Soft tissue Sarcomas
An overview
Outlines

Preview

Diagnostic approach

Staging

WHO classification

Grading

Molecular and cytogenetics

Discussion of some entities
Soft tissue sarcomas

- <1% of all the malignancies
- Sarcomas << benign soft tissue tumours
- children higher frequency than adults
- Common locations – extremities, retroperitoneum, head & neck and organ specific
- Around 10% detected with metastasis, common in lungs
- Around 75% are undifferentiated sarcomas (Sarcoma NOS)

- Therapy
  - Various combinations advocated
  - Surgery is the primary therapeutetic tool
  - Adjuvant radiotherapy needed in some conditions and situations
  - Necessary for chemotherapy depends on the subtype
    - Ewing’s, RMS, GIST etc.,
    - Choice of drugs also vary
An approach to the diagnosis of soft tissue and bone tumours

It starts at the clinic, a good case history helps a lot for the reporting pathologist.

Age, duration of lesion, growth rate, associated pain, trauma, family history, other signs and symptoms……
Imaging studies

1. Conventional x-ray
2. CT scan
   - small bone tumours
   - metastases
   - extent of involvement
3. MRI
   - soft tissue lesions, especially non-calcified
   - T1 and T2 weighted
   - normal anatomical structures
   - organ or tissue conservative surgeries
4. Isotope PET scan
   - uptake study – for diagnosing metastatic disease
   - (technetium, thallium, gallium, fluorodeoxyglucose)
5. Ultrasound
   - cystic masses
Staging Work-Up – What are we looking for?

- CT/MRI (primary)
  - Helpful to delineate soft tissue planes; pre-surgical evaluation
- CT (chest)
  - Look for metastatic disease in the lungs (common site of metastases)
- CT (body)
  - Look for lymph node involvement

- Bone Scan
  - Look for metastases to bone

- CT/PET
  - May give helpful information about tumor ‘activity’ and response to therapy

- Bone Marrow Evaluation
  - Look for metastatic disease
Tissue diagnostic procedures

1. frozen section (intra-operative assessment)
2. biopsy (guided)
3. FNAC
4. wedge resection
5. excision/resection (management)
6. Ancillary tests including IHC, EM and Molecular....
WHO classification of soft tissue tumours

- Adipocytic
- Fibroblastic / myofibroblastic
- Fibrohistiocytic
- Smooth muscle
- Pericytic cell (perivascular)
- Vascular
- Chondro-osseous tumours
- Peripheral nerve sheath
- Skeletal muscle
- Gastrointestinal stromal tumours
- Tumours of uncertain differentiation
- UNDIFFERENTIATED/UNCLASSIFIED SARCOMAS
Grading of soft tissue tumours
FNCLCC grading system

3 parameters: differentiation (1 to 3), mitosis (1 to 3), necrosis (0 to 2)

**Differentiation**
1 – resembling normal mesenchymal tissue and difficult to distinguish from the counterpart benign tumour (e.g. Well diff. liposarcoma and leiomyosarcoma)

2 – certain histologic type (e.g. myxoid liposarcoma)

3 – synovial sarcoma, embryonal sarcoma, sarcomas (undifferentiated)

*Note: subjective, and not included every subtype of sarcoma*

**Mitoses**
1 – 0 to 9/10 HPF
2 – 10 to 19/10 HPF
3 – ≥ 20/10 HPF

**Necrosis**
0 – no necrosis
1 – ≤50% necrosis
2 - >50% necrosis

**Histologic Grade**
1 – 2 or 3
2 – 4 or 5
3 – 6 to 8
# Tumor Differentiation Score According to Histologic Type in the Updated Version of the French Federation of Cancer Centers Sarcoma Group System

**Tumor Differentiation**

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated liposarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Round cell liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Pleomorphic liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Myxofibrosarcoma (myxoid malignant fibrous histiocytoma [MFH])</td>
<td>2</td>
</tr>
<tr>
<td>Typical storiform MFH (sarcoma, NOS)</td>
<td>3</td>
</tr>
<tr>
<td>MFH, pleomorphic type (patternless pleomorphic sarcoma)</td>
<td>3</td>
</tr>
<tr>
<td>Giant cell and inflammatory MFH (pleomorphic sarcoma, NOS with giant cells or inflammatory cells)</td>
<td>3</td>
</tr>
<tr>
<td>Well differentiated leiomyosarcoma</td>
<td>1</td>
</tr>
<tr>
<td>Conventional leiomyosarcoma</td>
<td>2</td>
</tr>
<tr>
<td>Poorly differentiated / pleomorphic / epithelioid leiomyosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Biphasic / monophasic synovial sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Poorly differentiated synovial sarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Pleomorphic rhabdomyosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Extraskeletal osteosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Ewing sarcoma / PNET</td>
<td>3</td>
</tr>
<tr>
<td>Malignant rhabdoid tumor</td>
<td>3</td>
</tr>
<tr>
<td>Undifferentiated sarcoma</td>
<td>3</td>
</tr>
</tbody>
</table>
Basic immunostains
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokeratins</td>
<td>Epithelioid sarcoma, synovial sarcoma, some angiosarcomas and leiomyosarcomas</td>
</tr>
<tr>
<td>Vimentin</td>
<td>All sarcomas</td>
</tr>
<tr>
<td>Desmin</td>
<td>Benign and malignant smooth and skeletal muscle tumors</td>
</tr>
<tr>
<td>Glial fibrillary acidic protein</td>
<td>Some schwannomas, myoepithelial tumors</td>
</tr>
<tr>
<td>Pan-muscle actin</td>
<td>Benign and malignant smooth and skeletal muscle tumors, myofibroblastic tumors and pseudotumors</td>
</tr>
<tr>
<td>Smooth muscle actin</td>
<td>Benign and malignant smooth muscle tumors, myofibroblastic tumors and pseudotumors, myoepithelial tumors</td>
</tr>
<tr>
<td>Caldesmon</td>
<td>Benign and malignant smooth muscle tumors</td>
</tr>
<tr>
<td>Myogenic nuclear regulatory proteins (myogenin, MyoD1)</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>S-100 protein</td>
<td>Benign and malignant peripheral nerve sheath tumors, cartilaginous tumors, normal adipose tissue, Langerhans cells,</td>
</tr>
<tr>
<td>Epithelial membrane antigen</td>
<td>Epithelioid sarcoma, synovial sarcoma, Perineurioma,</td>
</tr>
<tr>
<td>CD31</td>
<td>Benign and malignant vascular tumors</td>
</tr>
<tr>
<td>Von Willebrand factor (factor VIII–related protein)</td>
<td>Benign and malignant vascular tumors</td>
</tr>
<tr>
<td>CD34</td>
<td>Benign and malignant vascular tumors, solitary fibrous tumor, hemangiopericytoma, epithelioid sarcoma, dermatofibrosarcoma protuberans</td>
</tr>
<tr>
<td>Immunohistochemistry Marker</td>
<td>Sarcoma Type and Associated Conditions</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>CD99 (MIC2 gene product)</td>
<td>Ewing sarcoma/primitive neuroectodermal tumor, some rhabdomyosarcomas, some synovial sarcomas</td>
</tr>
<tr>
<td>CD68 and CD163</td>
<td>Macrophages, fibrohistiocytic tumors</td>
</tr>
<tr>
<td>Melanosome-specific antigens (HMB-45, Melan-A, tyrosinase, microphthalmia transcription factor)</td>
<td>PEComa, clear-cell sarcoma, Melanotic schwannoma</td>
</tr>
<tr>
<td>Claudin-1</td>
<td>Perineurioma</td>
</tr>
<tr>
<td>Mdm2 and CDK4</td>
<td>Well-differentiated and dedifferentiated liposarcoma</td>
</tr>
<tr>
<td>Glut-1</td>
<td>Perineurioma, infantile hemangioma</td>
</tr>
<tr>
<td>INI1</td>
<td>Expression lost in extrarenal rhabdoid tumor and epithelioid sarcoma</td>
</tr>
<tr>
<td>TLE1</td>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>TFE3</td>
<td>Alveolar soft part sarcoma</td>
</tr>
<tr>
<td>WT1 (carboxy-terminus)</td>
<td>Desmoplastic small round cell tumor</td>
</tr>
<tr>
<td>Brachyury</td>
<td>Chordoma</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>Osteogenic sarcoma</td>
</tr>
</tbody>
</table>
## Markers Useful in the Diagnosis of Selected Tumor Types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Useful Marker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiosarcoma</td>
<td>CD31, CD34, FLI1, von Willebrand factor</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Muscle (smooth) actins, desmin, caldesmon</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>MyoD1, myogenin; muscle (sarcomeric) actins; desmin</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>Cytokeratins, vimentin, desmin, carboxyl-terminal WT1</td>
</tr>
<tr>
<td>Chordoma</td>
<td>Cytokeratins, S100 protein, brachyury</td>
</tr>
<tr>
<td>Ewing sarcoma/PNET</td>
<td>CD99 (p30/32-MIC2), FLI-1</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Cytokeratin, EMA, TLE1</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>Cytokeratin, CD34, INI1 (loss of expression)</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>S-100, CD57, nerve growth factor receptor, EMA, claudin-1, Glut-1</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>MDM2, CDK4</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>S-100 protein</td>
</tr>
<tr>
<td>Osteogenic sarcoma</td>
<td>Osteocalcin</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>CD31, CD34, VEGFR3, HHV8</td>
</tr>
<tr>
<td>Myoepithelial tumors</td>
<td>Cytokeratins, smooth muscle actin, S100 protein, glial fibrillary acidic protein</td>
</tr>
<tr>
<td>Myofibroblastic lesions (e.g., nodular fasciitis)</td>
<td>Smooth muscle actins</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>CD117a (c-kit), CD34, DOG-1</td>
</tr>
<tr>
<td>Hemangiopericytoma, solitary fibrous tumor</td>
<td>CD34</td>
</tr>
<tr>
<td>Glomus tumors</td>
<td>Smooth muscle actins, type IV collagen</td>
</tr>
<tr>
<td>Angiomatoid (malignant) fibrous histiocytoma</td>
<td>Desmin, EMA, CD68</td>
</tr>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>TFE3</td>
</tr>
<tr>
<td>Perivascular epithelioid cell neoplasms</td>
<td>Smooth muscle actins, melanocytic markers</td>
</tr>
</tbody>
</table>
Cytogenetics
Tools of Molecular Pathology

A. Recombinant DNA Technology
B. Polymerase Chain Reaction
C. Southern Blot
D. Northern Blot
E. Cytogenetic-Karyotyping
F. FISH
G. CGH (Comparative genomic hybridization) / Loss of heterozygosity analysis

F. Array-based Technologies
<table>
<thead>
<tr>
<th>Type</th>
<th>Translocation</th>
<th>Fusion Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar soft part sarcoma</td>
<td>t(X;17)(p11.2;q25.3)</td>
<td>TFE3/ASPL</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13)(q35;q14)</td>
<td>PAX3/FKHR</td>
</tr>
<tr>
<td></td>
<td>t(1;13)(p36;q14)</td>
<td>PAX7/FKHR</td>
</tr>
<tr>
<td></td>
<td>t(X;2)(q13;q35)</td>
<td>PAX3/AFX</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)(q13;q12)</td>
<td>EWSR1-ATF1</td>
</tr>
<tr>
<td></td>
<td>t(2;22)(q33;q12)</td>
<td>EWSR1-CREB1</td>
</tr>
<tr>
<td>Congenital fibrosarcoma</td>
<td>t(12;15)(p13;q25)</td>
<td>ETV6/NTRK3</td>
</tr>
<tr>
<td>Note: The same translocation seen in congenital mesoblastic nephroma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DFSP and giant cell fibroblastoma</td>
<td>t(17;22)(p21;q13)</td>
<td>COL1A1-PDGFB (often within a ring chromosome)</td>
</tr>
</tbody>
</table>
GIST
c-kt Mutations (various)

Ewing sarcoma/pPNET
t(11;22)(q24;q12) EWS/FLI1
t(21;22)(q22;q12) EWS/ERG
t(7;22)(q22;q12) EWS/ETV1
t(17;22)(q21;q12) EWS/EIAF
t(2;22)(q33;q12) EWS/FEV
inv(22)(q12q12) EWS/ZSG

Extraskeletal myxoid chondrosarcoma

t(9;22)(q22-31;q12) EWS/CHN
t(9;17)(q22;q11) TAF2N/CHN

IMT

2p23 rearrangements ALK
Myxoid/round cell liposarcoma
  t(12;16)(q13;p11)
  t(12;22)(q13;q12)  
  FUS/CHOP  EWS/CHOP

Well-differentiated and dedifferentiated liposarcoma
  12q13-15 amplification
  CDK4 and MDM2
  (Supernumerary ring and giant marker)

Synovial sarcoma
  t(X;18)(p11.2;q11.2)  
  SYT/SSX1
  SYT/SSX2
  SYT/SSX4

Low grade fibromyxoid sarcoma & Hyalinizing spindle cell tumour with giant rosettes
  t(7;16)(q33;p11)
  t(11;16)(p13;p11)  
  FUS-CREB3L2
  FUS-CREB3L1

Malignant hemangiopericytoma
  t(12;19)(q13;q13)
Aneurysmal bone cyst
t(16;17)(q22;p13) CDH11-USP6
t(1;17)(p34.1-34.3;p13) TRAP150-USP6

Angiomatoid fibrous histiocytoma
t(12;22)(q13;q12) EWSR1-ATF1
t(2;22)(q33;q12) EWSR1-CREB1
(same as clear cell sarcoma)

Desmoplastic round cell tumour
t(11;22)(p13;q12) EWS-WT-1
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Chromosomal Abnormality</th>
<th>Associated Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leiomyoma of uterus</td>
<td>t(12;14)(q15;q24)</td>
<td>HMGA2-RAD51L1</td>
</tr>
<tr>
<td>Lipoblastoma</td>
<td>8q12 rearrangements</td>
<td>PLAG1</td>
</tr>
<tr>
<td>Chondroid lipoma</td>
<td>t(11;16)(q13;p13)</td>
<td>C11orf95-MKL2</td>
</tr>
<tr>
<td>Lipoma, conventional</td>
<td>12q15 rearrangements</td>
<td>HMGA2</td>
</tr>
<tr>
<td></td>
<td>6p21 rearrangements</td>
<td>HMGA1</td>
</tr>
<tr>
<td>Chondromyxoid fibroma</td>
<td>inv(6)(p25q13)</td>
<td></td>
</tr>
<tr>
<td>Aggressive angiomyxoma</td>
<td>12q15 rearrangements</td>
<td>HMGA2</td>
</tr>
<tr>
<td>GCT of tendon sheath</td>
<td>t(1;2)(p13;q37)</td>
<td>CSF1-COL6A3</td>
</tr>
<tr>
<td>Pericytoma</td>
<td>t(7;12)(p22;q13)</td>
<td>ACTB/GL1</td>
</tr>
<tr>
<td>Desmoplastic fibroblastoma</td>
<td>t(2;11)(q31;q12)</td>
<td>FOSL1</td>
</tr>
</tbody>
</table>
ATYPICAL LIPOMATOUS TUMOUR (ALT)
WELL DIFFERENTIATED LIPOSARCOMA (WDLS)

WDLS/ALT, most common variant of liposarcoma – 50%

Locally aggressive (depends on location)

Occurs almost exclusively in the adult (5th-8th decade) except in the Myxoid LS variant where the patients are younger.

May resemble normal fat / significant nuclear atypia in adipocytes and stromal cells.

Terminology – Confusion
Somatic soft tissue – ALT
Retroperitoneum, paratesticular region, head & neck – WDLS

M = F

Clinically, deep seated, painless slowly enlarging mass
In any location have a tendency to recur if incompletely excised, may be a major problem in retroperitoneal, paratesticular and head & neck Region.

In these locations multiple recurrences may lead to dedifferentiation (again vary based on location)

>20% (dedifferentiation), >80% (mortality) in retroperitoneum

<2% (dedifferentiation), 0 in extremities

**Three main variants**

(i) Lipoma – like

(ii) Sclerosing

(iii) Inflammatory
LIPOMA-LIKE

• Predominant mature adipocytic like cells

• Slight variation in sizes

• Nuclear hyperchromasia +

• Atypical stromal cells++ and diagnostic

• Lipoblasts may or may not be seen (not a diagnostic requirement)
SCLEROSING

• Fibrillary collagenous stroma

• Nuclear hyperchromasia ++

• Atypical stromal cells ++ and diagnostic

• Lipoblasts may or may not be seennic

• Lipogenic areas are minimal
INFLAMMATORY

• mature adipocytic like cells admixed with polytypic lymphocytes in a Aggregates

• Nuclear hyperchromasia +

• Atypical stromal cells++ and diagnostic

• Lipoblasts may or may not be seen

• Lipogenic areas scarce

ALL THREE VARIANTS CAN BE SEEN IN A TUMOUR, TO A VARIABLE DEGREE
GENETICS

• Supernumerary ring and giant marker chromosomes

• 12q14-15 region (MDM2 and CDK4)

• Amplification and overexpression of MDM2

• CDK4 (around 40%)
R-banded karyotype showing the abnormal chromosome 11 (thin arrow) and the three supernumerary marker chromosomes (thick arrow). Anne Forus et. al
ring chromosome.
Dedifferentiated liposarcoma

Progression of ALT/WDLS in primary or recurrence to high grade sarcoma

Most common in retroperitoneum AND paratesticular region

Rare in extremities

Long standing mass, with sudden increase in size

Variegated gross appearance
Histology

Undifferentiated pleomorphic sarcoma
Myxofibrosarcoma
Heterologous differentiation including myogenic, osteogenic, chondromatous and angiogenic

Pleomorphic liposarcoma like differentiation (lipogenic) is also seen

Immunophenotypically and cytogenetically similar to ALT/WDLS

Worse prognosis/ more recurrences/ distant metastasis
Pleomorphic MFH like appearance of Dedifferentiated Liposarcoma
Myxoid/round cell liposarcoma

Young adults
Deep-seated in extremities (thigh)
Rare in retroperitoneum or other sites
M = F

Metastatic deposits in unusual sites, even before to the lungs

Macroscopy
Multinodular, well circumscribed, glistening and gelatinous (myxoid)
Tan and fleshy (round cell areas)
Histology

- multinodular with increased cellularity at periphery of nodules
- myxoid matrix, occ. with mucin pools
- typical delicate branching vessels (chicken wire)
- bland round to oval mesenchymal cells and univacuolated lipoblasts
- progression to round cell liposarcoma histological continuum
characteristic translocation
\( t(12;16)(q13;p11) \)
Pleomorphic LS

- It’s rare and very high grade neoplasm
- Low incidence around 5%.
- Elderly
- Predominantly large muscles of extremities.
- Metastasis to lungs (common).
- Two variants – Pleomorphic and epithelioid.
- Very large pleomorphic lipoblasts
- The epithelioid variant which can be misdiagnosed as carcinoma.
- S100 protein may or may not be positive and cytokeratins may be present – should not be confused with carcinomas
Undifferentiated/unclassified sarcoma

Synonyms – UPS, Sarcoma NOS, Pleomorphic MFH

All ages

M=F

Upto 20% in all sarcoma typespe

Pleomorphic and spindle cell subtypes more common in older individuals

Round cell subtype most frequent in young patients
Grossly, heterogenous in appearance, no specific features
HISTOLOGY

- Admixture of round, oval, spindled and pleomorphic cells
- Collagenous to myxoid extracellular matrix
- Cellular atypia and nuclear pleomorphism (varying degree)
- Mitoses, including abnormal forms
- Tumor necrosis
- Giant cell variant: numerous osteoclast-like giant cells
- Inflammatory variant: numerous xanthoma cells and neutrophils, few tumor cells
Round cell morphology

- relative uniform round cells
- high N/C ratio
- resembles more defined other small round cell tumours including Ewing’s
- No specific immunohistochemical or genetic alteration
Inflammatory variant
Spindle cell morphology
Epithelioid morphology
Round cell morphology
Myxofibrosarcoma (Myxoid MFH)

Malignant fibroblastic neoplasm of varying grades, cellularity.

Elderly

M > F

Limb girdles

Slow growing and painless mass

Dermal and subcutaneous location (more common)

**Macroscopy**

Multiple, gelatinous to variegated (based on grade) mass
Histology

Broad spectrum of cellularity, pleomorphism and proliferation

Low-grade – more myxoid, hypocellular with characteristic vasculature (curvilinear)

Intermediate-grade – in-between low and high grade

High-grade – similar to pleomorphic sarcoma

Immunohistochemistry – MSA and SMA positivity in some

Prognosis:
- Low-grade – local recurrences
- High-grade – distant metastasis.
Summary

Multidisciplinary Approach:
- Clinical data
- Imaging
- Macroscopic features
- Histology
- Immunohistochemistry
- Ultrastructure
- Cytogenetics
Acknowledgements

1. Web articles
2. Text books
3. WHO – soft tissue tumours