Recent developments in soft tissue sarcoma diagnosis

Andrew Horvai MD PhD
UCSF
Outline

• Introduction: Background and perspective
• Update: Synovial sarcoma
• Update: Liposarcoma
• Conclusions
Background: Incidence

Source: American Cancer Society 2007
Background: Classification

- WHO recognizes over 100 distinct neoplastic soft tissue tumors (not including reactive proliferations)

- Traditional classification by differentiation
  - Leaves large “uncertain” category
  - Alveolar soft part sarcoma, Ewing sarcoma

- Traditional classification by grade
  - Leaves category with unpredictable behavior
  - Solitary fibrous tumor, myxoid chondrosarcoma
The “gold standard” of diagnosis

Rudolf Virchow

Synovial sarcoma
Biphasic synovial sarcoma

Synovial sarcoma

Keratin
Monophasic Synovial sarcoma

Synovial sarcoma

Malignant peripheral nerve sheath tumor
Synovial sarcoma genetics
t(X;18) Specific?

Malignant Peripheral Nerve Sheath Tumors with t(X; 18). A Pathologic and Molecular Genetic Study
Maureen J. O'Sullivan, Michael Kyriakos, Xiaopei Zhu, Mark R. Wick,¹ Paul E. Swanson, Louis P. Dehner, Paul A. Humphrey, John D. Pfeifer

L.V. Ackerman Laboratory of Surgical Pathology, Washington University Medical Center, St. Louis, Missouri.

• t(X;18) in 15/20 malignant peripheral nerve sheath tumors by RT-PCR

• “Nonspecificity of translocation-based markers not unexpected given the experience with immunohistochemical markers”
t(X;18) saved?

Letters to the Editor


Marc Ladanyi, M.D.
James M. Woodruff, M.D.
Memorial Sloan-Kettering Cancer Center,
New York, New York

Bernd W. Scheithauer, M.D.
Mayo Clinic, Rochester, Minnesota

Julia A. Bridge, M.D.
University of Nebraska Medical Center, Omaha,
Nebraska

Frederic G. Barr, M.D., Ph.D.
Hospital of the University of Pennsylvania,
Philadelphia, Pennsylvania

John R. Goldblum, M.D.
Cleveland Clinic Foundation, Cleveland, Ohio

Cyril Fisher, M.D.
The Royal Marsden NHS Trust, London, UK

Antonio Perez-Atayde, M.D.
Children’s Hospital, Boston, Massachusetts

Paola Dal Cin, Ph.D.
Christopher D. M. Fletcher, M.D.
Jonathan A. Fletcher, M.D.
Brigham and Women’s Hospital, Boston, MA

• 0/145 cases of MPNST with t(X;18)

• “Fundamental biologic differences between expression of normal antigens (keratin) by a tumor and detection of an abnormal gene fusion implicated in the development of that tumor.”
Synovial sarcoma: FISH

A

Break apart probes

18q

SYT

Xp

SSX

18q

SYT

Xp

SSX

t(X;18)

Bring together probes

B

C
Genetic and molecular testing for \( t(X;18) \)

Cytogenetics

Reverse transcriptase PCR
Synovial sarcoma subtype and SYT-SSX fusion variant
Outcome and SYT-SSX fusion variant

Survival with localized disease

% Surviving

Years since diagnosis

SSX1
SSX2

Liposarcoma

- Well-differentiated/dedifferentiated
- Myxoid
- Pleomorphic
Well-differentiated/Dedifferentiated liposarcoma
Liposarcoma

- Well differentiated
  - Prognosis ~ location
  - “Atypical lipomatous tumor”

- Dedifferentiated
  - Retroperitoneal sarcomas
  - Prognosis
    - Compared to other sarcomas
    - By grade


McCormic et al. AJSP 1994 18:1213-1223
Liposarcoma: Genetics

Well differentiated liposarcoma

Dedifferentiated liposarcoma

Array comparative genomic hybridization
Liposarcoma: 12q13-q15

- **MDM2**: p53
- **CDK4**: Rb

Well differentiated liposarcoma

MDM2, CDK4
### Dedifferentiated liposarcoma

The table below summarizes the percent positive cases for different types of sarcomas, specifically focusing on MDM2, CDK4, and MDM2 and CDK4.

<table>
<thead>
<tr>
<th>Type of sarcoma</th>
<th>MDM2</th>
<th>CDK4</th>
<th>MDM2 and CDK4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dedifferentiated liposarcoma</td>
<td>95</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Malignant peripheral nerve sheath tumor</td>
<td>64</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>42</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Embryonal Rhabdomyosarcoma</td>
<td>29</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Alveolar Rhabdomyosarcoma</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Pleomorphic Rhabdomyosarcoma</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Myxoid Liposarcoma</td>
<td>4</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pleomorphic Liposarcoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&quot;Malignant fibrous histiocytoma&quot;</td>
<td>11</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Binh et al. 2005 AJSP 29(10) 1340-1347
PPAR-γ

- Regulates growth and differentiation of adipocytes
- Agonist: Thiazolidinedione drugs (troglitazone)
- *In vitro*: arrests growth of liposarcoma cells
- *In vivo*:

**Induction of solid tumor differentiation by the peroxisome proliferator-activated receptor-γ ligand troglitazone in patients with liposarcoma**

(nuclear receptors/sarcoma/drug development/oncology/antineoplastic)

**George D. Demetri**†, **Christopher D. M. Fletcher**‡, **Elisabetta Mueller**§, **Pasha Sarraf**§, **Ryan Naujoks**§, **Natalee Campbell**¶, **Bruce M. Spiegelman**§, and **Samuel Singer**¶

Departments of †Adult Oncology and ¶Cell Biology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02115; and Departments of §Pathology and ¶Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115

- 3 patients, short follow up (6 wks – 2 yrs)
- Increased fat accumulation, decreased proliferation
PPAR-γ: Therapy?

A phase II trial with rosiglitazone in liposarcoma patients

G Debrock*,1, V Vanhentenrijk2, R Sciot2, M Debiec-Rychter3, R Oyen4 and A Van Oosterom1

1Department of Medical Oncology, University Hospital Gasthuisberg, Universiteit Leuven, Herestraat 49, Leuven 3000, Belgium; 2Department of Pathology, University Hospital Gasthuisberg, Universiteit Leuven, Herestraat 49, Leuven 3000, Belgium; 3Department of Human Genetics, University Hospital Gasthuisberg, Universiteit Leuven, Herestraat 49, Leuven 3000, Belgium; 4Department of Radiology, University Hospital Gasthuisberg, Universiteit Leuven, Herestraat 49, Leuven 3000, Belgium


- 9 patients, 2 dedifferentiated
- Follow-up 2 to 16 months
- Only 1 case (dediff) had upregulation of adipocyte genes, no clinical response
PPAR-γ: Diagnosis

“Undifferentiated” sarcoma

PPAR-γ
Conclusions

• Classification of sarcomas developing
• Histologic typing and grading most important predictive variables
• Molecular diagnosis
  – Increases accuracy
  – Insight into tumor biology – practical tools
  – Does not overrule a reasonable morphologic diagnosis