Klinisch belang van chromosomale translocatie detectie in sarcomen

Judith V.M.G. Bovée, M.D., Ph.D.
Department of Pathology
Leiden University Medical Center

Classification of bone and soft tissue tumours

- Bone and soft tissue tumours are difficult for pathologists:
  - Relatively rare
  - >40 entities
  - Considerable morphological overlap
  - Entities differ widely in treatment and outcome
- Increasing knowledge on genetic background of tumours
- 2002 WHO classification on bone and soft tissue tumours

Diagnosis of soft tissue tumours

- Classifying soft tissue tumours:
  - H&E
  - Immunohistochemistry
  - Molecular diagnostics

  Cornerstone of diagnosis

  • 15-20% of mesenchymal tumours carry translocations
  • Only in specific tumour types:
    - Ewing sarcoma, myxoid liposarcoma, synoviosarcoma up to 100%
    - Absent in osteosarcoma, chordrosarcoma, leiomyosarcoma

Techniques for translocation detection

- Conventional cytogenetics (fresh tissue)
- RT-PCR (frozen tissue, paraffin)
- FISH (paraffin material, not decalcified)
- (immunohistochemistry)

Relevance of translocations in sarcomas

1. Clues about the pathogenesis
2. Classification of sarcomas
3. Usefull in differential diagnosis
4. Detection minimal residual disease?
5. Prediction of outcome?
6. Identify targets for treatment

Translocations in sarcomas

<table>
<thead>
<tr>
<th>Protein name</th>
<th>Tumor</th>
</tr>
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<tbody>
<tr>
<td>FUS</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>ETV6</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>ETV4</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>PAX3</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>WT1</td>
<td>Angiosarcoma/bone sarcoma</td>
</tr>
<tr>
<td>NTRK3</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>ATF1</td>
<td>Clear cell sarcoma</td>
</tr>
<tr>
<td>CREB1</td>
<td>Clear cell sarcoma</td>
</tr>
<tr>
<td>GAD2P1</td>
<td>Myxoid round cell sarcoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RNA binding</th>
<th>DNA binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-PCR</td>
<td>FISH</td>
</tr>
<tr>
<td>Fresh tissue</td>
<td>Paraffin</td>
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<tr>
<td>DNA binding</td>
<td>RNA binding</td>
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</tbody>
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Conventional karyotyping

RT-PCR

FISH analysis

EWS1 translocation

Small blue round cell tumours: differential diagnosis

Ewing versus poorly diff synovio: immunohistochemistry
Ewing sarcoma

- t(11;22)(q24;q12) EWS-FLI1 85%
- t(17;22)(q12;q12) EWS-ETV4 <1%
- t(2;22)(q33;q12) EWS-FEV <1%
- t(16;21)(p11;q22) FUS-ERG

→ EWS-ETS fusionproteins

Ewing sarcoma / PNET specific translocations

Prognostic value of EWSR1-FLI1 fusion type?

Different variants:
- Type 1: 60%
- Type 2: 25%

Type 1 associated with better prognosis:

Spindle cell tumours: differential diagnosis

- Monophasic synovial sarcoma
- Malignant peripheral nerve sheath tumour
- Fibrosarcoma HE, vim+
- Leiomyosarcoma Muscle markers+, S100+, HMB45+
- Clear cell sarcoma EWSR1 rearrangement

Ewing sarcoma

- White, young persons (80% < 20 jaar)
- Male > female
- In bone and soft tissue
- Resection, with chemotherapy (incl pre-operative), radiotherapy
- 5 years survival 50%
**Synovial sarcoma**

- All ages, peak 10-35 yrs
- Soft tissue: 60% in lower extremity (esp thigh)
- High grade sarcoma
- 5 year survival 50%
- 10 year survival 20-30%

**Malignant Peripheral Nerve Sheath Tumors with t(X; 18). A Pathologic and Molecular Genetic Study**

- Biphasic: spindle and epithelial cell component
- Monophasic: only spindle (or epithelial) cells

**Aneurysmal Bone Cyst**

- t(16;17)(q22;p13) → oncogenic activation USP6 gene

**Clear cell sarcoma vs. melanoma**

<table>
<thead>
<tr>
<th>Clear cell sarcoma</th>
<th>melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100</td>
<td>+</td>
</tr>
<tr>
<td>HMB45</td>
<td>+</td>
</tr>
<tr>
<td>vimentin</td>
<td>+</td>
</tr>
<tr>
<td>keratin</td>
<td>↓ or −</td>
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</tbody>
</table>

**SYT-SSX fusion: prognostic value?**

- Association fusion type and morphology:
  - Monophasic: mostly SYT-SSX2
  - Biphasic: mostly SYT-SSX1
- SYT-SSX1 associated with early relapse

- Other groups: no association fusion type and prognosis (n=141 and n=91)
Clear cell sarcoma vs. melanoma

- "A soft tissue sarcoma of young adults with melanocytic differentiation, typically involving tendons and aponeuroses"
- Equal male-female distribution, 5-85 years (median 30 yrs.)
- Extremities
- Deep location
- Variable outcome, prognosis usually bad, recurrence sometimes after 10 years

Dermatofibrosarcoma protuberans

- Poorly recognized by clinicians
- Adults 20-50 years, male predominance
- Duration prior to diagnosis > 5 year; long clinical course
- Location: Trunk, head & neck, proximal extremity
- Regarded a superficial low-grade sarcoma
- Significant risk of local recurrence (<3 yrs)
  - Wide local excision (2-3 cm): 18%
  - Superficial / incomplete excision: 43%
  - Rarely metastases

Clear cell sarcoma: genetics

- Clear cell sarcoma
  - t(12;22)(q13;q12) ATF1-EWSR1
  - t(2;22)(q32;q12) EWSR1-CREB1
- Angiomatoid fibrous histiocytoma
  - t(2;22)(q32;q12) EWSR1-CREB1
  - t(12;22)(q13;q12) EWSR1-ATF1
  - t(12;16)(q13;p11) FUS-ATF1

Dermatofibrosarcoma Protuberans (DFSP)

- Poorly recognized by clinicians
- Adults 20-50 years, male predominance
- Duration prior to diagnosis > 5 year; long clinical course
- Location: Trunk, head & neck, proximal extremity
- Regarded a superficial low-grade sarcoma
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  - Wide local excision (2-3 cm): 18%
  - Superficial / incomplete excision: 43%
  - Rarely metastases

DFSP: genetics

- der(22)t(17;22)(q22;q13) COL1A1-PDGFB
**Conclusion**

Detection of translocations in sarcomas is relevant for:

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