INSM1 IMMUNOHISTOCHEMICAL EXPRESSION IN A LARGE COHORT OF EWING SARCOMA FAMILY OF TUMORS.

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INSM1 IMMUNOHISTOCHEMICAL EXPRESSION

• INSM1 (insulinoma-associated protein 1), also known as zinc-finger protein IA-1, is a developmentally regulated zinc-finger transcription factor.

• It localizes to the nucleus and is expressed in embryonic tissues undergoing neuroendocrine differentiation. Mapping to 20p11.23 chromosome.

• INSM1 is not present in normal adult tissues, but can be found highly expressed in neuroendocrine tumors.

Its expression has been tested in limited series of Ewing sarcoma family of tumors (ESFT).

Given the potential neuroendocrine differentiation in ESFT, we aimed to determine INSM1 expression in a large series of genetically-confirmed ESFT.

As a control we used a cohort of tumors with well-known neuroendocrine differentiation.
UNDIFFERENTIATED NEUROBLASTOMA

H/E

H/E

NB84

CD99
INSM1 Expression in Peripheral Neuroblastic Tumors and Other Embryonal Neoplasms

Hannah Wang¹,², Chandra Krishnan³, and Gregory W Charville¹,²

Table 1. Comparison of INSM1 to Other Neuroendocrine Markers.

<table>
<thead>
<tr>
<th>Tumor Subtype</th>
<th>INSM1</th>
<th>Synaptophysin</th>
<th>Chromogranin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuroblastic tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>39/50 (78)</td>
<td>35/35 (100)</td>
<td>33/35 (94)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>27/32 (84)</td>
<td>29/29 (100)</td>
<td>27/29 (93)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>1/3 (33)</td>
<td>3/3 (100)</td>
<td>2/3 (67)</td>
</tr>
<tr>
<td>Differentiating</td>
<td>21/24 (88)</td>
<td>21/21 (100)</td>
<td>20/21 (95)</td>
</tr>
<tr>
<td>Ganglioneuroblastoma</td>
<td>5/5 (100)</td>
<td>5/5 (100)</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Intermixed</td>
<td>9/9 (100)</td>
<td>5/5 (100)</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Nodulara</td>
<td>6/6 (100)</td>
<td>5/5 (100)</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Maturing</td>
<td>3/3 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matureb</td>
<td>0/6 (0)</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>7/14 (50)</td>
<td>2/14 (14)</td>
<td>1/1 (14)</td>
</tr>
<tr>
<td>Embryonal</td>
<td>3/7 (43)</td>
<td>2/7 (29)</td>
<td>1/7 (14)</td>
</tr>
<tr>
<td>Alveolar</td>
<td>4/6 (67)</td>
<td>0/6 (0)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>Pleomorphic</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
<tr>
<td>Nephroblastoma</td>
<td>7/22 (32)</td>
<td>1/13 (8)</td>
<td>0/13 (0)</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>4/20 (20)</td>
<td>0/9 (0)</td>
<td>0/9 (0)</td>
</tr>
</tbody>
</table>
ES: HISTOLOGICAL SUBTYPES (Conventional, PNET)

IMMUNOHISTOCHEMISTRY: TESTED ANTIBODIES
Llombart, A et al. Prothets consortium Roma 2013

**DIAGNOSTIC**
- CD99
- HNK1
- FLI1/ERG
- CAVEOLIN 1
- NNX2.2

**MOLECULAR TARGETS**
- C-KIT
- EPO
- EPOR
- GSCF
- GSCFR
- IGFR1a

**CELL CYCLE/PROGNOSIS**
- P53, P14, P16
- P21, P27
- Ki67 (MIB 1)

**NEUROENDOCRINE MARKERS**
- CHROMOGRANIN
- SYNAPTOPHYSIN

**MOLECULAR PATHWAYS**
- β-CATENIN
- SNAIL
- SLUG
- GSK-3β
- AKT
- PI3K
- WNT
- NOTCH

**EPITHELIAL DIFFERENTIATION**
- CK, EMA, CEA
- E-CADHERIN
- OCCLUDIN
- ZO-1
- DESMOPLAKIN

**CCN3**
- K19
- NH2
- NH3
- NH4
- NH5
IMMUNOHISTOCHEMISTRY ES: CD99, CAVEOLIN, NXK2.2
NEUROSECRETORY GRANULES: PNET
# INSM1 expression and its diagnostic significance in extraskeletal myxoid chondrosarcoma

Akihiko Yoshida\textsuperscript{1,2}, Naohiro Makise\textsuperscript{1,3}, Susumu Wakai\textsuperscript{1}, Akira Kawai\textsuperscript{2,4} and Nobuyoshi Hiraoka\textsuperscript{1}

<table>
<thead>
<tr>
<th>Entities</th>
<th>N</th>
<th>5–25%</th>
<th>26–50%</th>
<th>51–75%</th>
<th>76–100%</th>
<th>Positive cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraskeletal myxoid chondrosarcoma</td>
<td>31</td>
<td>9</td>
<td>2</td>
<td>5</td>
<td>12</td>
<td>28 (90%)</td>
</tr>
<tr>
<td>Other mesenchymal tumors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skeletal chondrosarcoma</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chordoma</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Myxofibrosarcoma</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Intramuscular myxoma</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Low-grade fibromyxoid sarcoma</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Soft-tissue myoepithelioma</td>
<td>20</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Ossifying fibromyxoid tumor</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Angiomatoid fibrous histiocytoma, myxoid</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Dedifferentiated liposarcoma, myxoid</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>10</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>CIC-rearranged sarcoma</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Poorly-differentiated synovial sarcoma</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>BCO\textsubscript{R}-CCNB3 sarcoma</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Miscellaneous tumors\textsuperscript{a}</td>
<td>22</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Includes 5 cases of clear-cell sarcoma and 17 cases of other sarcomas.
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: STUDY CASES

- 433 ESFT
- 54 Merkel Cell Carcinomas (MCC)
- 97 Synovial sarcomas (SS)
- 28 Solitary fibrous tumor (SFT)
- 200 GIST
- 13 Extraskeletal myxoid chondrosarcomas (EMC).
INSM1 IMMUNOHISTOCHEMICAL TECHNIQUE

• Antibody  SANTA CRUZ BIOTECHNOLOGY, INC.
  INSM1 (A-8): sc-271408

• Technical procedure
  • Immunohistochemistry: paraffin-embedded sections
  • Dilution: 1:50.

Pancreas (positive control)
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION

- Nuclear staining of moderate/strong intensity in at least 5% of tumor cells was considered positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

POSITIVITIES

- 100% MCC  nuclear diffuse and strong intensity
- 61% ESFT  nuclear strong or focal intensity
- 70% EMC  nuclear diffuse or low intensity
- 21% SFT  nuclear low intensity
- 2% SS  occasional focal intensity
- 0.5% GIST  very occasional

Cases were evaluated independently by two pathologists: (ALLB, IM)
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

• MERKEL CELL CARCINOMA CASES: 54/54 positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

• EWING SARCOMA CASES: 433/263 positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

- EWING SARCOMA CASES: 433/263 positive staining was not correlated with the histological subtypes of srct
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

• EXTRASKELETAL MYXOID CHONDROSARCOMA: 13/9 positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

- SOLITARY FIBROUS TUMORS: 28/6 positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

• SYNOVIAL SARCOMAS: 97/2 positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: RESULTS

• GASTROINTESTINAL STROMAL TUMORS: 200/1 positive
INSM1 IMMUNOHISTOCHEMICAL EXPRESSION: CONCLUSION

• INSM1 expression in ESFT is higher than described previously, nevertheless this finding does not distinguish these tumors from other “small round cell tumors” (SRCT) such as MCC, EMC or SS that may show focal or diffuse staining for this marker.

• Therefore, INSM1 immunoreactivity should be interpreted within a specific clinicopathological context.

• Strong and diffuse INSM1 expression in cutaneous SRCT, strongly supports the possibility of MCC, but in soft tissue/bone tumors this immunoreactivity may not exclude a metastatic neuroendocrine tumor, EMC or ESFT.

• New studies are underway to check the prognostic significance of this marker as well as the already-confirmed neuroendocrine differentiation of ESFT.
VALENCIA: CITY OF ARTS AND SCIENCES

THANK YOU FOR YOUR ATTENTION