorly differentiated areas with foci of rhabdoid morphology with diffuse TLE-1 positivity were noted in one patient of monophasic SS (Case No 10) (FIG. 2B).

All the 22 cases were analysed for the mitotic activity (FIG. 2C) per 10 high power field (HPF) (range, 2 to 12; mean 4.4), of which 18 cases (82%) showed between 1 and 9 mitotic figures/10 HPF, 10-19/10 HPF in 4 cases (18%) and >20/10 HPF in none of the cases. Microscopic tumour necrosis (<50%) was noted in seven cases and one case had >50% tumour necrosis. FNCLCC grading was performed based on the total score and five cases (22.7%) were found to be grade 3 (Table 2).

*Immunohistochemical findings*

Tumour cells showed diffuse and strong nuclear positivity for TLE-1(17/17, 100%) (FIG. 2D); cytoplasmic membrane positivity for bcl-2 (7/8, 87.5%) (FIG. 2E), CD56 (14/14, 100%) (FIG. 2F), focal EMA (16/17,9.1%) (FIG. 2G), focal pancytokeratin (AE1/AE3) (8/12, 66.7%) (FIG. 2H), CD99 (11/11, 100%), vimentin (5/5, 100%) and SMA (2/5, 40%). The tumour cells were negative for CD34, desmin, calretinin, STAT6, synaptophysin and h-caldesmon. In 5 cases, TLE-1 was not carried out due to the very scanty nature of tumour tissue in the paraffin block.

*Molecular Characteristics*

Among the 22 patients, RT-PCR was performed on eleven patients and not done in remaining patients due to cost constraints. Of 11 cases, 6 cases were confirmed to exhibit molecular rearrangement of SS18-SSX fusion by RT-PCR (Table 2). Specific fusion transcript SYT-SSX1(FIG. 3) was seen in 4 cases of monophasic synovial sarcoma while one case each of monophasic and biphasic synovial sarcoma had SYT-SSX2 fusion transcript. 5 cases were negative for RT-PCR for SYT-SSX fusion transcript.

Of the 22 patients, the immunohistochemical profile in 16 cases (5 cases negative for RT-PCR for SYT-SSX fusion transcript and 11 cases where RT-PCR was not done for SYT-SSX fusion transcript) favoured the diagnosis of synovial sarcoma in the appropriate setting of clinical and histological features.

*Treatment characteristics*

Five patients were found to be operable and had been offered surgery as lobectomies or surgical excisions, of which 4 of them had tumour size <10cm. The patient with tumour >10cm (13x11x10cm) received neoadjuvant chemotherapy followed by surgery.

Four patients received postoperative radiation

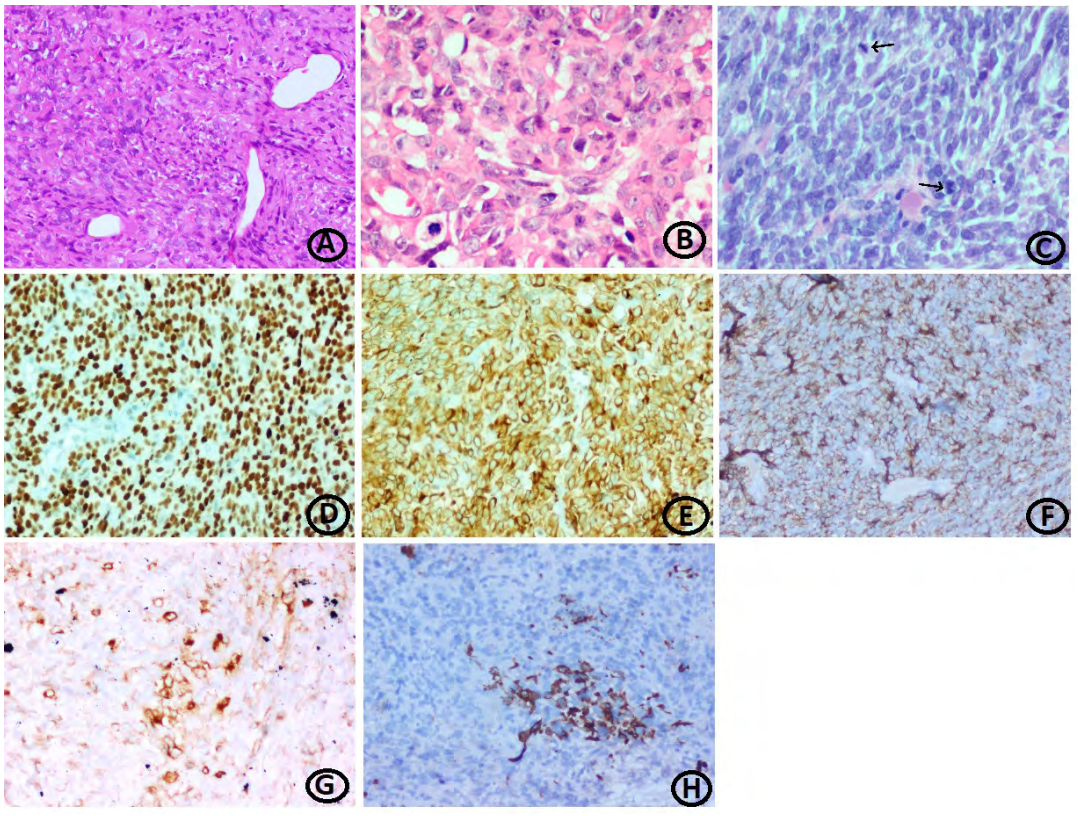


FIG. 2: (A) Monophasic synovial sarcoma displaying densely cellular interlacing fascicles of monomorphic spindle shaped cells with hyalinised stroma and staghorn or hemangiopericytoma-like vasculature (H&Ex100). Case 10 Monophasic synovial sarcoma with poorly differentiated areas with rhabdoid morphology (B) and hypercellular zone with mitotic figures (C) (thin arrows) (B-C, H&Ex200). Immunohistochemical stains showing diffuse and strong nuclear positivity for TLE1(D); cytoplasmic membrane positivity for BCL2(E) and CD56 (F), (D-F, IHCx200). Monophasic synovial sarcoma showing focal cytoplasmic membrane positivity for EMA (G) and pancytokeratin(H), (G-H, IHCx100).

therapy and one received palliative radiation therapy. Two patients received whole-brain radiation for brain metastases. Almost all 14 patients had received Doxorubicin and Ifosfamide based chemotherapy.

*Follow up*

The follow-up period of all cases ranged from 3 days to 107 months with the median follow-up of 6 months and 21 days. Out of 22 cases, 8 (36%) were lost to follow-up, in which, 6 had metastases (at presentation) and 2 did not have any metastases.

The overall median survival time in the 14 cases that came for follow-up was 20 months and 21 days (12 days to 107 months). At the end of the follow-up period, 8 (57%) were alive and 6 (43%) had succumbed to the disease. When these 2 groups were compared (p=0.028), the median overall survival times were 27 months (15 months to 107 months) and 7 months (12 days to 57 months) respectively. Most of the patients (5/6) who succumbed to the disease had metastases.

Among the 8 who were alive, 3 had no evidence of disease at 26, 92 and 107 months respectively; all of whom had resection followed by systemic chemotherapy and radiation therapy and 5 had progression of disease at 14, 17, 24, 29 and 63 months; of which 3 had metastatic disease and 2 had localised disease.

Fourteen of 22 (64%) cases had a metastatic disease process where as eight (36%) had localised disease. Considering 8 of these were lost to follow-up, the remaining localised (6) and metastatic (8) groups were compared (p=0.039) and it was found that the median overall survival time of the non-metastatic group [46 months (29 days to 107 months)] was longer than that of the metastatic group [16 months (12 days to 57 months)].

**Table 2: Pathological and molecular characteristics of primary pulmonary synovial sarcoma.**

| Case No | Age/Sex | Subtype | Mitotic rate (/10 HPF) | Grade (FNCLCC) | RT-PCR |
|---|---|---|---|---|---|
| 1 | 46 M | MSS | 4 | 2 | SYT-SSX1 |
| 2 | 62 M | MSS | 4 | 2 | SYT-SSX1 |
| 3 | 31 F | MSS | 5 | 2 | SYT-SSX1 |
| 4 | 25 M | BSS | 2 | 2 | SYT-SSX2 |
| 5 | 65 M | MSS | 12 | 3 | SYT-SSX1 |
| 6 | 29 M | MSS | 3 | 2 | SYT-SSX2 |
| 7 | 64 M | MSS | 2 | 2 | Negative |
| 8 | 72 F | MSS | 5 | 2 | Negative |
| 9 | 39 F | BSS | 5 | 2 | Negative |
| 10 | 16 M | MSS | 10 | 3 | Negative |
| 11 | 38 M | MSS | 4 | 3 | Negative |
| 12 | 34 M | MSS | 10 | 3 | ND |
| 13 | 25 M | MSS | 2 | 2 | ND |
| 14 | 49 M | MSS | 10 | 3 | ND |
| 15 | 26 M | MSS | 2 | 2 | ND |
| 16 | 15 M | MSS | 2 | 2 | ND |
| 17 | 30 F | MSS | 3 | 2 | ND |
| 18 | 26 M | MSS | 2 | 2 | ND |
| 19 | 32 M | MSS | 2 | 2 | ND |
| 20 | 26 M | MSS | 5 | 2 | ND |
| 21 | 24 F | MSS | 2 | 2 | ND |
| 22 | 67 M | MSS | 2 | 2 | ND |

M, male; F, female; MSS, monophasic synovial sarcoma; BSS, biphasic synovial sarcoma; HPF, high power field; ND, not done.

Of the 14 metastatic cohort, 11 had metastases at presentation and 3 developed metastases later. One of the 11 patients who initially had skin metastases at presentation, also progressed to other sites like brain, adrenal and parotid gland. Common sites of metastases that developed later after diagnosis were pleura, brain, adrenal and parotid. When the metastases at presentation group and metastases developing later group were compared (p=0.016), the median overall survival times were 13 days (3 days to 18 months) and 29 months (17 months to 57 months) respectively.

## DISCUSSION

The term SS was first described by Simon G in 1865 because of the microscopic features similar to those of the developing synovium or early developmental stages of joints but without any evidence that this tumour differentiates towards or arises from synovium. These tumours are rare aggressive mesenchymal tumours accounting for approximately 10% of all soft tissue sarcomas and 0.1%-0.5% of all lung tumours with slight male predominance and typically seen in adolescents and young adults.[1,2] The most common site for these tumours is extremities followed by unusual locations including the trunk, head and neck region, lung, kidney, adrenal gland, retroperitoneum, mediastinum, bone, central nervous system, liver and prostate.[2,8]

The present study revealed male predominance occurring in young adults with cystic masses similar to literature as seen in the study by Cummings *et al*., which revealed PPSS presenting as cystic masses with recurrent pneumothorax in young adults with male predominance.[10]

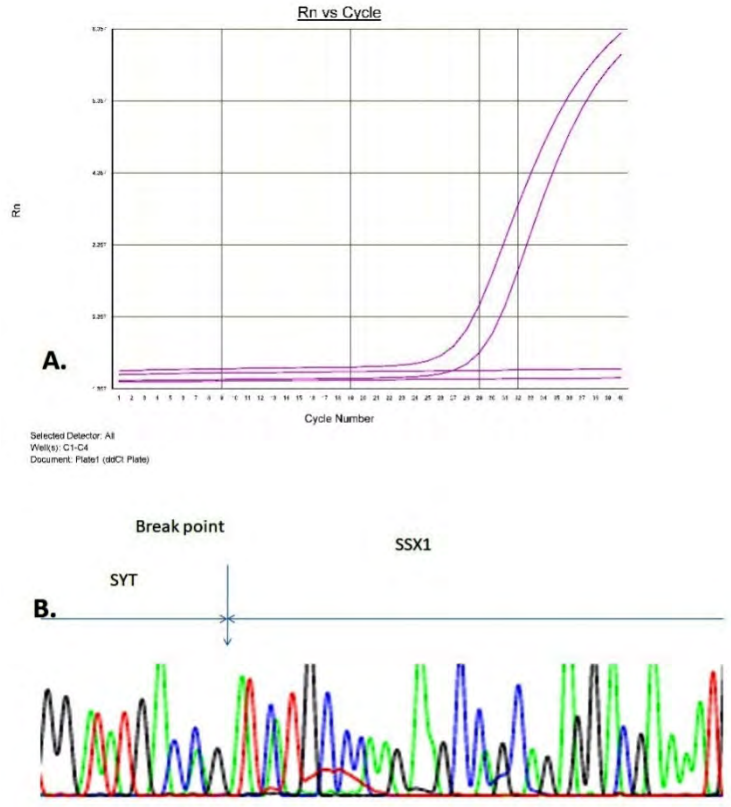


FIG. 3: A. Amplification plots of synovial sarcomas indicating the presence of an SYT-SSX1 rearrangement. B. DNA sequence of fusion transcript indicating SYT-SSX1 break point.

The monophasic SS is the most common subtype followed by biphasic subtype. The tumour entrapped pneumocytes may resemble the epithelial component of a biphasic tumour. Histomorphology shows increased cellularity with interlacing fascicles of spindle cells, hyalinised stroma, hemangiopericytoma-like vasculature, focal myxoid change and stromal mast cells.[14]

In our study, the tumour size ranged from 3cm to 13cm. There were 90.9% monophasic and 9.1% biphasic SSs, which was higher when compared to the study by Begueret *et al*.,[4] who observed 60% monophasic and 2.5% biphasic SSs. The mitotic activity analysed in our study revealed 82% falling in the 1-9 mitoses/10 HPF group and remaining 18 % in the 10-19 mitoses/10 HPF group. These findings were in stark contrast to 15 % in the 1-9 mitoses/10 HPF group, 48.6% in the 10-19 mitoses/10 HPF group and 40 % in the > 20 mitoses/10 HPF group respectively of the Begueret *et al*. study.[4] Histologic grade according to the FNCLCC in our study revealed 22.7% and 77.3% of grade 3 and grade 2 synovial sarcomas respectively, which was in contrast to 70% and 30% of respective grade 3 and grade 2 tumours in the study by Begueret *et al*.[4]

Immunohistochemical features of PPSS are similar to soft tissue synovial sarcomas.[3,4] In our series, tumour cells stained positive for TLE1 (100%), Bcl-2 (87.5%); focal EMA (94%), CD99 (100%), focal pancytokeratin (AE1/AE3) (66.6%) and CD56 (100%); negative for CD34, S100 protein, desmin, calretinin, STAT6, synaptophysin and h-caldesmon. In another study by Lan *et al*., diffusely positive immunostaining for TLE1 (91.7%), BCL-2 (95.7%) and CD99 (5%) were noted. At least focal positivity for EMA (84.6%), CK7 (55.6%), cytokeratin (AE1/AE3) (68%), CD34 (5%) and S-100 protein (21.7 %) were identified.[5] In a study by He *et al*., 94% of soft tissue SSs stained positive for TLE1 and only 9% of the non-synovial sarcomas stained for TLE1.[15] The sensitivity and specificity of TLE1 for the diagnosis of SS were 94% and 91% respectively.[15]

CT radiological findings in PPSS show a nodular tumour with circumscribed margins and heterogeneous enhancement with internal

necrotic, cystic changes, intra-tumoural vessels and calcification.[3] In our study, findings of a nodular tumour with solid and cystic changes were noted.

Cytogenetic analysis is considered to be the gold standard confirmatory diagnostic test for SS. The diagnostic sensitivity of this test approaches to 100%. The most common translocation found in synovial sarcoma is t(X;18) (p11.2; q11.2) due to fusion of the SYT gene on chromosome 18 to either of the closely related genes, SSX1, SSX2 and rarely SSX4 on chromosome X.[11,16]

SYT–SSX1 fusion gene transcripts are detected more commonly than SYT–SSX2 and very rarely SYT-SSX4 translocation. The biphasic variant of SS usually harbours SYT-SSX1 fusion, while the monophasic tumours can have either of the two translocations.[9]

In our study, the RT-PCR revealed diagnostic translocation in six of 11 cases of PPSS, of which five were monophasic and one case was a biphasic tumour. The characteristic t(X,18) translocation involving SYT-SSX1 in four cases (monophasic SS) and SYT-SSX2 in two cases (one monophasic and one biphasic SS) were identified. Five cases (5/11) of SS were negative for SYT-SSX translocation. The possible reasons for failure to produce an SYT-SSX amplification in five of the 11 synovial sarcoma cases tested could be poor RNA quality, atypical fusion transcript, absence of translocation in those particular tumour specimens, lack of SYT-SSX4 probe or breakpoints within the region of probable binding might have been altered; suggesting that FISH may be a more appropriate test in this context.[5,17]

In the study by Begueret *et al*., 56.4% of PPSS contained SYT-SSX1 translocation and 43.6% tumours revealed SYT-SSX2 translocation.[4] The Lan *et al*. study showed that fusion transcripts identified by RT-PCR belonged to SS18-SSX1 (68.2%), SS18-SSX2 (27.3%) and SS18-SSX4 (4.5%) fusions. The remaining four cases where RT-PCR was not done or negative were positive by FISH for SS18 rearrangement.[5] Thorson *et al*. observed that five out of 22 cases of SS were negative for SYT-SSX transcript, possibly due to lack of intact RNA or the presence of a PCR inhibitor.[17]

In our study, the RT-PCR for SS was not done in 11 cases, which posed a diagnostic challenge on histology alone particularly in small biopsy samples, especially monophasic subtype which resembles other spindle cell tumours including malignant peripheral nerve sheath tumour, leiomyosarcoma, solitary fibrous tumour and dermatofibrosarcoma protuberans with fibrosarcomatous transformation. Of the 11 cases, TLE-1 was diffusely positive in 6 cases and remaining 5 cases were positive for pancytokeratin, EMA, CD56 and BCL2 and all were negative for CD34, H-caldesmon, S100 and synaptophysin. Hence, immunohistochemical profile in the appropriate histological and clinical setting favoured SS in the differential diagnosis.

The differential diagnosis of pulmonary SS particularly the monophasic variant is broad and very problematic, especially in small biopsy samples. PPSS must be differentiated from secondary SS and other primary spindle cell tumours of the lung. Pulmonary metastatic SS is more common than the primary form and metastatic disease should be excluded.[5,16]

The main differential diagnosis of these tumours includes: 1) Spindle cell variant of squamous cell carcinoma, which has moderate to marked nuclear atypia and nuclear pleomorphism. The tumour cells are immunopositive for pancytokeratin, p63, p40 and negative for CD99, BCL-2. 2) Leiomyosarcoma which has cigar-shaped nuclei and immunopositive for desmin, SMA and negative for pancytokeratin, EMA. 3) Malignant solitary fibrous tumour which shows stag-horn shaped blood vessels, ropy collagen and immunopositive for CD34, STAT6 and BCL-2; negative for CD99 and pancytokeratin. 4) Fibrosarcoma which shows fibroblastic proliferation with herringbone pattern and immunopositive for vimentin; negative for BL-2 and CD99. 5) Malignant peripheral nerve sheath tumour which can be difficult to differentiate histologically and rarely positive for cytokeratin/epithelial membrane antigen. 6) Atypical carcinoid tumour which may show more spindle cell morphology. However, the tumour cells are immunopositive for pancytokeratin, synaptophysin and chromogranin A and negative for CD99 and CD34. 7) Malignant melanoma/clear cell sarcoma of soft tissue with spindle cell morphology may resemble synovial sarcoma. The tumour cells are positive for S100, Melan A and HMB45 and negative for pancytokeratin, CD99 and CD34. 8) Sarcomatoid carcinoma and mesothelioma must always be considered in the differential diagnosis of SS which show positivity only for epithelial markers and negativity for CD99 and CD34.[5,16,18]

Extensive surgical resection combined with radiotherapy and or chemotherapy is the mainstay of treatment for PPSS, thus partly or

markedly reducing the recurrence or metastatic rate. Chemotherapy is the preferred treatment for unresectable tumours and the preferred drugs are ifosfamide and doxorubicin.[5,19] In our series, five patients underwent lobectomy or surgical excisions followed by adjuvant chemotherapy and radiotherapy, while the remaining patients received only chemotherapy.

PPSSs are aggressive mesenchymal tumours with very poor prognosis, and the 5-year survival rate is 50%. Poor prognostic factors include: large tumour size >5 cm, male sex, age >20 years, extensive tumour necrosis, increased mitosis (>10/10 high-powered fields), neurovascular invasion, incomplete resection and SYT-SSX1 variant.[20,21]

In conclusion, PPSS is a rare aggressive mesenchymal tumour with poor prognosis occurring mostly in a young age group with male predominance. Monophasic SS is more common than biphasic tumour. Immunohistochemically, almost all the cases reacted with TLE1, Bcl-2, CD99, CD56 and focal positivity was seen with epithelial markers [EMA, pancytokeratin (AE1/AE3)]. There were 90.9% (20/22) monophasic and 9.1% (2/22) biphasic SSs. The characteristic translocation t(X;18) was demonstrated in 54.5% (6/11) of SS, where SYT-SSX1 translocation noted in 4 monophasic SSs and SYT-SSX2 translocation was demonstrated in each one case of monophasic and biphasic SSs. Extensive surgical resection of the tumour followed by adjuvant therapy should be encouraged. The diagnosis of PPSS might be challenging, especially in small core biopsies. In this context, a combination of clinical, histomorphological analysis, a panel of immunomarkers including TLE1 and translocation studies help confirm the diagnosis of PPSS because of its rarity and diversity of tumours at this site.

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*Conflict of interest:* The authors declare no conflict of interest.

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