Cancer Association of South Africa (CANSA)

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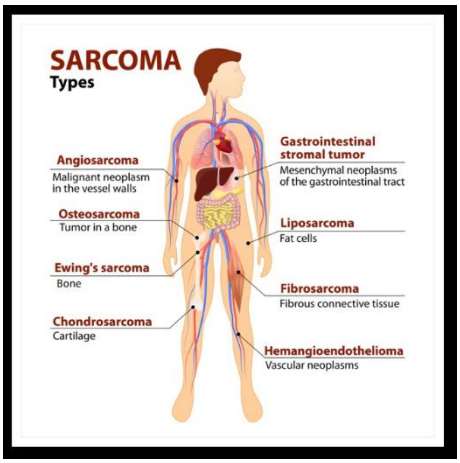
Fact Sheet
on
Synovial Sarcoma

Introduction

Cancerous (malignant) tumours of connective tissues are called "sarcomas". The term sarcoma comes from a Greek word meaning fleshy growth. Sarcoma arises in the connective tissue of the body. Normal connective tissue include, fat, blood vessels, nerves, bones, muscles, deep skin tissues, and cartilage.



[Picture Credit: Sarcoma]

Sarcomas are divided into two main groups, bone sarcomas and soft tissue sarcomas.

They are further sub-classified based on the type of presumed cell of origin found in the tumour. They all share certain microscopic characteristics and have similar symptoms.

Sarcomas can develop in children and adults. For children under 20 approximately 15 percent of cancer diagnosis are sarcomas.

Synovial Sarcoma

Synovial sarcoma is a cancer that can come from different types of soft tissue, such as muscle or ligaments. It is often found in the arm, leg, or foot, and near joints such as the wrist or ankle. It can also form in soft tissues in the lung or abdomen. Synovial sarcoma may also be called malignant synovioma or synovial cell sarcoma. Synovial sarcoma accounts for 5% to 10% of soft-tissue tumours.

One third of patients with synovial sarcoma will be diagnosed under the age of 30. It is somewhat more common in males. It is a high grade tumour which spreads to distant sites in up to 50% of cases.

It is known that in synovial sarcoma, chromosomes (the parts of your cells that contain all of your genes) break apart and get put back together in the wrong way. This can cause cells to not function like they should. In synovial sarcoma, a gene called *SYT* is joined to *SSX* genes. Doctors will look for this change in chromosomes to confirm that it is synovial sarcoma.

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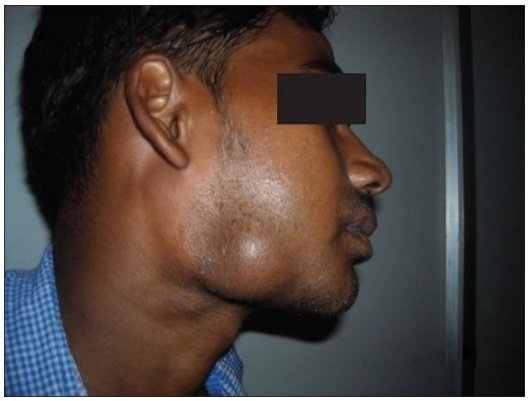
Despite its name, synovial sarcoma is not related to the synovial tissues that are a part of the joints. The disease starts most commonly in the legs or arms, but it can appear in any part of the body. On a pathology report, synovial sarcoma may be classified in different subtypes depending on what it looks like under the microscope or what specific gene mutation is involved.



[Picture Credit: Synovial Sarcoma in Adult]

Hale, R., Sandakly, S., Shipley, J. & Walters, A. 2019.
Synovial Sarcomas (SS) are a type of Soft Tissue Sarcoma (STS) and represent 8-10% of all STS cases. Although SS can arise at any age, it typically affects younger individuals aged 15-35 and is therefore part of both pediatric and adult clinical practices. SS occurs primarily in the limbs, often near joints, but can present anywhere. It is characterized by the recurrent pathognomonic chromosomal translocation t(X;18)(p11.2;q11.2) that most frequently fuses SSX1 or SSX2 genes with SS18. This leads to the expression of the SS18-SSX fusion protein, which causes disturbances in several interacting multiprotein complexes such as the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, also known as the BAF complex and the Polycomb Repressive Complex 1 and 2 (PRC1 and PRC2). Furthermore, this promotes widespread epigenetic rewiring, leading to aberrant gene expression that drives the pathogenesis of SS. Good prognoses are characterized predominantly by small tumor size and young patient age. Whereas, high tumor grade and an increased genomic complexity of the tumor constitute poor prognostic factors. The current therapeutic strategy relies on chemotherapy and radiotherapy, the latter of which can lead to chronic side effects for pediatric patients.

Cai, H.J., Cao, N., Wang, W., Kong, F.L., Sun, X.X. & Huang, B. 2019.
BACKGROUND: Synovial sarcoma, a rare mesenchymal tumor type with unclear histological origin and direction of differentiation, accounts for 6%-10% of soft tissue tumors. It is mainly located near the joints and tendons of the limbs, and occurs primarily in children or young adults. Primary renal synovial sarcoma (PRSS) is very rare, accounting for approximately 1% of synovial sarcomas. It is a spindle cell tumor type affecting mesenchymal tissue, and has morphological, genetic, and clinical characteristics, and a certain degree of epithelial differentiation. It is highly malignant and has the fourth highest incidence among soft tissue sarcomas. Here, we report a case of PRSS and share some valuable information about the disease.
CASE SUMMARY: A 54-year-old male patient was admitted to the hospital for a space-occupying lesion in the right kidney for 2 d upon ultrasound examination. The patient had no cold or fever; no frequency, urgency or pain of urination; and no other discomfort. The results of a hemogram, blood biochemistry, and tumor markers were in the normal range. The patient was examined by computed tomography (CT), which indicated the presence of a soft tissue density shadow with a diameter of approximately 6.8 cm in the right renal pelvis area, showing uneven enhancement. Ultrasound indicated a cystic solid mass of approximately 6.8 cm × 6.5 cm in the right kidney, with an unclear boundary and irregular shape. Meanwhile, color Doppler flow imaging showed dotted blood flow signals in the periphery and interior. Contrast-enhanced ultrasound (CEUS) showed "slow in and fast out" hyperenhancement of the right renal mass after contrast agent injection. The postoperative pathological diagnosis was (right kidney) synovial sarcoma. Despite postoperative adjuvant chemotherapy, tumor recurrence was detected two years later.
CONCLUSION: PRSS is a rare malignant tumor. To date, no characteristic imaging findings have been observed. The diagnosis is confirmed primarily through postoperative pathological immunohistochemistry and SS18 (SYT) gene detection. In this case, CEUS was used preoperatively. We found that PRSS has the characteristic

of "slow in and fast out" hyperenhancement, and its particular characteristics have diagnostic value. Postoperative adjuvant chemotherapy is not very effective.

Shein, G., Sandhu, G., Potter, A., Loo, Christine, Jacobson, I. & Anazodo, A. 2019.
"Primary laryngeal synovial sarcoma is an extremely rare tumor predominantly affecting young adults. There are currently no well-defined guidelines to direct investigation and management, and treatment is largely based on what is known for synovial sarcoma of the upper and lower limbs. This PROSPERO-registered study aims to review the diagnostic methods, treatment regimens, and survival outcomes for patients with synovial sarcoma of the larynx. A systematic search of databases Medline, Embase, SCOPUS, and Web of Science was undertaken in December 2017. The literature search identified 1031 potentially relevant studies, and after the deletion of duplicates and excluded papers, 98 full-text articles were screened. A total of 39 cases were reviewed from 32 studies in the data extraction. The average age at the time of laryngeal synovial sarcoma diagnosis was 32 years (range, 11-79 years). In all cases (n = 39), patients underwent wide surgical excision, with 20 patients requiring a partial or total laryngectomy. A total of 18 patients received adjuvant and 3 received neoadjuvant radiotherapy. Chemotherapy was used in 10 cases, with ifosfamide the most frequently used agent. There was considerable variability in the order and combinations of the abovementioned treatments. No clinicopathologic factors or treatment regimens were associated with improved overall survival or lower rate of recurrence. There is a paucity of literature and heterogeneity in clinical approaches to this highly aggressive sarcoma. Reporting of cases must be standardized and formal guidelines must be established to guide clinical management."

Incidence of Synovial Sarcoma
The South African National Cancer Registry does not provide any information regarding any of the Sarcoma types.

Signs and Symptoms of Synovial Sarcoma
In the early stages of the condition, synovial sarcoma may cause no noticeable signs or symptoms. However, as the tumour grows larger, affected people may notice a lump or swelling. In some cases, the tumour can limit range of motion or cause numbness and/or pain if it presses on nearby nerves.

A slow-growing painless mass is common and may give the false impression that it is harmless. When a tumour is painless and deep-seated within the body, it may go unnoticed for a long time.

The following symptoms may arise:
- The mass may hinder a bodily function. For example, in the head and neck region, it may cause difficulties swallowing and breathing or it may alter the voice.
- The mass may be painful, in particular if nerves are involved.

Primary site distribution of Synovial Sarcoma:
- Extremities: 68.7%
- Trunk: 15.7%
- Head and neck: 6.3%
- Intra-thoracic: 5.3%
- Intra-abdominal: 1.8%

- Other: 2.2%

Causes and Risk Factors for Synovial Sarcoma

The origin of synovial sarcoma is unclear. Its name notwithstanding, this sarcoma is not associated with synovial joints. The basis for the name synovial cell sarcoma was the similarity between cells of this tumour and primitive synoviocytes.

It has been suggested that there is a neurologic origin for this sarcoma. There is a histologic resemblance between neural cells of malignant peripherical nerve sheath tumour (MPNST) and synovial sarcoma. Synovial sarcoma is associated with a history of a long-standing nodule, sometimes present for years, which increases rapidly in size over a few months; therefore, it is sometimes overlooked. The tumour spreads along fascial planes and can be much more widespread than it appears on initial evaluation.

Some potential risk factors may include:

- having certain inherited conditions such as Li-Fraumeni syndrome or neurofibromatosis type 1
- exposure to radiation
- exposure to chemical carcinogens

Diagnosis of Synovial Sarcoma

Diagnosis may starts with imaging studies:

- X-ray
- Sonogram
- CT scan
- MRI scan

Followed by a Biopsy – removal of a sample of the tumour for further analysis

Cytogenetic analysis may aid the treating physician in detecting the specific chromosomal translocation

Baranov, E., McBride, M.J., Bellizzi, A.M., Ligon, A.H., Fletcher, C.D.M., Kadoch, C. & Hornick, J.L. 2020. "Synovial sarcoma (SS), an aggressive soft tissue sarcoma with a predilection for the extremities of young adults, harbors the pathognomonic t(X;18)(p11;q11) translocation, resulting in SS18-SSX rearrangements. SS includes monophasic, biphasic, and poorly differentiated variants, which show considerable histologic overlap with a range of other tumor types, making the diagnosis challenging on limited biopsies. Immunohistochemistry (IHC) is routinely used in the differential diagnosis; however, presently available markers lack specificity. Thus, cytogenetic or molecular genetic techniques are often employed to confirm the diagnosis. Here, we report the development and characterization of 2 novel antibodies: an SS18-SSX fusion-specific antibody (E9X9V, designed to the breakpoint) as well as an SSX-specific antibody (E5A2C, designed to the SSX C-terminus). We validated the selectivity and specificity of the antibodies using immunoblotting, immunoprecipitation, and chromatin immunoprecipitation followed by next-generation sequencing in SS cell lines and demonstrated that both antibodies capture SS18-SSX on chromatin at established target sites (eg, TLE1 and BCL2) genome-wide. Using IHC in whole sections from 400 tumors including 100 genetically confirmed cases of SS and 300 histologic mimics, the SS18-SSX fusion-specific antibody revealed strong diffuse nuclear staining in 95 of 100 (95%) SS cases, whereas none of the 300 control tumors showed any staining. The SSX antibody showed strong diffuse nuclear staining in all 100 (100%) SS cases; 13 (4%) of the 300 other

tumors were also positive, 5 of which displayed >50% nuclear staining. In summary, a novel SS18-SSX fusion-specific antibody is highly sensitive (95%) and specific (100%) for SS, and an antibody to the SSX C-terminus is also highly sensitive (100%), but slightly less specific (96%). IHC using the SS18-SSX antibody could replace molecular genetic or cytogenetic testing in most cases, and these reagents together will also provide the research community with valuable tools for further biochemical and genomic interrogation of the SS18-SSX fusion protein."

Treatment of Synovial Sarcoma

Once a tumour has been deemed malignant, further imaging studies such as a PET scan of the whole body and/or CT scan of the chest, abdomen or pelvis may be used to look for possible metastases. Doctors use the material gathered during diagnosis to develop a patient's treatment plan. During this process, the treating physician may consider various factors that are specific to the patient, including:

- the size of the tumour
- how invasive it is
- whether or not there is metastasis at the time of diagnosis
- whether or not the lymph nodes are involved

Surgery is the mainstay of treatment for synovial sarcoma. The goal is to remove the cancer and a margin of healthy tissue around it. This can sometimes mean the removal of an entire muscle or muscle group, or even amputation. To decrease the chances of recurrence, the treating physician may suggest a regimen of radiation therapy or chemotherapy (or a combination of the two) in addition to surgery.

Guo, P., Zhao, R., Zhou, Y. & Shen, Y. 2020.

"Limb synovial sarcoma (LSS) patients with metastasis at presentation usually have a very poor prognosis. Little is known about survival prediction and risk factors in these patients owing to the condition's rarity. Thus, this study examined the survival and prognostic variables of metastatic LSS.Clinical data for LSS patients with metastasis at presentation from 1975 to 2016 were obtained from the surveillance, epidemiology, and end results database. The Kaplan-Meier method was used to determine the survival curves. Univariate and multivariate Cox regression analysis were conducted to identify the prognostic predictors.The study enrolled 217 patients. Male predominance was observed in the metastatic LSS group. The median age at diagnosis of this population was 40 years. The subtypes were "not otherwise specified" (49.8%), spindle cell (32.7%), biphasic (17.1%), and epithelioid cell (0.5%). The 3-year overall and cancer-specific survival rates of the entire group were 27.2% and 28.3%, respectively. Tumor size <10 cm, surgery, radiotherapy, and chemotherapy were independent predictors of improved overall and cancer-specific survival in the multivariate analyses.Comprehensive treatment for LSS patients with metastasis at diagnosis is necessary and effective and can prolong survival."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers

- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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