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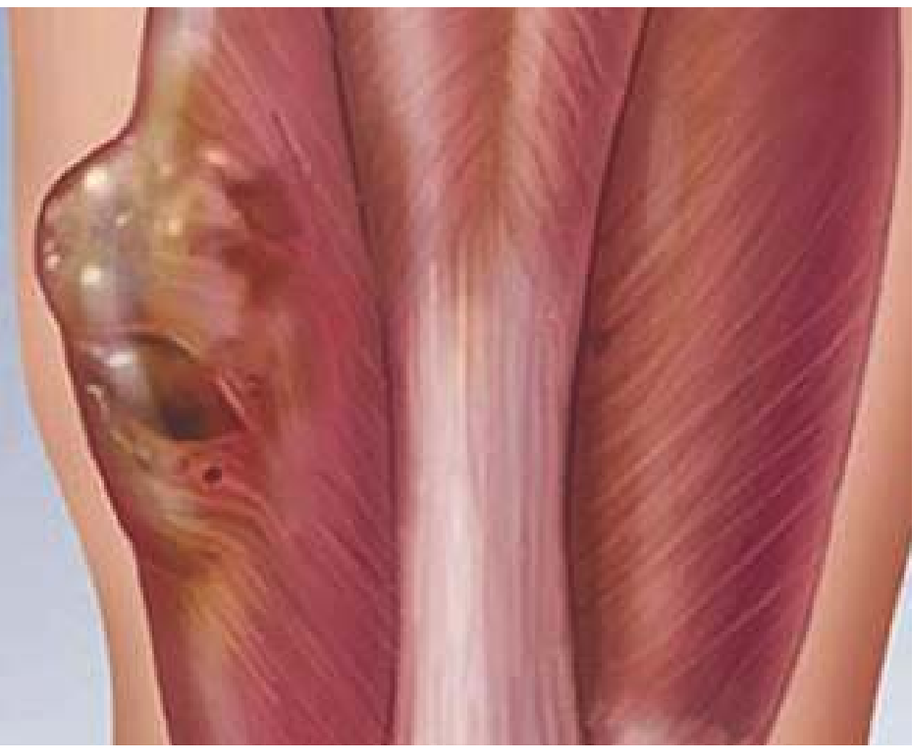
CANCER NEWS



SPECIAL ISSUE

SOFT TISSUE SARCOMA

Highlights:

Challenges in treating soft tissue sarcoma

New horizons in limb salvage for soft tissue sarcoma

Newly described soft tissue tumor entities

Rajiv Gandhi Cancer Institute and Research Centre
A Unit of Indraprastha Cancer Society
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From the Desk of Director Research

Soft tissue sarcomas (STSs) are a group of rare cancers affecting the tissues that connect, support and surround other body structures and organs. The tissues that can be affected by STSs include fat, muscle, blood vessels, deep skin tissues, tendons and ligaments. About 12,390 new cases of STSs will be diagnosed and 4,990 patients are expected to die of these tumors during the year 2017 in United States.

STSs arise most often in the limbs (particularly the lower extremity), followed in order of frequency by the abdominal cavity / retroperitoneum, the trunk / thoracic region and the head and neck. Signs of STSs include a lump or swelling in soft tissue. Sometimes there are no signs or symptoms until the tumor is big.

The diagnosis of STSs is usually made by physical examination, scans and biopsy. It definitely requires ancillary techniques such as immunohistochemistry in significant number of cases and molecular diagnostics in certain cases such as synovial sarcoma, Ewing sarcoma and alveolar rhabdomyosarcoma that have specific underlying molecular signatures. Nearly one-third sarcomas are associated with a specific translocation that has helped in their accurate diagnosis which directly influences their management. There are no standard screening tests for sarcoma. Radiation therapy and certain diseases and inherited conditions can increase the risk of STSs.

These tumors account for <1% in all adult tumours and 15% in pediatric cases. Treatment often works better in children and they may have a better chance of being cured than adults. Rhabdomyosarcoma is the most common type of soft tissue sarcoma in children. Gastrointestinal stromal tumors are most common in adults and may be benign or malignant. Ewing sarcoma, Kaposi sarcoma and uterine sarcoma are other types of STS.

Surgery is typically the first and main treatment for STS that is small and located in only one area. Rarely, for patients with a very large tumor involving the major nerves and blood vessels of the arm or leg, surgical removal of the limb, called amputation, is necessary to control the tumor. In some sarcomas, radiotherapy is used before or after surgery to enhance the chance of cure. Chemotherapy is often used when a sarcoma has already spread. It may be given alone or in combination with surgery, radiation therapy or both.

Clinical trials are studying ways to improve the effect of chemotherapy on tumor cells, including the regional hyperthermia therapy and isolated limb perfusion etc. Targeted therapy targets cancer's specific genes, proteins or the tissue environment that contributes to cancer growth and survival, usually by blocking the action of proteins in cells called kinases. Cytotoxic therapy that usually consists of anthracyclines and alkylating agents has been the mainstay of treatment for many years. Despite recent improvements in therapeutic management of sarcoma, ongoing challenges in improving the response to therapy warrant new approaches in terms of both agents and modes of delivery, to improve overall patient survival.

The present issue of the Cancer News highlights the newer advances in the field of Soft Tissue Sarcoma and features the regular article, such as Special Feature, Guest Article and Perspective. We are grateful to Dr Prakash Nayak, Orthopaedic Oncologist, Assistant Professor, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai for contributing the Guest Article.

Dr Anurag Mehta

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SPECIAL FEATURE

CHALLENGES IN TREATING SOFT TISSUE SARCOMA

Introduction

Soft tissue sarcoma (STS) is a rare and heterogeneous group of malignant tumors of mesenchymal origin. It represents less than 1% of all cancers in adults and 12% in pediatric population. STS in children is divided into two distinct groups: rhabdomyosarcoma (RMS) and non rhabdomyosarcoma (NRSTS). RMS is the single most frequent childhood STS, accounting for more than 50% of cases. NRSTS represents biologically and clinically heterogeneous group that are allocated into more than 50 histological types and 150 molecular subtypes. This huge diversity and varied location of tumor pose unique challenges for every case. Therefore, multi disciplinary care involving coordinated efforts of surgeon, pediatric oncologist, radiotherapist, pathologist and radiologist is essential for favorable outcome. In this review we discuss various challenges in the management of soft tissue sarcomas in children and young adults.

Epidemiology

Nearly 25000 and 12000 new cases of soft tissue sarcoma are diagnosed every year in the US and Europe respectively. However, there is no population based registry to arrive at accurate estimate of incidence of RMS in India, but unpublished reports from large centres in India report 3% incidence of RMS in children less than 15 years of age. Additionally, data from the hospital based cancer registries across 7 cities in India has revealed an incidence of 1-4.5% of RMS amongst all childhood malignancies. As a group, NRSTS account for 2–3% of cancers in children less than 15 years of age and 6% of cancers in 15 to 19 year-old patients.

Clinical Features

Clinical presentation of STS is highly varaible and depends on size, site and grade of tumor. Most common presentation is painless mass or lump which is generally progressive over a period of time (weeks-months). These rarely present with systemic signs like loss of weight, anorexia or fever, and if present, are suggestive of metastatic or aggressive disease. In extremity, the lump may or may not be associated with pain or difficulty in walking. A retroperitoneal mass may well present with intestinal obstruction altered bladder bowel habits, vomiting, and sometimes intestinal bleed. Head &neck mass will usually be associated with headache, visual disturbance, vomiting with or without lymphadenopathy.

Detecting these malignancies early is important as it will not only reduce the treatment burden but will also improve survival. It is important to understand that on an average, only 1 in 200 swellings or lumps examined will turn out to be malignant. Unfortunately, not all general physician are well aware of what swellings are alarming, and where diagnostic delays may be lethal. This is not only due to the rarity of STS but also due to their diverse manifestations. In various studies, it was seen that swellings >5cm, progressively enlarging with or without pain should raise the suspicion of a neoplastic process unless proven otherwise.

Of the three well established, good prognostic factors in soft tissue sarcomas (STS), size less than 5 cm, low histological grade and location superficial to the deep fascia, only size can be affected by early as opposed to late diagnosis.

Diagnosis

The initial investigations include radiograph and or USG depending on the site of the tumor. Subsequently MRI or CT are done as a part of regional imaging to know the extent, type of swelling (cystic/solic/heterogeneous), site, size, nerve or vascular invasion, lymph node status and for spread of disease.

These investigations are not diagnostic or sometimes may even not be suggestive of a neoplastic process, unless biopsied. One requires a high index of suspicion, to further investigate such swellings. Also, one has to accept the hard truth of lack of optimum infrastructure and expertise in developing countries like ours, where specific investigations like CT or MRI are not accessible to every patient. Post imaging, one need to do a biopsy for accurate diagnosis and subtyping of disease. Moreover, many times, patients report to an oncology centre, with prior biopsy, which either contaminates the plane of surgery (making optimal surgery a challenge), or is inadequate or is merely an FNAC on which diagnosis may well have been missed, further delaying the diagnosis and upstaging the disease. This is not uncommon to encounter patients who are operated elsewhere, or excision biopsy is done for diagnosis, and lymph nodes are either not sampled or inadequately sampled thus making staging difficult.

Table 1. List of Nonrhabdomyosarcoma Soft Tissue Sarcomas in Children

Types	Chromosomal aberration
Synovial sarcoma	t(X;18)(p11.2;q11.2)
Infantile fibrosarcoma	t(12;15)(p13;q26); trisomy 8, 11, 17, 20
Peripheral neuroectodermal tumor	t(11;22)(q24;q12); t(21;22)(q12;q12)
Malignant fibrous histiocytoma	Complex abnormalities
Leiomyosarcoma	Deletion of 1p Other complex abnormalities
Neurogenic tumors: Malignant schwannoma Neurofibrosarcoma Malignant peripheral nerve sheath tumor	Complex abnormalities
Rare tumors: Alveolar soft-part sarcoma Angiosarcoma Hemangiopericytoma Clear cell sarcoma Epitheloid sarcoma Desmoplastic small round cell tumor Extraskeletal chondrosarcoma	 t(X;17)(p11.2;q25) t(12;19),t(13;22) t(12;22)(q13;q12); t(2;22)(q33;q12); Inactivation of SMARCB1 t(11;22)(p13;q12) t(9;22)(q22;q12); t(9;17)(q22;q11)

The world is moving towards an era of molecular diagnosis, tissue banking and targeted therapy. Some of these translocations are unique to specific STS and help clinch the diagnosis while others harbor prognostic significance (Table 1). Adequate tissue sampling is pivotal for performing these tests.

Staging

Local staging of soft tissue sarcomas is primarily achieved with MR imaging. Currently, in most cases, CT of the thorax is performed. Additional investigations may be performed based on individual circumstances, including radiography, bone scanning, and PET/CT (Positron emission tomography). PET-CT has an emerging role in the evaluation and staging of soft tissue sarcomas. PET results may allow distinction between low- and high-grade tumors and direct the choice of the biopsy site to the more aggressive region of the mass. There are few centers which have in-house facilities for PET scan in which case local MRI and CT chest would usually suffice.

Staging may be tailored to the subtype and site. The system often used to stage sarcomas is the TNM system of American Joint Committee on Cancer (Tables 2, 3). An improperly done biopsy will upstage the disease if it contaminates sterile tissue planes.

Treatment

Management of softtissue sarcomas provides a perfect example where the multidisciplinary approach is essential for the optimization of local control, function preservation, and limb salvage. Management is not only influenced by histologic subtype and grade, but by recurrence patterns based on anatomic location. The three main pillars of management are surgery, chemotherapy and radiotherapy.

Surgery

Surgery is the mainstay of management of soft-tissue sarcomas, with the goals of complete removal of the tumor and, if necessary, reconstruction of the adjacent soft tissue, bone, and neurovascular structures. The surgical margin is an important concept. Intralesional and marginal excision harbors an unacceptable risk of local recurrence owing to the presence of residual tumor. Thus it becomes pivotal that surgery is done by an experienced onco-surgeon, who is well aware of the consequences of an intralesional or marginal resection.

The goal of surgery is a wide excisional margin, which is defined as 2 cm of skin, fat, or muscle, to resect the adjacent microscopic disease. Fascia is an excellent barrier to tumor spread, such that 1 mm of fascia can still be

Table 2. Tumor Node Metastasis (TNM) Staging of Rhabdomyosarcoma: TNM Pretreatment Staging Classification (Intergroup Rhabdomyosarcoma Studies [IRS] IV)

Stage	Sites	T-invasiveness	T-size	N	M
I	Orbit Head and necka Genitourinaryb	T1 or T2 T1 or T2 T1 or T2	a or b a or b a or b	N0 N1 or Nx N0 N1 or Nx N0 N1 or Nx	M0
II	Bladder/prostate Extremity Cranial parameningeal Otherc	T1 or T2 T1 or T2 T1 or T2 T1 or T2	a a a a	N0 or Nx N0 or Nx N0 or Nx N0 or Nx	M0
III	Bladder/prostate Extremity Cranial parameningeal Otherc	T1 or T2 T1 or T2 T1 or T2 T1 or T2	a b b b	N1 N0 N1 or Nx N0 N1 or Nx N0 N1 or Nx	M0
IV	All	T1 or T2	a or b	N0 or Nx	M1

T (tumor): T1, confined to anatomic site of origin; T2, extension; a ≤ 5 cm in diameter; b > 5 cm in diameter.
N (regional nodes): N0, not clinically involved; N1, clinically involved; Nx, clinical status unknown.
M (metastases): M0, no distant metastases; M1, distant metastasis present. a Excluding parameningeal; b Nonbladder-nonprostate; c includes trunk, retroperitoneum, etc.

considered a wide margin. The reactive zone of edema surrounding the tumor, which can often extend quite far from the mass, is considered to contain microscopic disease. For this reason, marginal excision is not adequate if surgery is the only treatment.

In certain circumstances, the surgical approach may involve a "planned positive" margin along a critical anatomic structure, such as a blood vessel, bone, or nerve. A planned positive margin is not associated with an increased risk of poor local control as long as the

Table 3. The American Joint Committee on Cancer (AJCC) Staging for Soft Tissue Sarcoma

Stage	Size	Nodal status	Metastasis	Grade
Stage IA	T1a T1b	N0 N0	M0 M0	G1 G1
Stage IB	T2a T2b	N0 N0	M0 M0	G1 G1
Stage IIA	T1a T1b	N0 N0	M0 M0	G2 G2, 3
Stage IIB	T2a T2b T2b	N0 N0 N0	M0 M0 M0	G2 G2 G2
Stage III	T2a, T2b Any T	N0 N1	M0 M0	G3 Any G
Stage IV	Any T	Any N	M1	Any G

T1 is defined as tumor less than or equal to 5 cm in greatest length with T2 greater than 5 cm. The a designated a superficial tumor as located exclusively above the superficial fascia without invasion of the fascia.
b designates a deep tumor is located either exclusively beneath the superficial fascia, superficial to the fascia with invasion of or through the fascia, or both superficial yet beneath the fascia. N1 and M1 are positive findings for nodal or distant metastatic spread. The G designates a grade on a three-point scale G1 well differentiation; G2 moderate differentiation, G3 poor or undifferentiation.

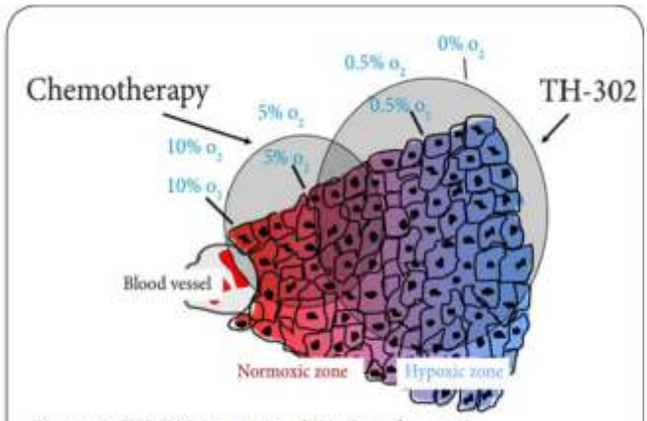


Figure 2. TH-302 is activated in tissue hypoxia.
Sarcomas develop as bulky tumors without a significant amount of angiogenesis (blood vessel formation). As oxygen diffuses through cell layers from capillaries through cell layers, the amount of oxygen available for cellular activity decreases. Thus, those cells farther away from the capillaries have an increasingly more hypoxic microenvironment. TH-302 is converted into its active form in these hypoxic regions and diffuses through the adjacent malignant cells resulting in death of these cells.

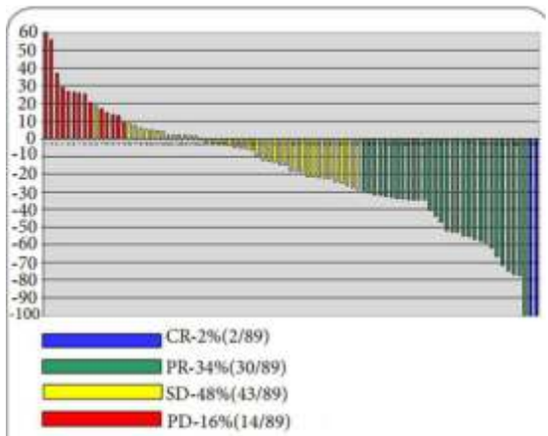


Figure 3. Waterfall plot of results from the 403 phase 1/2 trials of TH-302+doxorubicin in soft tissue sarcomas.
Shown is the percent change in size of tumors from the beginning to the end of the trials for the 89 patients receiving TH-302 in combination with doxorubicin for metastatic sarcoma. 84% of patients experienced SD (stable disease), PR (partial response), or CR (complete response) while only 16% had PD (progressive disease).

Hendifar et al. 2015

Fig. 1

remaining margins are adequate and adjuvant chemotherapy and radiation are included in the treatment regimen. The planned positive margin is akin to a "margin negative" marginal resection.

When vascular reconstruction is necessary, additional surgical expertise may be required. Of note is that surgical oncology has progressed beyond amputation, and limb salvage with vascular reconstructions, is restricted to only handful private and public hospitals.

Lymph nodes are rarely involved by softtissue sarcomas and are generally assessed with physical examination. In cases of epithelioid sarcoma, rhabdomyosarcoma, clear cell sarcoma, extra skeletal chondrosarcoma, and angiosarcoma, local MR imaging with attention to regional lymph node chains should be performed, as these histologic subtypes are associated with a higher risk of occult lymph node metastasis.

Sentinel node biopsy has an uncertain role at this time. It may be warranted in the high-risk groups noted earlier. Isolated lymph node metastases have a much better prognosis than pulmonary metastases and have a prognosis comparable with that of a stage III large, deep sarcoma. This fact will be reflected in upcoming changes to the American Joint Committee on Cancer staging system. All lymph node metastases should be managed aggressively, including surgical resection, with radiation therapy considered for extra capsular spread or when the next station of lymph node drainage immediately beyond overt disease has not been dissected and may still harbor microscopic disease.

Radiotherapy

External-beam radiation therapy (EBRT), delivered preoperatively or postoperatively, and brachytherapy are the usual modes of administration. Radiation therapy requires multidisciplinary consultation, which should address the biopsy site and the anticipated resection technique (including whether the overlying skin is to be removed).

Brachytherapy has several advantages over EBRT. It can be promptly initiated after surgery, is more easily administered with chemotherapy (when this is part of the treatment regimen).

However, brachytherapy is a very complex technique that demands multidisciplinary collaboration and interaction between radiation oncologists, surgical oncologists, and radiologists; such collaboration and interaction are not available at all centers. The challenge is, the availability of the resources, to combat local recurrences, amputations, and target high risk disease. It is surprising to know that only 40 out of 640 districts in India have Linear accelerator installations. Nonetheless considering all the sources, it was noted that during the year 2006, there were 347 teletherapy units in the country as against a requirement of 1059. The state-wise analysis of the distribution of regional cancer centres, and radio-therapy units shows wide gaps in the availability of facilities. The existing treatment facilities for cancer control interms of radiotherapy and surgical oncology services and financial allocation are woefully inadequate to take care of even the present load.

Chemotherapy

Systemic chemotherapy is an essential component of treatment for several sarcomas that occur predominantly in the young (eg, RMS, and synovial sarcoma). However, the value of adjuvant chemotherapy in patients undergoing resection of the adult-type localized extremity STS (eg, leiomyosarcoma, liposarcoma,) remains controversial due to the complexity of the group of diagnoses involved.

The addition of systemic chemotherapy to local therapy significantly improves outcomes for the common pediatric RMS. Most modern treatment plans utilize initial (induction or neoadjuvant for 4 cycles every three weeks) chemotherapy followed by local treatment and adjuvant chemotherapy for 6-8 months. Active agent includes vincristine, actinomycin D, cyclophosphamide, doxorubicin, ifosfamide and etoposide.

To date, adjuvant chemotherapy may be recommended as a reasonable option for NRSTS high-risk individual patient (having a G2–3, deep, >5 cm tumor, chemosensistive histology) who should be well informed on the possible risks and benefits of treatments. Doxorubicin and ifosfamide, for 6 cycles comprise the standard chemotherapy regimens for NRSTS known to be chemoresponsive.

Novel Therapies

Cytotoxic therapy that usually consists of anthracyclines and alkylating agents has been the mainstay of treatment for many years. However, recent advances in molecular pathogenesis, the development of novel targeted therapies, changes in clinical trial design and increased international collaboration, have led to the development of histology-driven therapy. Furthermore, genomic profiling has highlighted that some STS are driven by translocation, mutation or amplification and others have more complex and chaotic karyotypes. Some of these promising are listed below:

1. TH-302 : a pro-drug activated by tumor hypoxia, is a promising new therapeutic agent for soft tissue sarcomas. This novel agent has been shown to be safe in phase I and II clinical trials with minimal added toxicity. The data has suggested that TH-302 was addition in doxorubicin may have promising activity when compared to traditional combination therapy. A phase 3 study comparing TH-302 with addition of doxorubicin against doxorubicin alone has completed accrual (figure 1).

2. Receptor Tyrosine Kinase Inhibitors:

- Imatinib: GIST (targets KIT mutation), Desmoid tumor, Dermatofibrosarcoma Protuberans (DFSP) (targets PDGFB overexpression/ Tenosynovial GC
- Pazopanib: Metastatic STS to target angiogenesis (non-lipogenic)
- Sunitinib: GIST (2nd line targeting KIT mutation), ASPS (target angiogenesis), Angiosarcoma, Desmoplastic round blue cell tumor (target PDGFRA)

3. mTOR Inhibition: RTK mutation and IGF-1R overexpression

- Ridaforolimus
- Everolimus (ongoing trial)
- Temsirolimus

4. MDM2 inhibitors: in WD LPS
5. CDK4 inhibitors:Palbociclib (in WD LPS)
6. Met Inhibitors: a/w Clear cell sarcoma/ASPS/LM-Trametinib9.
7. RANK Ligand inhibitors: Denosumab (in Giant Cell Tumor)

Although targeted therapy owns the future in cancer therapy, specially in advanced diseases, but availability and affordability pose a great challenge in their usage. Also, all these drugs are yet not approved for upfront treatment and are also tumor specific, for instance.

Conclusion

It is imperative to recognize the need for data pooling and registries that can help build molecular pool and proper reporting of incidence in rare tumors like STS. The biggest challenge is to create awareness amongst people and treating physicians, for early clinical suspicion and early referral to a dedicated oncology centre. One should have an increased suspicion in any swelling >5cm, progressive with or without pain and should be considered malignant unless proven otherwise. Management of cancers like STS, requires a multidisciplinary approach for which human-resource as well as infrastructural needs should be sought at state and national level. Novel therapies indeed hold promise for this otherwise potentially incurable disease.

(Dr Payal Malhotra, Attending Consultant; Dr S Jain, Consultant; Dr G Kapoor, Medical Director Rajiv Gandhi Cancer Institute and Research Centre, Niti Bagh & Director Dept of Pediatric Hematology Oncology, RGCIRC, Rohini, New Delhi)

GUEST ARTICLE

NEW HORIZONS IN LIMB SALVAGE FOR SOFT TISSUE SARCOMA

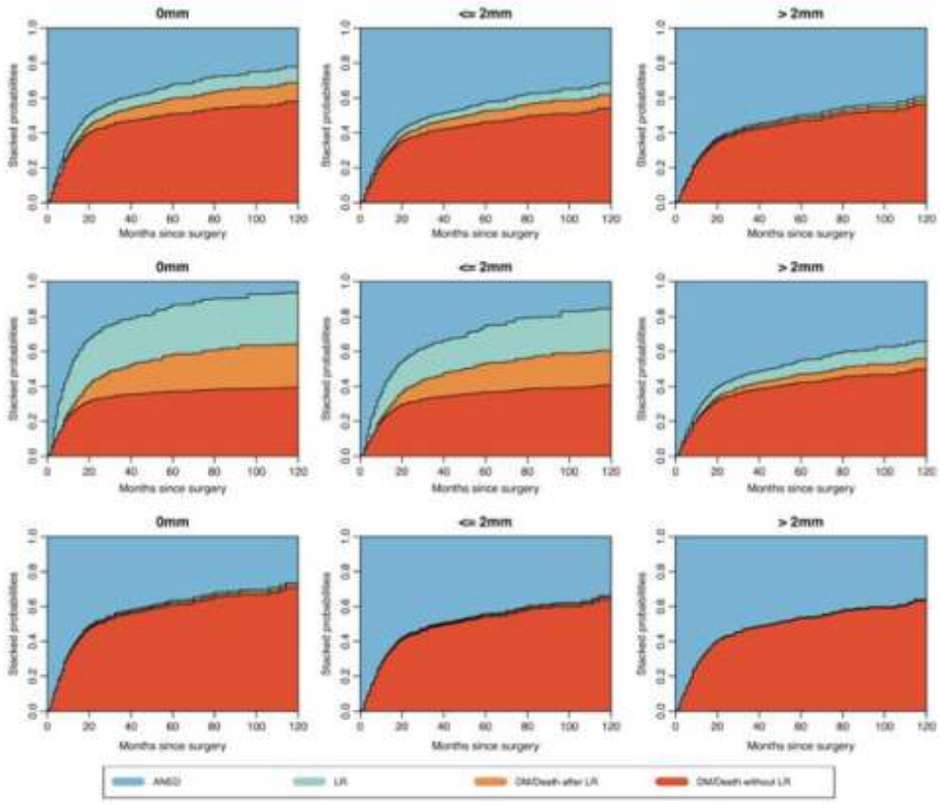
Soft tissue sarcomas are an uncommon group of mesenchymal cancers that account for less than 1% of adult cancers and 7 to 10 % of pediatric cancers (1). Their incidence is highest in the middle aged and the elderly. About half of them succumb to metastatic disease at 5 years (2). Negative margin surgical excision with pre or post operative radiotherapy is the standard of care in all intermediate and high grade sarcomas (2). The role of chemotherapy to impact overall survival is controversial. Modern multi disciplinary care has allowed limb salvage in over 90 % patients. Margins as close as 1-2 mm over a critical structure like nerve, blood vessel or bone has acceptable local control with the use of peri-operative radiation (3).

Despite their heterogeneity, clinical studies are forced to study them as one group due to their rarity. This approach fails to consider different biological and clinical behaviour which impacts outcomes and decision making. As we take a plunge toward personalised cancer medicine, the new horizons shall consider some specific genetic events in each sarcoma to customize therapy. They shall also consider patient specific factors to estimate probability for local recurrence and metastatic disease. The advances on the horizon fall into these broad groups.

Who Would Benefit from Neo Adjuvant Therapy?

These would be based on patient and tumor factors to help decrease size of tumor or make closer margins safer and hopefully decrease distant relapses.

Beacuse of the rarity of these tumors and low index of suspicion, many of our patients undergo inadvertant unplanned community excisions. Tumor bed resection followed by radiation is often recommended for optimal



Stacked state occupation probabilities for patients for different margins after surgery, based on the model in
nels: patient A: a woman aged 74 years with a large (>10 cm), high-grade myxofibrosarcoma of the upper leg
rant radiotherapy. *Middle panels*: patient B: a man aged 60 years with a 7 cm angiosarcoma of the arm, rese
radiotherapy. *Lower panels*: patient C: a woman aged 70 years with a large (>10) synoviosarcoma of the upp
after neoadjuvant radiotherapy. From left to right: *Left panels*: a 0 mm margin. *Middle panels*: margins smalle
mm. *Right panels*: margins wider than 2 mm.

Fig. 1: This figure cited from (4) shows 3 graphs with different clinical scenarios leading to different predicted outcomes. They help visualize the impact of margins, radiation, age, tumor size on local and systemic disease free survival, potentially helping with clinical decision making. For instance the third panel suggests a uniformly poor systemic outcome irrespective of local success, which means, the least morbid local option and focus on available systemic modalities would best serve the patient.

local control. The impact of this strategy on the overall prognosis of a specific individual patient is not known (4). In a large study by Willeumier et al (4), a multi state model examined the interaction between various baseline states of an individual patient and their transition into local, systemic recurrence or both to help predict or infer future events. This approach not only helps prognosticate an individual patient, but also helps predict clinical behaviour of similar other patients, allowing appropriate clinical decisions and trial design. This was a first of its kind study that takes modifiable and non modifiable risk factors for an individual at start of treatment, creates a stack of charts that helps visualise the impact of each on overall patient outcome. This involves morbid plastic reconstructive surgery to fill large post resection defects.

What Neo Adjuvant Therapy?

Factors predicting which amongst chemotherapy, radiotherapy or targeted therapy, would be most useful in impacting local recurrence free and overall survival.

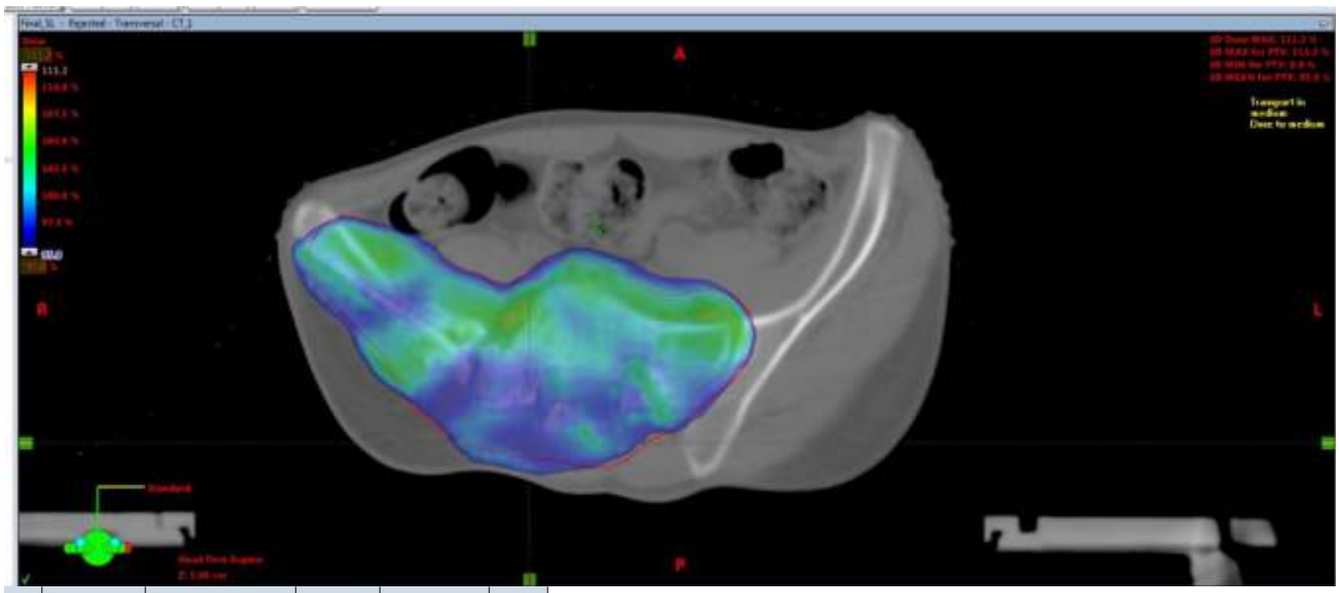
The last 4 years witnessed the approval of 4 new drugs in the treatment of soft tissue sarcoma, pazopanib, trabectidin, eribulin and olaratumab, a pace of progress that hadn't taken place in the last 4 decades. Over 70% of the current WHO list of soft tissue sarcomas have specific translocations and there is continual progress in understanding genetic determinants of their clinical behaviour. This shall help identify patients whose primary mode of failure is going to be systemic. These patients may be spared morbid local surgery and focus may shift to their systemic treatment.

The advent of proton beam and carbon ion heavy particle based radiation therapy has revolutionized both delivery and radiobiology of radiation therapy, allowing significant local control rates in unresectable sarcomas. As their availabilty and access improves, a large number of unresectable tumors shall benefit from superior local control without amputation (5). The jury is still out on long term risks including second malignacies with this approach. But considering a significant number of these patients with unresectable, deep, high grade tumors succumb to systemic disease, a less morbid approach may be attractive.

Intra-operative Assessment of Margins

Improved precision and accuracy of intra operative assessment of margins using navigation or visual fluorescence aids is a novel approach.

Deformable registration has been a barrier to the use of navigation in aiding surgical margins for soft tissue. Some progress has been made in the use of in vivo auto-fluroscence in aiding visualization of surgical margins in soft tissue sarcoma (6). With improved sensitivity and better optics, surgeons will have live tools of precision to help with surgical margins.



Units | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

Machine/Energy	MLC	Field Weight	Scale	Gantry Rtn [deg]	Coll Rtn [deg]	Couch Rtn [deg]	Wedge	Field X [cm]	X1 [cm]	X2 [cm]	Field Y [cm]	Y1 [cm]	Y2 [cm]	X [cm]	Y [cm]	Z [cm]	Calculated SSD [cm]	MU	Ref. D [cGy]
Unique - 6X	Dose Dynamic	1.000	Varian IEC	350.0	0.0	0.0	None	21.8	+8.5	+13.3	34.0	+17.0	+17.0	-6.00	4.50	-5.00	92.6	203	
Unique - 6X	Dose Dynamic	1.000	Varian IEC	315.0	0.0	0.0	None	18.2	+7.9	+10.3	34.0	+17.0	+17.0	-6.00	4.50	-5.00	91.8	238	
Unique - 6X	Dose Dynamic	1.000	Varian IEC	280.0	0.0	0.0	None	13.4	+6.5	+6.9	34.0	+17.0	+17.0	-6.00	4.50	-5.00	91.7	117	
Unique - 6X	Dose Dynamic	1.000	Varian IEC	240.0	0.0	0.0	None	20.8	+11.8	+9.0	33.8	+16.8	+17.0	-6.00	4.50	-5.00	91.5	255	
Unique - 6X	Dose Dynamic	1.000	Varian IEC	200.0	0.0	0.0	None	23.1	+14.8	+8.3	33.0	+16.0	+17.0	-6.00	4.50	-5.00	93.0	207	
Unique - 6X	Dose Dynamic	1.000	Varian IEC	160.0	0.0	0.0	None	22.3	+13.5	+8.8	32.8	+15.8	+17.0	-6.00	4.50	-5.00	92.9	193	

User doc Group: Oncologist Site Man CAP NUM SCRL

Fig. 2: The above picture depicts the typical dose distribution in a pelvic sarcoma using image modulated radiation therapy which allows precise sculpting of rays along the tumor sparing normal structures around the tumor and decreasing radiation induced side effects some of which can be permanent.

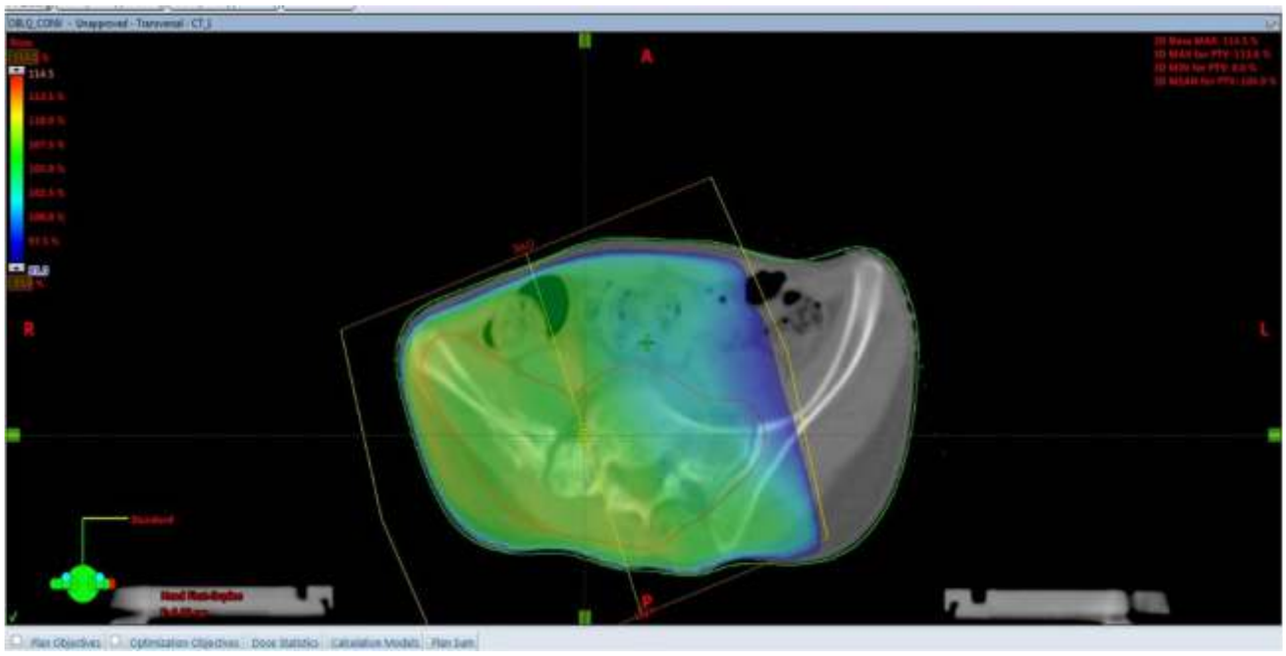


Fig. 3: As a contrast to Fig. 2, this figure depicts conventional delivery of radiation using 2 fields which involves a large extent of the pelvis and normal structures like bowel and bladder in the field of radiation significantly adding to the morbidity.

This technique aims to be more sensitive than the tactile and MRI based measurements that surgeons use currently to infer intraoperative margins.

Virtual Reality and Auto-Segmentation in Cancer Surgery

Google VR has brought virtual reality into our drawing rooms. There are various manual tumor segmentation softwares like Pinnacle, that have been in vogue and successfully deployed by radiation oncologists to sculpt radiation beams around complex shaped tumors. A recent publication (7) has explored and compared multiple complex algorithms to help auto segment CT images to help aid surgeons in planning margins in retroperitoneal tumors. These approaches would be applied to extremity tumors to aid virtual planning, maximize margins, minimize morbidity and incorporate radiation planning all into one intuitive software taking multidisciplinary care to a new level.

Available Modalities for Borderline Limb Salvage

The modern techniques that have already allowed successful salvage in borderline salvageable cases with acceptable morbidity and local recurrence rates are?

1. Precise delivery of radiation using adaptive IGRT/IMRT (Fig 2, 3) with lesser doses to skin, bone decreasing wound complication rates and improving function as contrasted with conventional dosimetry techniques. Brachytherapy is another well tested techique that allows precise dosedistribution and completion of therapy within a week of peri-operative phase.
2. Limb perfusion and limb hyperthermia have allowed higher delivery of anti-tumor drugs without systemic toxicity to achieve local tumor shrinkage in upto 50 % of cases, leading to slightly better metastasis free survival (8). Availability, cost and lack of wide expertise and uncertain clinical benefit with wide application have limited its application in the Indian subcontinent.

Immediate Priorities

The biggest impact toward limb salvage in the Indian subcontinent is likely to be from early diagnosis, correct placement of biopsies and prompt referral to a sarcoma unit. These low hanging fruits of logistical challenges should be more urgently adressed by our community to better serve our patients. Multiple studies have either suggested or denied the predictive role of margin status and local recurrence on overall survival. Recent studies have shown grade, presence of residual disease on re-excision and high grade to predict overall survival (9). Certain biologies like myxofibrosarcoma, margin less than 1 mm (R1 resection) or worse predict local failure. All this data points to limitations of surgery and limb savage in predicting and affecting overall survival.

We must not forget, that excellent and consistent progress with plastic reconstructive surgery has allowed coverage of large defects , which is the keystone to a successful limb salvage effort. A detailed analysis of the progress and the advances is beyond the scope of this article.

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RESEARCH & DEVELOPMENT

HINDQUARTER RESECTIONS FOR SARCOMA: IS IT WORTH IT?

The goal of this study is to determine prognostic factors for outcome and analyse quality of life after resection, in order to better select patients who are more likely to benefit from this operation. Prospectively collected database was searched for all patients treated with a hindquarter amputation between 1989 and 2015. 82 patients underwent a hindquarter resection in the given time frame. Of these patients, 63 were treated with a curative intent. The median hospital stay was 25 days, and 49% of the patients had wound complications. The in-hospital mortality was 6%. The 5-year overall survival in the whole group was 31%, while disease free survival was 26%.For those patients treated with curative intent, younger age was correlated with better survival, while higher histological grade was correlated with worse disease free survival. The functional and social outcome for patients who survived more then one year varied widely, with about 50% of the patients living an acceptable social life with reasonable pain levels and mobility status.

(Ann Surg Onco, Mar 2017)

NEW THERAPY FOR SOFT TISSUE SARCOMA

The U.S. Food and Drug Administration had added a new therapeutic for treating certain patients with soft tissue sarcoma (STS), a molecular targeted therapy called olaratumab (Lartruvo). The drug had been granted accelerated approval to olaratumab for the patients not amenable to curative treatment with radiotherapy or surgery and with a histologic subtype for which an anthracycline containing regimen is appropriate. The approval was based on data from a randomized, active controlled, clinical trial involving 133 patients with metastatic STS. The patients were randomized (1:1) to receive the combination of olaratumab plus doxorubicin or doxorubicin as a single agent. A number of 66 patients were randomized to the combination treatment and 67 to doxorubicin alone. The group of patients receiving the combination treatment had a median overall survival of 26.5 months compared to 14.7 months in other group. The median progression free survival was 8.2 months for patients who received the combination treatment and 4.4 months for those receiving doxorubicin alone.

(US FDA, Oct, 2016)

PERSPECTIVE

NEWLY DESCRIBED SOFT TISSUE TUMOR ENTITIES

Soft tissue tumors (STT) are a heterogeneous group with approximately 50 sarcomas and innumerable benign entities. New entities are carved out regularly from the existing ones on the basis of novel molecular data and even brand new diagnoses are being added on a regular basis. The 2013 'WHO classification' has acknowledged, refined and reallocated some of these diagnostic entities but many, either described post revision or not yet accepted uniformly by the experts, are part of the growing literature. This article makes an attempt to discuss some of these "Newly Described Soft Tissue Tumor Entities" without any pretense of being comprehensive. The newly described entities discussed in this article are listed below

1. Superficial CD34+ Fibroblastic Tumor
2. Angiofibroma of Soft Tissue
3. Biphenotypic Sinonasal Sarcoma
4. Hemosiderotic Fibrolipomatous Tumor
5. Epithelioid Inflammatory Myofibroblastic Tumor
6. Gastrointestinal Neuroectodermal Tumor
7. Spindle Cell Liposarcoma
8. Spindle Cell Rhabdomyosarcoma of Childhood and Adult
9. Undifferentiated Round Cell Sarcoma (Ewings like Sarcomas)

Superficial CD34+ Fibroblastic Tumor

Carter and colleagues described this unique fibroblastic neoplasm in a report of their 18 cases. This tumor located in superficial soft tissues is a locally aggressive tumor with rare metastasis and has distinctive morphological and immunohistochemical features. A tumor of adults with age range of 20–76 years, it shows no gender bias and occurs as painless, slow-growing, superficial mass of some duration with a size variance of 1.5 to 10 cm. It preferentially involves lower extremities but upper arm, groin, shoulder and hip have also been affected. The subfascial involvement occurs as an extension from subcutis but never as a primary site.

Histologically, the tumor is characterized by spindle cell in fascicles separated by fine branching blood vessels lending at places a hemangipericytomatous pattern of growth. Ectatic vessels may be seen. Bland spindle cell morphology dominates in part of the tumor which merges with areas of high nuclear atypia, hyperchromasia, prominent nucleoli and intranuclear inclusions. These regions of the tumor may exhibit epithelioid morphology and solid arrangement. Mitoses are rare.

Immunohistochemically, this entity is diffusely and strongly positive for CD34 in all cases. Focal staining with pancytokeratin is noted in approximately 70% of the tumors. Ki 67 labeling is remarkably low (<1%).

Differential diagnoses include 'Cutaneous Undifferentiated Pleomorphic Sarcoma', 'Myxofibrosarcoma', 'Atypical Fibroxanthoma', 'Myxoinflammatory Fibroblastic Sarcoma' (Inflammatory Myxohyaline tumor) and 'Pleomorphic Hyalinizing Angiectactic Tumor'. However, remember that low Ki 67 labeling coupled with CD 34 staining is characteristic of Superficial CD34+ Fibroblastic Tumor alone.

Angiofibroma of Soft Tissue

Angiofibroma of nasal cavity and Cellular Angiofibroma of genital region are well known. The Angiofibroma of Soft Tissue, however, is an altogether different entity described in 2012 by Marino-Enríquez and Fletcher. This neoplasm is not yet a recognized WHO category.

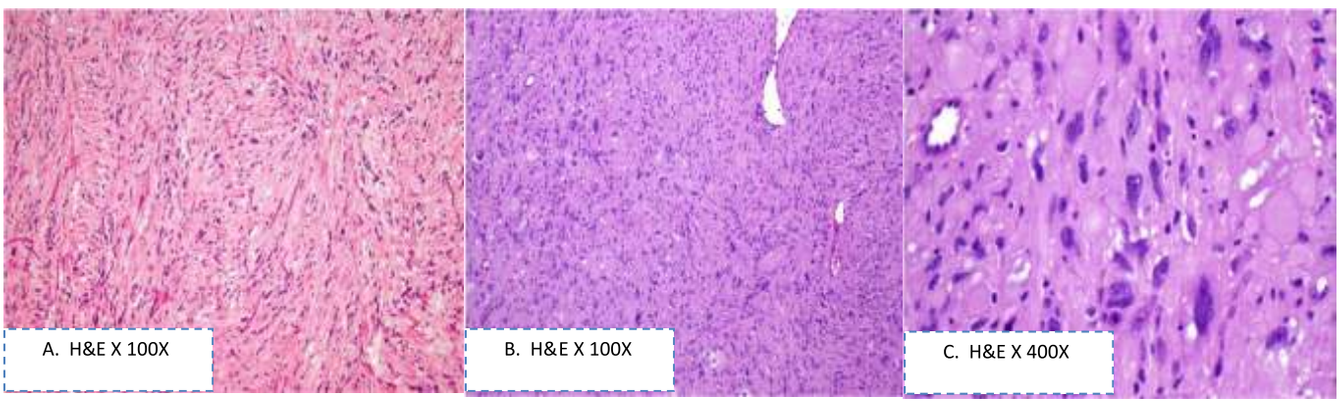

Fig. 1: H&E stained sections reveal alternating bland and bizarre areas. (A) Fasciculated spindle cell area with rudimentary hemangiopericytomatous background; (B) Bizarre cellular morphology, magnified in (C) to show characteristic nuclear features and epithelioid morphology.

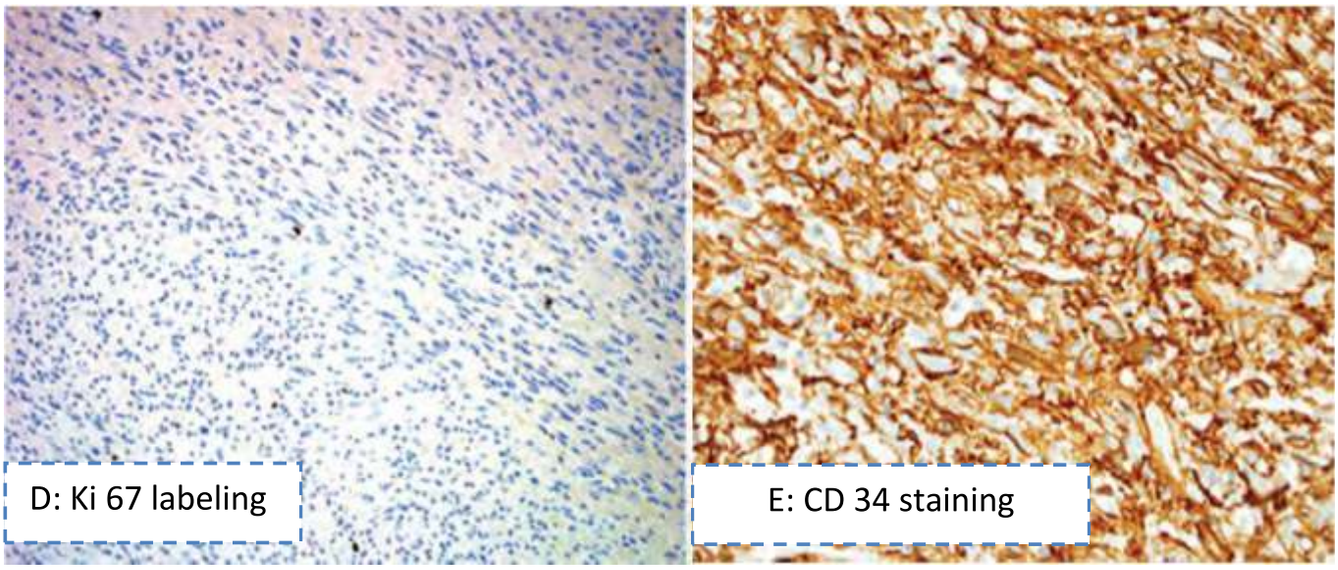

Fig. 2: Low Ki 67 labeling (D) and strong and intense CD 34 staining is observed in image (E).

The tumor occurs largely in middle-aged adults, affecting women twice as often as men. The tumor grows slowly producing a painless mass located in the subcutis or deep soft tissue of limbs, mainly the lower limbs and often proximate to a joint or fibrotendinous structures. It can, however, display a broad anatomic distribution. The tumor is benign with rare local recurrences and no metastatic potential.

Histologically, the tumor is well circumscribed and vaguely lobular. It has nondescript spindle cells in patternless arrangement. The cellular density can vary with some areas being more cellular than the rest (red arrow). The characteristic feature is the vascularity of this tumor which is composed of plexiform thin walled vessels like in Myxoid Liposarcoma (Myxoid LPS) albeit somewhat thicker (green arrow). Less numerous larger ectatic vessels are also noted. The stroma is variably collagenous or myxoid.

Immunohistochemistry is non-contributory. Ki 67 labeling is useful in demonstrating extremely low (>1%) population in cell cycle.

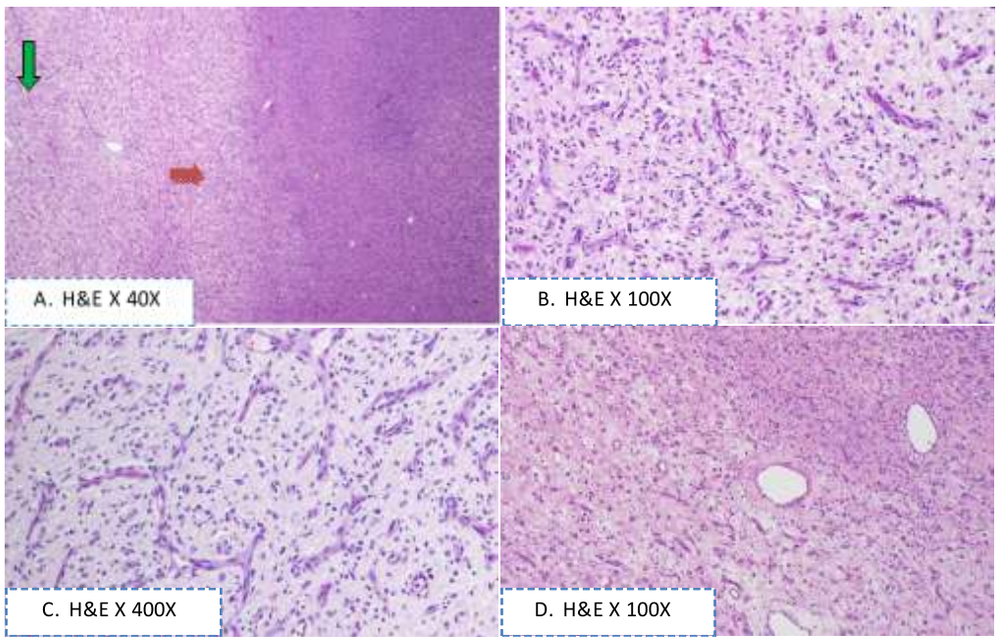

Fig. 3: (A) A scanner view of 'Angiofibroma of Soft Tissue' exhibits bland spindle cell proliferation with varying cellular density and vague nodularity (red arrow). The green arrow points to the plexiform vascularity. The characteristic vascularity is better seen at higher power in image (B) a further magnified view of which is shown in (C). This vascularity resembles that in Myxoid LPS but is more numerous and not as thin and delicate as in Myxoid LPS. Also note the bland spindle cell in patternless arrangement in myxoid background. Image (D) illustrates limited presence of ectatic vascular channels and varying collagenization.

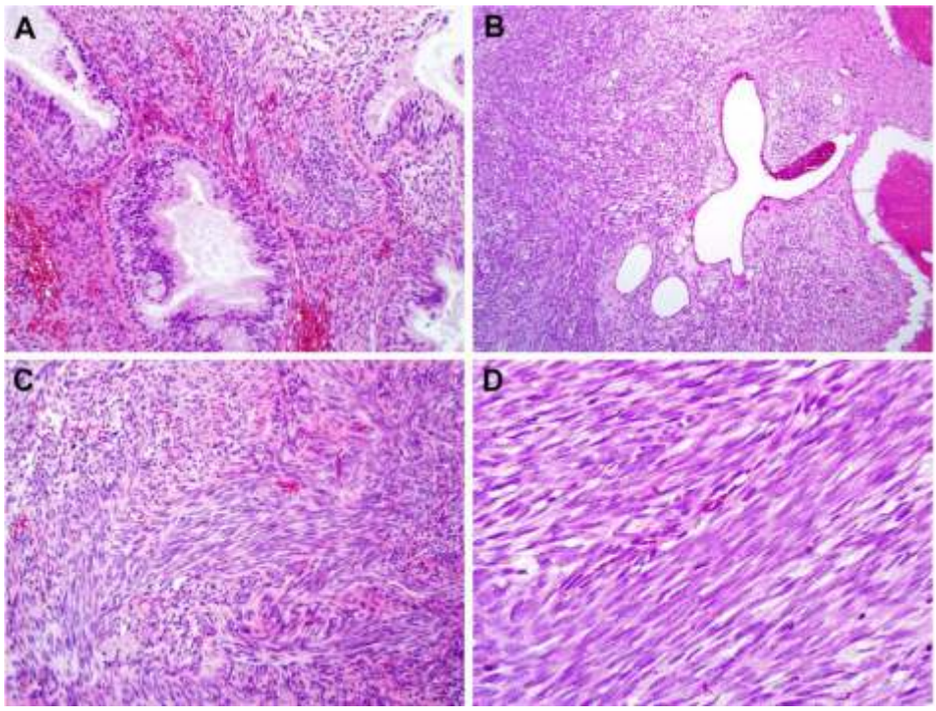

Fig. 4: Morphologic characteristics of BSNS. Image (A) shows entrapped hyperplastic surface epithelium within spindled neoplastic proliferation. (B, C, D) demonstrate bland spindle cells in long and short fascicles. Note lack of mitosis and necrosis.

Differential diagnosis is genuinely difficult with Myxoid LPS, Low grade Fibromyxosarcoma (LGFMS) & Low grade Myxofibrosarcoma sharing morphology in terms of myxoid back ground and branching vascularity. Patternless arrangement of bland cells and the most abundant vascular proliferation along with extremely low Ki67 labeling shall help to come to a correct diagnosis.

In addition, this tumor has its specific gene rearrangement in form of (5:8) producing AHRR/NCOA2 and NCOA2/AHRR chimeras. The pathway to carcinogenesis, however, has not been unraveled as yet.

Biphenotypic Sinonasal Sarcoma (BSNS)

BSNS is a recently recognized low-grade sarcoma showing myogenic and neural differentiation that is currently considered to be distinctive to the sinonasal tract. This tumor was first described in 2012 by Lewis etal. in their series of 28 cases. The tumor involves the ethmoidal sinus, frontal sinus and the nasal cavity in that order. The age range is wide with cases occurring from 24-85 years of age. Tumors occur more frequently in women than men.

The tumor appears as a polypoidal mass with an average size of 4 cm and has an infiltrative growth. Resection is usually difficult owing to complexity of the location of occurrence. A recurrence rate of 30-40% and a rare death from disease have been reported.

Histopathology

BSNS is a spindle cell sarcoma in fascicular arrangement. The fascicles are medium-to-long. Constituent cells have elongated ovoid nuclei with wavy "neural" looks. The cytology is bland, pleomorphism is mild if at all and mitoses and necrosis are rare. Most tumor cells

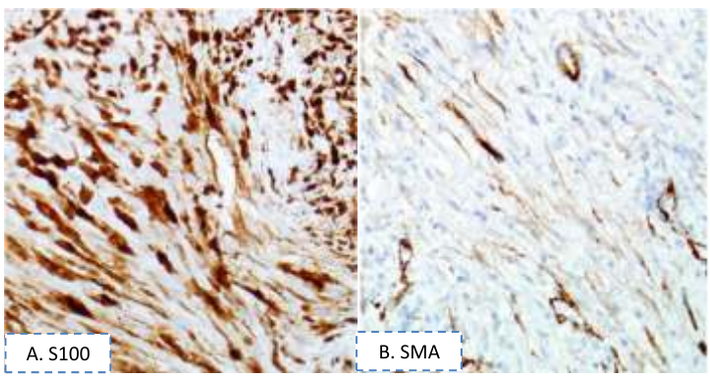

Fig. 5: The characteristic immunophenotype of BSNS. Strong S100 and Focal, moderately strong SMA positivity is shown in Image (A & B) respectively.

cells have scant palely eosinophilic cytoplasm and poorly defined cell borders, which may appear somewhat fibrillary. Overlying respiratory epithelium may be hyperplastic with inward pleating resulting in glands like structures entrapped in the tumor, which may mimic a biphasic malignant neoplasm. Bone invasion can happen.

Immunohistochemistry: BSNS show focal and dual expression of S-100 and SMA. Recently, nuclear B-catenin expression has also been reported. The SOX10 is negative.

Genetic Features: PAX3 gene rearrangement with MAML3 and FOXO1 has been described.

Differential Diagnosis: Comprise malignant peripheral nerve sheath tumor (MPNST), leiomyosarcoma, spindle cell RMS and synovial sarcoma monophasic type or biphasic type due to entrapped glands being misconstrued as being neoplastic. Additionally, spindle cell melanoma and SFT can also be confused with BSNS. Low grade morphology, low mitotic activity and dual differentiation as shown by S 100 and SMA staining shall help arrive at correct diagnosis.

Hemosiderotic Fibrolipomatous Tumor (HFLT)

It is an unencapsulated, locally aggressive tumor. The tumor occurs in all ages and has a striking predilection for dorsum of foot, followed by other ankle and foot sites. Reports from dorsum of hand, thigh and face are available in literature. Local recurrence is common if HFLT is not fully removed.

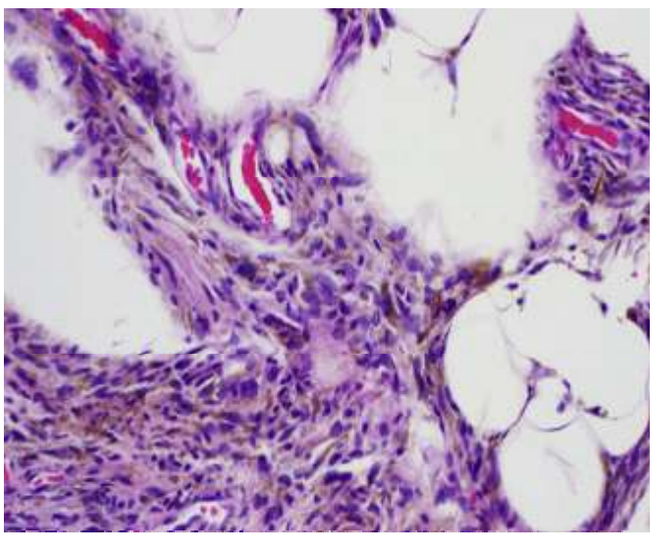

Fig. 6: Different components of HFLT; Fat, spindle cells of which many contain hemosiderin and giant cells.

Histologically, the tumor shows admixture of mature adipocytes and spindle cells in whorls, fascicles and honeycombs. In addition, hemosiderin laden macrophages are seen within the spindle component mixed with inflammatory cells and osteoclasts. The hemosiderin is also observed within the spindle cells themselves.

The neoplasm can occasionally show changes overlapping with Pleomorphic Hyalinizing Angiectactic Tumor (PHAT) and Myxoinflammatory Fibroblastic Sarcoma (MIFS) with which it shares the genetic alteration.

Immunohistochemistry is non-specific with staining by CD34 and calponin.

Genetic alteration is in form of a recurrent translocation t (1; 10) which fuses TGFBR3 with MGEA5. The same genetic change also characterizes the PHAT & MIFS.

The differential diagnosis is limited by unique histology of both hemosiderin deposition and admixed adipose tissue in HFLT which would be unusual for any other entity. However, features of PHAT and MIFS when present can cofound the diagnosis.

Epithelioid Inflammatory Myofibroblastic Tumor: Inflammatory Myofibroblastic Tumor is a known entity. However, 'Epithelioid Inflammatory Myofibroblastic Tumor' is a recently described variant. It has more aggressive behavior and many soft tissue pathologists believe that it is better called 'Epithelioid Inflammatory Myofibroblastic Sarcoma'. The epithelioid variant is associated with ALK-RANBP2 gene fusion; this fusion results in characteristic nuclear membrane staining, as RANBP2 localizes ALK to the nuclear membrane.

Histologically, the tumors are composed predominantly of loose sheets of epithelioid-to-round cells set in a myxoid background with abundant mixed inflammation. The tumor cells have eosinophilic-to-amphophilic cytoplasm and large round vesicular nuclei with prominent nucleoli. Moderate to plentiful inflammatory, infiltrate comprising neutrophils, lymphocytes and plasma cells, is noted in the background.

Immunochemistry is definitive with Alk protein nuclear expression. CD30 is also positive cofounding the diagnosis with ALCL. Desmin is expressed in 90% tumors. S100, SMA and CD34 are always negative.

Genetic make of this tumor is unique too with ALK-RANBP2 rearrangement.

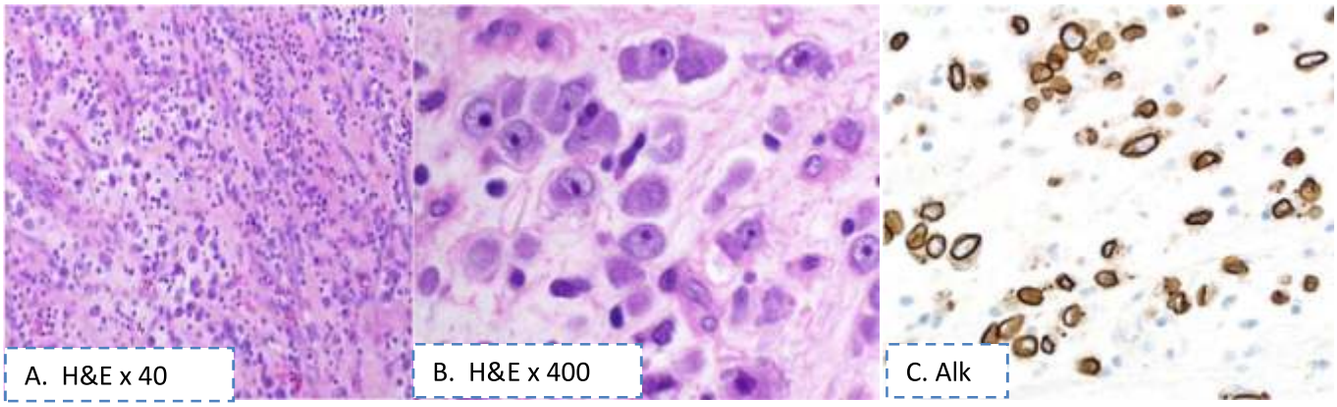

Fig. 7: Epithelioid Inflammatory Myofibroblastic Tumor. Note the inflammatory background and large epithelioid tumor cells haphazardly mixed with each other (A). The tumor cells are large, epithelial looking & have prominent nucleoli. Singly scattered tumor cells in inflammatory background lend a picture of hematolymphpoid neoplasm, especially ALCL (B). The immunostaining with ALK is unique with nuclear membrane taking up the stain (C).

The differential diagnosis includes Anaplastic Large Cell Lymphoma (ALCL), Epithelioid Leiomyosarcoma, Epithelioid Sarcoma and Rhabdomyosarcoma (RMS). Of these ALCL is the most challenging, resolution of which depends upon LCA & Desmin staining being exclusive to ALCL and Epithelioid Inflammatory Myofibroblastic Tumor.

Gastrointestinal Neuroectodermal Tumor (GNET). Clear-cell sarcoma (CCS) was first described by Enziger in 1965 in the deep soft tissue of the distal limbs. This tumor shared features with the "malignant neuroendocrine tumor of the jejunum with osteoclast-like giant cells", described by Alpers and Beckstead in 1985 and by Ekfors and colleagues in the duodenum in 1993. CCS was separated from so called CCS of the GI tract with the latter exhibiting a primitive neural phenotype contrary to melanotic phenotype of CCS. In 2012, Stockman and coworkers renamed the CCS of the GI tract as "Gastrointestinal Neuroectodermal Tumor". GNET is now recognized as a rare neoplasm that predominantly arises from the small intestine, stomach, esophagus and the colon in descending order of frequency. GNET is a fully malignant tumor with capabilities to metastasize to regional lymph nodes, liver and lung (especially the esophageal GNET).

Lesions are based primarily in the submucosa and muscularis propria and may grow in an exophytic fashion protruding into the bowel lumen or in infiltrative pattern imitating a carcinoma. Punctate opening is seen at the apex of the lesion similar to gastric GIST.

Histologically, the tumor is arranged in varying sized nests of epithelioid cell of clear or eosinophilic cytoplasm. The nuclei are vesicular with thick nuclear membrane and a small nucleolus. Alveolar, papillary, microcystic, fascicular and cords of cells make up the other minor growth patterns. Mitotic activity varies from a few to many.

Immunohistochemistry: The tumor is immunoreactive for S100, SOX10 and neuroendocrinal proteins albeit variably. Tumor is negative for CD117, DOG1, SMA, melanocytic proteins & Cd34.

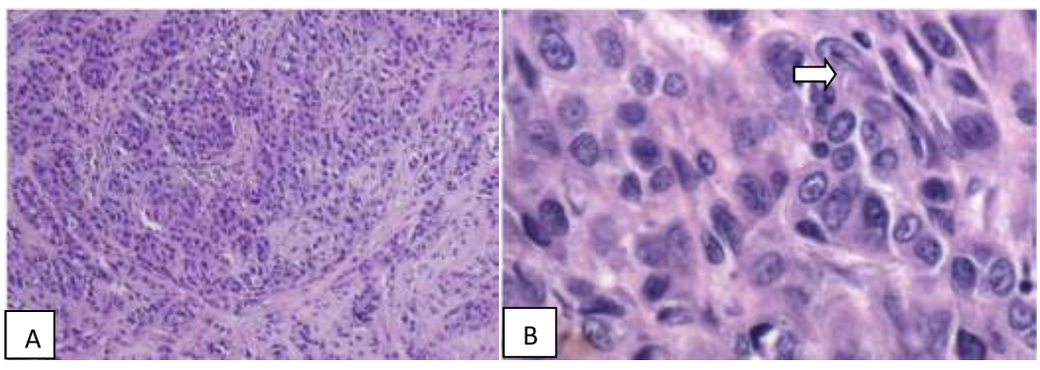

Fig. 8: Nests of epithelioid tumor cells (A). Large cells with vesicular nuclei and conspicuous nucleoli. The chromatin is emarginated along the nuclear envelop. An odd cell shows intranuclear inclusion (B).

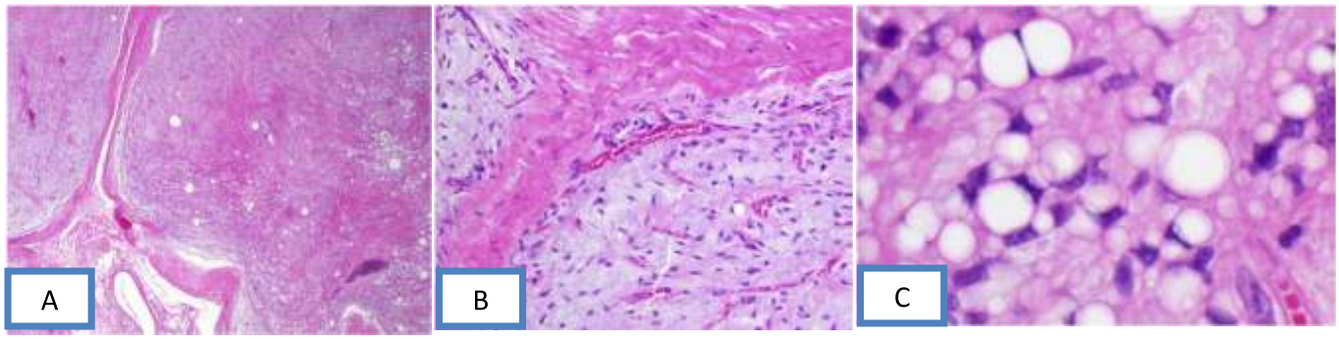

Fig. 9: (A) Nodular tumor. (B) Loosely textured myxoid background with thin chicken wire vasculature and parallel bland fibroblastic cells. Note (C), the hour glass and ice cream cone lipoblasts.

Genetic alterations: EWSR1- CREB1/ EWSR1-ATF1 are the translocations noted in GNET. These are not unique and may be seen in clear cell sarcoma of soft tissue and angiomatoid fibrous histiocytoma. Unlike many other STT where FUS replaces EWS as a translocation partner, GNET has so far not been observed to have FUS translocation.

Differential diagnosis: GIST, monophasic synovial sarcoma, melanoma, soft tissue clear cell sarcoma involving the GI tract and rarely variants of perivascular epithelioid cell tumor (PEComa) and epithelioid MPNST form the differentials. S100 and SOX 10 positivity along with split signals for EWSR1 on chromosome 22 are useful for separating GNET from other differentials.

Spindle Cell Liposarcoma: It is a distinct group of low grade adipocytic neoplasm with prominent spindle cell component. Most of these tumors arose in adults (mean age: 50 years), although 2 cases were in adolescents. They presented as superficial or deep soft tissue masses with a wide size range (mean: 7.5 cm) arising in the groin and paratesticular region, as well as buttock, thigh, flank, and shoulder. Recurrence or metastasis has not been identified.

Histologically, the tumor is nodular and composed of relatively uniform fibroblast-like spindle cells arranged parallel and embedded in a loosely textured myxoid material with an arborizing capillary vasculature. The entire range of lipocyte differentiation is seen from bland fibroblasts-like cells with inconspicuous lipid droplet, as well as more differentiated spindle cells that display minute cytoplasmic lipid droplets. In some of these, the lipid droplets are larger and indent the nucleus, forming univacuolated ("ice cream cone") and bivacuolated ("hourglass") spindled lipoblasts. Signet ring lipoblasts are also seen.

Immunohistochemically the tumor reveals no specific marker.

Genetically; the usual amplification of 12q13-15 with MDM2 and CDK4 gene amplification are absent. Likewise, the tumor is also negative for FUS - DDIT3 / EWSR1- DDIT3 fusion. Lack of these characteristic genetic alterations for WDLS/ALT and Myxoid liposarcoma necessitates the separate classification of spindle cell LPS, and help in differential diagnosis of this condition from WDLS as well as Myxoid liposarcoma.

Spindle Cell Rhabdomyosarcoma of Childhood and Adult: It is an uncommon subtype of rhabdomyosarcoma occurring in both children and adults; and is composed of largely cellular proliferation of predominantly spindled cells. While in children most tumors occur in paratesticular region, in adults the commonest site is head and neck region (> 50% of cases) with cases reported in retroperitoneum, extremities, trunk & vulva. Prognostically also the childhood and adult type spindle cell RMS are different with an excellent prognosis in childhood spindle cell RMS but up to 50% recurrences in adults and a much poorer prognosis.

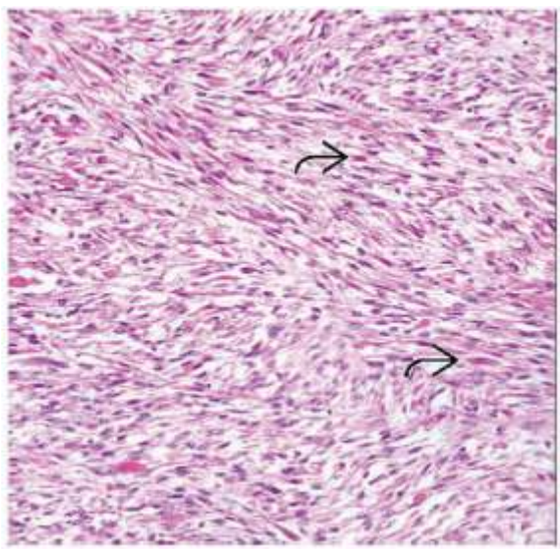

Fig. 10: Spindle cells in fascicular arrangement. Tumor cells at arrow show cross striations.

Histopathological examination shows long intersecting fascicles in herringbone arrangement resembling fibrosarcoma or monophasic synovial sarcoma. Tumor cells are spindly and possess elongated, vesicular nuclei. A few scattered rhabdomyoblasts with cross striations are seen. Frankly pleomorphic areas are absent. No round cell foci exist. Necrosis is absent and mitotic figures are readily observed.

Immunohistochemistry: Desmin expression is characteristically strong and diffuse. Myogenin and MYOD1are also regularly expressed and nuclear expression is specific for RMS. It may be scanty or focal and any cytoplasmic staining should be disregarded.

Differential diagnosis is wide and all spindle cell tumors with fasciculation make up the differential. Being aware and using the right IHC is the answer to making a correct diagnosis.

Genetic alterations are noted in form of NCOA2 rearrangement in childhood spindle cell RMS. No specific genetic alteration has been recurrently identified in the adult type spindle cell RMS.

Sclerosing rhabdomyosarcomas occur in extremities of children and adults alike and are characterized by spindled cells with nested, microalveolar or trabecular growth patterns in a sclerotic stroma. Sclerotic areas can mimic osteoid. Areas of transition from spindle cell RMS are frequently observed. The striated rhabdomyoblasts are noted though rare. Desmin is positive. Myogenin is seen only in a rare cell.

Undifferentiated Round Cell Sarcoma

These tumors are in pattern less sheets of small cells with dense cellularity and high N:C ratio and have uncanny resemblance to Ewing's sarcoma. Ewing's sarcoma has a variety of translocation as shown below. Rarely the EWS gene is replaced by FUS gene.

1. t (11;22) ~85%: EWS-FLI1
2. t(21;22) ~10-15%: EWS-ERG
3. Other (rare)
   a) t(2;22) - EWS-FEV
   b) t(7;22) - EWS-ETV1
   c) t(17;22)- EWS-E1AF

However, many newly described "Ewings like Undifferentiated Round Cell Sarcoma" have been defined with different rearrangements and heterogeneous clinical course and unpredictable therapeutic response. These include broad categories of

1. Those with EWS fusion with non-ETS family member:

a) EWS-NFATC2
b) EWS-PATZ1 (EWS-ZNF278)
c) EWS-SP3 EWS-SMARCA5
d) EWS-POU5F1

2. Those without EWS fusion but with a similar genetic profile:

a) CIC-DUX4 fusions
   • t(4;19)
   • t(10;19)
b) BCOR-CCNB3 fusion

The CIC – DUX4 and BCOR-CCNB3 fused are more common of the two groups above and are described in brief below.

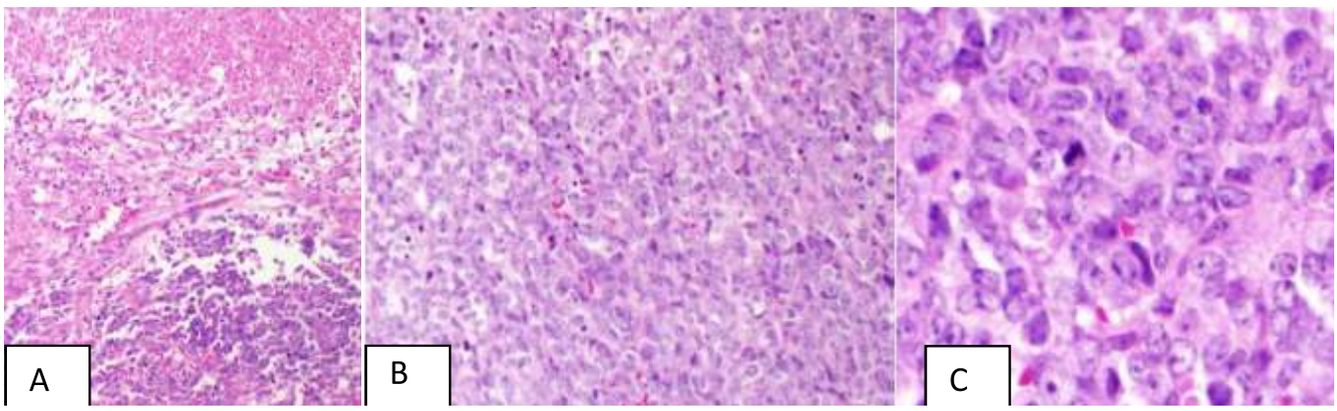

Fig. 11: Undifferentiated round cell sarcoma - morphology is similar to Ewing's sarcoma (A & B). CIC-DUX 4 rearranged Undifferentiated Round cell sarcoma reveals small nucleoli C.

CIC-DUX4 Translocated Undifferentiated Round Cell Tumor

- Usually extraskeletal
- Most often in extremities
- Aggressive course with early metastasis
- More like atypical Ewing sarcoma with nucleoli, more abundant cytoplasm, and extensive necrosis and mitoses
- Variable CD99 positivity
- Frequently WT1 positive
- Fusion gene contains:

o The binding site for TLE proteins, similar to synovial sarcoma (CIC);

o DNA binding site (DUX4);

o Upregulates several ETS family genes, similar to Ewing type fusions;

- Alternate partners for CIC have been described, similar to EWS
- CIC-DUX4 appears to be particularly common in EWS FISH negative Ewing-like tumors.

BCOR-CCNB3 Sarcomas

- Usually arise in bone
- Resembles Ewing sarcomas clinically and morphologically
- Rare, <5%
- Fuses BCOR, an epigenetic repressor, to cyclin B3
- Amplifies the ability of cyclin B3 to drive cell cycle events
- Causes loss of function of BCOR, and epigenetic instability

Conclusions

The molecular genetics of soft tissue sarcoma is helping define new categories of soft tissue tumors and is also separating out previously defined entities into new taxonomically better biological and therapeutic categories. Deeper insights into molecular tumorigenesis will further expand as well as telescope the diagnostic categories as exemplified by HFLT, PHAT & MIFS. This attempt will also help explain the differential response to therapeutic interventions in a morphological akin but molecularly separate tumors as typified by differences in EWS rearranged versus non EWS rearranged Ewing's and Ewing's like sarcomas.

(Dr Anurag Mehta, Director Laboratory Services & Research, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi)

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