ALK FUSION-POSITIVE MESENCHYMAL TUMORS

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Companion Meeting of the International Society of Bone and Soft Tissue Pathology
The Evolving Concept of Mesenchymal Tumors

Anaplastic Lymphoma Kinase

Fusion of a Kinase Gene, ALK, to a Nucleolar Protein Gene, NPM, in Non-Hodgkin’s Lymphoma

Stephan W. Morris,* Mark N. Kirstein, Marcus B. Valiente, Kristopher G. Dittmer, David N. Shapiro, David L. Saltman, A. Thomas Look

Hematolymphoid
ALK+ anaplastic large-cell lymphoma
ALK+ diffuse large B-cell lymphoma
Systemic histiocytosis

Epithelial
Lung adenocarcinoma
Renal cell carcinoma
Other carcinomas (very rare)

Melanocytic
Spitz tumor

Mesenchymal
Inflammatory myofibroblastic tumor
Epithelioid fibrous histiocytoma

Tumor types with ALK rearrangements

ACCME/Disclosures

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Dr. Jason Hornick declares he has no conflicts of interest to disclose.
Dramatic Responses to Crizotinib


Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer

NATURE Vol 448 2 August 2007

Many different ALK fusion partners have been identified

<table>
<thead>
<tr>
<th>Fusion partner</th>
<th>Tumor types</th>
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<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATIC</td>
<td>ALC and IMT</td>
<td>NPM</td>
<td>ALC, DLBCL</td>
</tr>
<tr>
<td>CARS</td>
<td>IMT</td>
<td>PPFIKP1</td>
<td>IMT</td>
</tr>
<tr>
<td>CLTC</td>
<td>ALC, DLBCL, IMT</td>
<td>RANPB2</td>
<td>EIMS</td>
</tr>
<tr>
<td>DCTN1</td>
<td>IMT</td>
<td>SEC31A</td>
<td>IMT</td>
</tr>
<tr>
<td>EML4</td>
<td>Lung AdCA, IMT</td>
<td>SQSTM1</td>
<td>DLBCL, EFH</td>
</tr>
<tr>
<td>KIF5B</td>
<td>Lung AdCA</td>
<td>TFG</td>
<td>ALC, lung AdCA</td>
</tr>
<tr>
<td>KLC1</td>
<td>Lung AdCA</td>
<td>TPM3</td>
<td>ALC, IMT</td>
</tr>
<tr>
<td>MSN</td>
<td>ALC</td>
<td>TPM4</td>
<td>IMT</td>
</tr>
<tr>
<td>MYH9</td>
<td>ALC</td>
<td>VCL</td>
<td>EFH, RCC</td>
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Identical ALK gene fusions are shared by different hematolymphoid neoplasms

<table>
<thead>
<tr>
<th>Gene fusion</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM-ALK</td>
<td>Anaplastic large-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Systemic histiocytosis</td>
</tr>
</tbody>
</table>

Identical ALK gene fusions are shared by neoplasms of different lineages

<table>
<thead>
<tr>
<th>Gene fusion</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>EML4-ALK</td>
<td>Lung adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Inflammatory myofibroblastic tumor</td>
</tr>
<tr>
<td>TMP3-ALK</td>
<td>Inflammatory myofibroblastic tumor</td>
</tr>
<tr>
<td></td>
<td>Anaplastic large-cell lymphoma</td>
</tr>
<tr>
<td>SQSTM1-ALK</td>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td></td>
<td>Epithelioid fibrous histiocytoma</td>
</tr>
</tbody>
</table>

ALK fusion partner sometimes results in distinctive patterns of staining by IHC

<table>
<thead>
<tr>
<th>Fusion partner</th>
<th>Tumor types</th>
<th>ALK staining pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPM</td>
<td>ALCL, DLBCL</td>
<td>Cytoplasmic/nuclear/nucleolar</td>
</tr>
<tr>
<td>TPM3</td>
<td>ALCL, IMT</td>
<td>Diffuse cytoplasmic</td>
</tr>
<tr>
<td>EML4</td>
<td>Lung AdCA, IMT</td>
<td>Diffuse cytoplasmic</td>
</tr>
<tr>
<td>CLTC</td>
<td>ALCL, DLBCL, IMT</td>
<td>Punctate cytoplasmic</td>
</tr>
<tr>
<td>RANBP2</td>
<td>EIMS</td>
<td>Nuclear membrane</td>
</tr>
</tbody>
</table>
Anaplastic Large Cell Lymphoma
NPM-ALK

Lung Adenocarcinoma
EML4-ALK

Inflammatory Myofibroblastic Tumor
TPM3-ALK

Epithelioid Inflammatory Myofibroblastic Sarcoma
RANBP2-ALK
**ALK protein expression levels vary considerably – implications for selection of antibodies for IHC**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Level of fusion protein expression</th>
<th>Monoclonal antibody</th>
<th>IHC result</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALCL</td>
<td>High</td>
<td>ALK1</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5A4, D5F3</td>
<td>Positive</td>
</tr>
<tr>
<td>IMT</td>
<td>Intermediate</td>
<td>ALK1</td>
<td>Usually positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5A4, D5F3</td>
<td>Positive</td>
</tr>
<tr>
<td>Lung AdCA</td>
<td>Low</td>
<td>ALK1</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5A4, D5F3</td>
<td>Positive</td>
</tr>
</tbody>
</table>

**MESENCHYMAL TUMORS WITH ALK REARRANGEMENTS**

- Inflammatory Myofibroblastic Tumor
- Epithelioid Fibrous Histiocytoma

**“Inflammatory Pseudotumor”**

- First described in lung
- Various designations:
  - “Plasma cell granuloma,” “plasma cell pseudotumor,” “post-inflammatory tumor,” “myxoid hamartoma,” “inflammatory myofibrohistiocytic proliferation,”
- Reparative/post-inflammatory condition?
- Similar lesions other sites
- Distinctive clinical features:
  - Predilection for children
  - Subset with systemic symptoms
Inflammatory myofibroblastic tumor (plasma cell granuloma). Clinicopathologic study of 20 cases with immunohistochemical and ultrastructural observations.
Ferritsno CT, Manivel JC, De Rosa N, Dehner LP.

20 cases (19 lung)
– Immunohistochemical and ultrastructural features of fibroblasts and myofibroblasts
1 patient 2 recurrences
10 pts with follow-up, ANED

Inflammatory fibrosarcoma of the mesentery and retroperitoneum. A tumor closely simulating inflammatory pseudotumor.
Meiss JD, Exeinger FM.

38 cases
Intra-abdominal, retroperitoneal
Children and adolescents
27 cases with follow-up
– 10 (37%) local recurrence
– 3 (11%) metastasis
– 5 (19%) died from disease

Extrapulmonary inflammatory myofibroblastic tumor (inflammatory pseudotumor). A clinicopathologic and immunohistochemical study of 84 cases.
Coffin CM, J, Watters J, Field JB, Dehner LP.

84 extrapulmonary cases
Significant clinical/histologic overlap with “inflammatory fibrosarcoma”
Mostly children, young adults
75% abdomen, pelvis or retroperitoneum
53 cases with follow-up
– 13 (25%) local recurrence
– No metastases

Inflammatory Myofibroblastic Tumor
• Predilection for children/adolescents
• Wide age range
• Most common sites:
  – Abdominopelvic region, retroperitoneum, lung
• Most present with mass
• Subset with constitutional symptoms
• Wide size range (mean, 5-6 cm)
• Subset in abdomen multiple discrete masses
Inflammatory Myofibroblastic Tumor: Histologic Features

- Fascicles of uniform, elongated spindle cells with vesicular nuclei
- At most mild nuclear atypia
- Prominent inflammatory infiltrate:
  - Primarily plasma cells and lymphocytes
- Occasionally myxoid stroma
- Sometimes hypocellular/fibrous
- Subset contain “ganglion-like” cells
**Inflammatory Myofibroblastic Tumor: Prognosis**

- **WHO**
  Intermediate biologic potential, rarely metastasizing

- **Local recurrence:**
  <2% lung
  25% extrapulmonary (intra-abdominal++)

- **Metastasis:**
  1-3%
  Lung, brain, liver, bone

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**Inflammatory Myofibroblastic Tumor:**

- In general, poor correlation between histology and behavior
- May occasionally recur with higher-grade histology:
  - Increased cellularity or nuclear atypia, high mitotic rate
  - Histiocytoid or round cell cytology
- Referred to as “round cell transformation”
- May also be seen de novo – distinctive aggressive variant
Inflammatory Myofibroblastic Tumor

Abdomen
Primary

Recurrence (3 yrs)

Inflammatory Myofibroblastic Tumor

ALK in IMT

- ALK rearrangement in 60% of IMT <10% in adults >50 yrs
- Heterogeneous fusion partners
- Strong correlation between detection of ALK expression by IHC and ALK rearrangement (new highly sensitive antibodies better)
- ALK negative in other myofibroblastic and smooth muscle tumors, GIST

Recurrent Involvement of 2p23 in Inflammatory Myofibroblastic Tumors
Constance A. Griffin, Anita L. Hawkins, Covil Dvorek, Carol Berkle, Tara Ellingham, and Elizabeth J. Pollman

TPM3-ALK and TPM4-ALK Oncogenes in Inflammatory Myofibroblastic Tumors
Brandon Lawrence, Antonia Pena-Alvarez, Michele K. Hibbard, Brian P. Rubin, Patrick C. Cui, Jack L. Pritch, Olga O. Pintor, Xiong Xiao, Eunhwa Y. Li, Christopher D. Pletcher, and Jonathan A. Pletcher

Inflammatory Myofibroblastic Tumor

Comparison of Clinicopathologic, Histologic, and Immunohistochemical Features Including ALK Expression in Atypical and Aggressive Cases

Cheryl M. Coffin, MD,* Jason L. Hornick, MD, PhD,†
and Christopher D. M. Fletcher, MD, FRCPath†

Am J Surg Pathol • Volume 31, Number 4, April 2007

Selected for local recurrence or metastasis
Included 6 metastatic tumors
None of the metastatic tumors were positive for ALK
ALK favorable prognostic indicator?

Epithelioid Inflammatory Myofibroblastic Sarcoma: An Aggressive Intra-abdominal Variant of Inflammatory Myofibroblastic Tumor With Nuclear Membrane or Perinuclear ALK

Adrián Martínez-Enriquez, MD,*† Wei-Lin Wang, MD,‡ Alexander Roy, MD, PhD,*‡
Dolores Lopez-Torrelo, MD, PhD,§ Alexander J. F. Lazar, MD, PhD,*∥
Christopher D. M. Fletcher, MD, FRCPath,* Cheryl M. Coffin, MD,§
and Jason L. Hornick, MD, PhD†

Am J Surg Pathol • Volume 35, Number 1, January 2011

Predilection for young male adults
Epithelioid morphology, myxoid stroma, prominent neutrophils
Nuclear membrane pattern of ALK staining
RANBP2-ALK fusion
Aggressive sarcoma with rapid recurrences

FISH
ALK 2p23
3' red (t)
5' green (c)

Courtesy of Paola Dal Cin
Epithelioid Inflammatory Myofibroblastic Sarcoma

Small intestine

Mesentery

Omentum

desmin
Epithelioid Inflammatory Myofibroblastic Sarcoma

Targeted Therapy

- Small molecule inhibitors of ALK kinase
- Clinical benefit for patients with advanced EML4-ALK+ lung adenocarcinomas
- Efficacy in ALK+ IMT promising

Multifocal Recurrent EIMS Treated with ALK Inhibitor Crizotinib

3 months

3 of 7 patients with ALK-rearranged IMT partial response
4 of 7 patients with stable disease

Same patient with EIMS from the NEJM case report

1 patient with IMT who progressed on another TKI had a partial response

ALK-Negative Inflammatory Myofibroblastic Tumors?

• Until recently, molecular pathogenesis unknown
• Recent reports identified fusions involving receptor tyrosine kinase genes other than ALK
8-year-old boy with IMT harboring TFG-ROS1 fusion
Inflammatory Myofibroblastic Tumor

Lung Adenocarcinoma

CD74-ROS1
ROS1

TFG-ROS1

ALK-CLTC
ROS1
Epithelioid Fibrous Histiocytoma

- Also known as “epithelioid cell histiocytoma”
- Traditionally considered morphologic variant of cutaneous benign fibrous histiocytoma (dermatofibroma)
- Flesh-colored nodule on extremities of young to middle-aged adults
- Exophytic, well-circumscribed, sometimes with epidermal collarette
- Uniform bland epithelioid cells with vesicular nuclei, small nucleoli, and moderate amounts of eosinophilic or amphophilic cytoplasm; some binucleate cells
**Is epithelioid fibrous histiocytoma related to conventional fibrous histiocytomas?**

<table>
<thead>
<tr>
<th>Histologic feature</th>
<th>Fibrous histiocytoma</th>
<th>Epithelioid fibrous histiocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overlying epidermal hyperplasia</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Tumor margins</td>
<td>Lateral entrapment of hyaline collagen</td>
<td>Sharply circumscribed</td>
</tr>
<tr>
<td>Cytology</td>
<td>Short spindle cells</td>
<td>Epithelioid cells</td>
</tr>
<tr>
<td>Prominent inflammatory infiltrate</td>
<td>Lymphocytes, foam cells</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Fusions involving protein kinase C and membrane-associated proteins in benign fibrous histiocytomas

Anna Plassczyca 1, Jenny Nilsson 1, Linda Magnusson 1, Otte Brosjö 2, Olle Larsson 1, Fredrik Vult von Steyern 1, Henrik A. Domanski 1, Henrik Lillebøj 1, Thoa Fioretos 3, Johnbosco Teyebwa 3, Nils Mandahl 4, Karolin H. Nord 3, Fredrik Mertens 5

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2 Department of Pathology, Karolinska University Hospital, SE-171 77, Sweden
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5 Department of Pathology, University of Lund, Lund University, SE-221 85, Lund, Sweden
**Table 1** Summary of immunohistochemical staining for ALK in epithelioid fibrous histiocytoma and other tumor types

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Total cases</th>
<th>ALK positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid fibrous histiocytoma</td>
<td>33</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Aneruymary fibrous histiocytoma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Atypical fibrous histiocytoma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Atypical fibroblastoma</td>
<td>5</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cellular fibrous histiocytoma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Conventional fibrous histiocytoma</td>
<td>11</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cutaneous syncytial myoepithelioma</td>
<td>10</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Doyle et al. Mod Pathol 2015*
Epithelioid Fibrous Histiocytoma

ALK

Gene fusion detection in formalin-fixed paraffin-embedded benign fibrous histiocytomas using fluorescence in situ hybridization and RNA sequencing

2 ALK-negative epithelioid fibrous histiocytomas with PRKCB rearrangement

Some epithelioid fibrous histiocytomas related to other fibrous histiocytoma variants?

Practice Points I

- Diverse benign and malignant neoplasms harbor ALK rearrangements
- ALK fusion partner correlates with pattern of staining by IHC
- Majority of IMT (60%) harbor ALK rearrangements
- Small subsets of IMT harbor ROS1, NTRK3, RET, and PDGFRB fusions
Practice Points II

- Epithelioid IMT with nuclear membrane ALK (*RANBP2-ALK*) aggressive variant
- Targeted therapy directed against tyrosine kinase receptors promising treatment for patients with aggressive tumors
- Epithelioid fibrous histiocytoma distinctive cutaneous neoplasm usually with *ALK* rearrangement