Pediatric Pathology Specialty Conference: Case 3

Cheryl M. Coffin, M.D.
USCAP Annual Meeting

March 22, 2015
Case 3: Clinical History

- 8 yr. old boy, healthy
- Incidental abdominal mass on P.E.
- 6 cm mesenteric mass on imaging
- No fever, weight loss or laboratory abnormalities
- Resection
Mesenteric mass
Mesenteric mass
Mesenteric mass
Mesenteric mass
Smooth muscle actin

Desmin
Case 3: Diagnostic Adjuncts

- Immunoreactive for vimentin, smooth muscle actin, muscle specific actin, desmin, cytokeratin
- Non-reactive for myoglobin, KP1, ER
- EM: fibroblasts, myofibroblasts, plasma cells and histiocytes in a myxoid matrix with scattered collagen bundles
Case 3: Diagnosis and Follow Up

- Inflammatory myofibroblastic tumor
- Recurrence 12 months after resection, with tumor around mesenteric artery
- Re-excision
- Chemotherapy with VP16 for 3 yrs.
- No evidence of disease 66 mos. after initial diagnosis
Inflammatory Myofibroblastic Tumor

- 150-200 cases per yr. in U.S.
- Infancy to adulthood, peak in 1st 3 decades
- Mesentery, omentum, retroperitoneum, lung, mediastinum, head/neck, liver
- Clinical syndrome: fever, weight loss, growth failure, anemia, thrombocytosis, polyclonal hyperglobulinemia, elevated ESR
- Local recurrence in 25%, rare metastases (<2%)
Points for Discussion

• Review of IMT history, diagnostic criteria and classification
• Genetic abnormalities in IMT
• Therapeutic options
• Differential diagnosis
Timeline of IMT Research

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early 20th Century</td>
<td>Tumor and syndrome IMT, 84 cases. WHO Path-Px factors, 2p23 ALK: IMT, mimics, ALKomas</td>
</tr>
<tr>
<td>1981</td>
<td>New WHO Further studies, New WHO</td>
</tr>
<tr>
<td>1994-5</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td></td>
</tr>
<tr>
<td>2001-2</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
</tr>
<tr>
<td>21st century</td>
<td></td>
</tr>
</tbody>
</table>
The Recognition and Definition of IMT, 1939-1994

- 1939-1954: Lung and mediastinal tumors with fibroinflammatory features, variable nomenclature, debated nosology (Brunn, 1939; Childress, 1950; Umiker, 1954)
- 1981: Reactive pseudosarcomatous proliferation with clinicopathologic syndrome (Dehner, 1981)
- 1991: Pulmonary “IMT” (Pettinato, 1991)
- 1994: Extrapulmonary IMT, 84 cases, tendency for local recurrence, rare metastases (Coffin, 1994)
Age and Site of IMT

Age Distribution of 84 IMTs

- 0-4 years: 30 patients
- 5-9 years: 20 patients
- 10-14 years: 15 patients
- 15-19 years: 10 patients
- 20-24 years: 5 patients
- 25-29 years: 2 patients

Body sites:
- Meninges: 1
- Orbit: 1
- Pharynx: 3
- Larynx: 4
- Trachea: 2
- Mediastinum: 3
- Liver/Porta hepatitis: 6
- Mesentery: 23
- Palm: 1
- Breast: 1
- Heart: 3
- Spleen: 1
- Stomach and omentum: 10
- Misc. abd. sites: 16
- Inguinal region: 1
- Lower extremity: 2
Inflammatory Myofibroblastic Tumor
Immunohistochemistry of IMT

The bar chart shows the expression levels of various markers in IMT:
- **Vim**: High expression
- **SMA**: Moderate expression
- **MSA**: High expression
- **Des**: Low expression
- **CK**: Moderate expression
- **CD68**: Low expression
Inflammatory Myofibroblastic Tumor

• WHO 1994: a benign “miscellaneous” tumor composed of differentiated myofibroblastic spindled cells usually accompanied by numerous plasma cells and/or lymphocytes

• Occur almost exclusively in abdominal cavity or mediastinum of children; may recur locally

• Uncertain whether tumors involving multiple sites represent multifocal disease or distant metastases
The Discovery and Characterization of Genetic Aberrations in IMT, 1996 - Present

- Aneuploidy in a subset (Biselli, 1996)
- Recurrent involvement of 2p23 (Griffin, 1999), with \( ALK \) rearrangements detectable by IHC or FISH (Coffin, 2001)
- No association with EBV infection (Meis, 1998)
- Lacks \( p53 \) mutation or \( MDM2 \) gene amplification (Yamamoto, 2003)
- Morphologic-genetic-prognostic subtypes may exist (Chan 2008; Marino-Enriquez 2011)
**ALK Genetic Abnormalities in IMT**

- Chromosome 2p23 abnormalities with *ALK* gene rearrangements in 50-70%
- Fusion partners: *TPM3*, *TPM4*, *CLTC*, *DCNT1*, *CARS*, *ATIC*, *RANBP2*, *SEC31L1*, *PPFIBP1*, *EML4*, *FN1*, others
- *ALK* aneuploidy
- *ALK* mutation
IMT Karyotype and \textit{ALK} FISH

\textit{ALK} rearrangement (~50\%) and Aneuploidy (~16\%)
Inflammatory Myofibroblastic Tumor

- WHO 2002 and 2013: locally recurring, rarely metastasizing fibroblastic-myofibroblastic neoplasm
- Distinctive lesion: myofibroblastic spindle cells accompanied by an infiltrate of plasma cells, lymphocytes, and eosinophils
- Occurs primarily in soft tissue and viscera of children and young adults
- $ALK$ rearrangements in 50-70%
The Search for Prognostic Indicators: 1999-Present*

- Unreliable: atypia, ganglion-like cells, aneuploidy
- Unreliable: immunohistochemistry for proliferative (Mib1), apoptotic (c-myc, cyclin D1, caspase 3, bc12, MCL-1), and “prognostic” (survivin, p27, CD56, p53, MDM2) markers
- ALK-positivity might be A/W lower risk and negativity might confer a higher risk of metastasis
- Recurrence is A/W size, abdominopelvic site, older age
- Do IMTs with specific ALK rearrangements have prognostic significance?

* Hussong 1999; Coffin 2007; Marino-Enriquez 2011
Atypical histologic features in IMT: no prognostic significance
Metastatic IMT: not predictable on the basis of pathology
Epithelioid/ Round Cell IMT: A New Morphologic- Prognostic- Molecular Subtype?*

- Males
- Intraabdominal
- Mean age 35 yr. (7mo.- 59 yr.)
- Rapid local recurrence in 100%
- Metastases in 25 %
- Death in 38%
- ALK- positive with RAN-BP2 fusion (2q13)
- Epithelioid inflammatory myofibroblastic sarcoma?

*Marino-Enriquez, 2011
Round cell IMT with *ALK-RANBP2*
The Ongoing Search for Effective Treatment

- Surgery is the mainstay for resectable IMTs
- Questionable effectiveness of steroids, NSAIDs
- For unresectable or metastatic IMTs:
  - Chemotherapy (Dishop, 2003)
  - Anti-TNFα-binding Ab (infliximab; Germanidis, 2005)
  - Small molecule ALK tyrosine kinase inhibitors (Butrynski, 2010; Sasaki, 2010)
ALKomas: Tumors with ALK Abnormalities

- *ALK* gene fusions: IMT, ALCL, pulmonary/breast/ovary/colon adenoCA, renal medullary CA, Spitz nevi and atypical Spitz neoplasms
- *ALK* mutations: Neuroblastoma (sporadic vs. familial), anaplastic thyroid CA, IMT
- *ALK* amplification: Rhabdomyosarcoma, neuroblastoma, IMT
ALK KINASE FUSIONS

- ALK gene fusions have been found in several tumor types, including NSCLC, lymphoma (ALCL, DLBCL), and inflammatory myofibroblastic tumor.
  - Case reports in breast, colon, ovarian, kidney, and other cancers.

- All fusions contain the entire ALK tyrosine kinase domain with various 5’ fusion partners (depicted as “X” in the figure above).
  - At least 12 different ALK fusions described in NSCLC alone to date.

- In NSCLC, ALK fusions are (for the most part) non-overlapping with other oncogenic driver mutations (EGFR, KRAS).
Targeted Treatment for IMT

• Activated ALK expression via ALK fusions, ALK mutations, or increased ALK copy numbers is a targetable driver

• Crizotinib inhibits growth, but resistance develops, with ALK F1174L mutation which leads to increased ALK phosphorylation, increased downstream signaling, and diminished crizotinib sensitivity

• Future directions to circumvent acquired resistance:
  - More selective ALK inhibitors (bypass F1174L)
  - Treatments to target compensatory pathways
IMT treated with crizotinib
IMTs Harbor Multiple Potentially Actionable Kinase Fusions

- 37 archival FFPE IMT samples from 33 patients
- Diagnostic tests: ALK IHC, ALK FISH, RT-PCR
- Next Gen sequencing with kinase capture platform (higher sensitivity and specificity)
- 85% had kinase fusions involving \textit{ALK}, \textit{ROS1}, or \textit{PDGFRB}
- New \textit{ALK} fusion partners: \textit{LMNA}, \textit{PRKAR1A}
- New non-\textit{ALK} fusions: \textit{TFG-ROS1}, \textit{YWHAE-ROS1}, \textit{NAB2-PDGFRβ}
ROS1 immunohistochemistry is a good surrogate for *ROS1* rearrangement (Hornick et al, 2015)


Next Gen sequencing with kinase capture platform (higher sensitivity and specificity)

68-85% have kinase fusions involving *ALK, ROS1, PDGFRB, RET, or ETV6-NTRK3* (Lovly et al, 2014; Antonescu et al, 2015)
And What About Our Patient With IMT?*

- ALK-1 immunohistochemistry negative
- FISH unanalyzable
- *TFG-ROS1* fusion detected with Next Gen sequencing
- ROS1 immunohistochemistry positive (courtesy of Jason Hornick, M.D., Ph.D.)

* Coffin, 1995 and 2007; Saab, 2011; Lovly, 2014
Case 3: IMT with *TFG-ROS1*
Case 3: Mesenteric mass negative for ALK-1
ROS1 (courtesy of J. Hornick, M.D., Ph.D.)
IMT: What It Is Not

- A “pseudotumor” (abandon the term!)
- IgG4- related sclerosing disease
- Lymphoma, dendritic cell neoplasms, carcinoma, melanoma, GIST, other sarcomas
- Inflammatory fibroid polyp, calcifying fibrous pseudotumor, reactive nodular fibrous pseudotumor, plexiform fibromyxoma
Retroperitoneal Fibrosis / IgG4 Sclerosing Disease
Hodgkin Disease
Follicular dendritic cell tumor
S100Malignant Melanoma
Myxoinflammatory fibroblastic sarcoma
Calcifying fibrous pseudotumor
Conclusions

• The diagnosis of IMT is based on morphology, enhanced with use of immunohistochemical and genetic adjuncts
• Genetic variability is typical, with common pathways and potential for targeted treatment
• Prognostic indicators remain elusive
• Immunologic aspects are mostly unexplored
• Morphologic variability and many mimics create diagnostic pitfalls
• Progress is due to multidisciplinary, multi-institutional collaboration
Defining a disease entity
Discovering a molecular genetic abnormality
Exploring genotype-phenotype correlations
Searching for prognostic indicators
Searching for better treatments
Tools, ideas, and teams

IMT: A Pathologic Paradigm
Acknowledgments

• Louis P. Dehner, M.D.
• Christopher D.M. Fletcher, M.D.
• Jason Hornick, M.D., Ph.D.
• Christine Lovly, M.D., Ph.D.
• H.A. and Edna Benning Presidential Endowed Chair, University of Utah
• Ernest W. Goodpasture Endowed Professorship in Investigative Pathology, Vanderbilt University
• Krista Spilker, Kristi Hargrove, Lindsey Walker, and Devin Jacobsen
• Dahl-Chase Pathology Associates, Bangor, ME (Drs. Jay Ye and George Eyerer)