BEYOND GIST: RECENT ADVANCES IN GASTROINTESTINAL MESENCHYMAL TUMORS

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## Tumors Not to be Confused with GIST

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<th>Rare</th>
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Inflammatory Fibroid Polyp

- Most common in antrum and ileum
- Wide age range
- Intussusception (small bowel)
- Polyp > mural mass
- Often ulcerated
- Most often submucosal
- Ill-defined margins
- Benign – do not recur
Stomach

Inflammatory Fibroid Polyp
Stomach

Inflammatory Fibroid Polyp
Ileum

Inflammatory Fibroid Polyp
Inflammatory Fibroid Polyp
Inflammatory Fibroid Polyp
Inflammatory Fibroid Polyp
Inflammatory Fibroid Polyp
Inflammatory Fibroid Polyp: Molecular Findings

- Long debate: neoplastic or reactive
- Activating mutations in PDGFRA
Gain-of-function PDGFRA mutations, earlier reported in gastrointestinal stromal tumors, are common in small intestinal inflammatory fibroid polyps. A study of 60 cases

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¹Department of Soft Tissue Pathology, Armed Forces Institute of Pathology, Washington, DC, USA; ²Department of Scientific Laboratories, Armed Forces Institute of Pathology, Washington, DC, USA and ³Division of Gastrointestinal Pathology, Armed Forces Institute of Pathology, Washington, DC, USA
Inflammatory Fibroid Polyp

PDGFRA
Inflammatory Myofibroblastic Tumor

• Most common in children and young adults

• Outside of lung, most common sites: abdomen (mesentery, GI tract, omentum), pelvis, retroperitoneum

• May be multifocal at presentation in abdominal cavity
Inflammatory Myofibroblastic Tumor: Prognosis

- WHO: Intermediate biologic potential, rarely metastasizing
- Local recurrence:
  - <2% lung
  - 25% extrapulmonary (intra-abdominal++)
- Metastasis:
  - 1-2% (lung, brain, liver, bone)
- In general, poor correlation between histology and behavior
Inflammatory Myofibroblastic Tumor
Inflammatory Myofibroblastic Tumor
Inflammatory Myofibroblastic Tumor
ALK in Inflammatory Myofibroblastic Tumor

- *ALK* gene rearrangement in 60% IMT <10% in adults >50 yrs

- Heterogeneous fusion partners

- Strong correlation between detection of ALK expression by IHC and *ALK* rearrangement in IMT

- ALK negative in other myofibroblastic and smooth muscle tumors, GIST
Inflammatory Myofibroblastic Tumor

TPM3-ALK

ALK
ALK 2p23
3' red (t)
5' green (c)
Epithelioid Inflammatory Myofibroblastic Sarcoma

- Distinctive aggressive variant of inflammatory myofibroblastic tumor (rapid recurrences)
- Predilection for young male adults
- Nearly all intra-abdominal (mesentery, omentum)
- Epithelioid morphology
- Often myxoid stroma; prominent neutrophils
- Nuclear membrane >> perinuclear pattern of ALK
- $RANBP2$-ALK >> $RRBP1$-ALK fusion
Epithelioid Inflammatory Myofibroblastic Sarcoma
Epithelioid Inflammatory Myofibroblastic Sarcoma

Omentum
Mesentery

Epithelioid Inflammatory Myofibroblastic Sarcoma
Epithelioid Inflammatory Myofibroblastic Sarcoma

Mesentery
Epithelioid Inflammatory Myofibroblastic Sarcoma
ALK oncoproteins in atypical inflammatory myofibroblastic tumours: novel RRB1-ALK fusions in epithelioid inflammatory myofibroblastic sarcoma

Jen-Chieh Lee,1,2* Chien-Feng Li,2,3† Hsuan-Ying Huang,2,4‡ Mei-Jun Zhu,5† Adrián Mariño-Enríquez,5 Chung-Ta Lee,6 Wen-Bin Ou,5,7,8 Jason L Hornick5 and Jonathan A Fletcher5,*
Epithelioid Inflammatory Myofibroblastic Sarcoma

RANBP2-ALK

ALK
Epithelioid Inflammatory Myofibroblastic Sarcoma

RRBP1-ALK

ALK
Crizotinib in ALK-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D’Adamo, M.D., Ph.D.,
Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D.,
Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D.,
Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D.,
Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D.,
Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D.,
George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.

Multifocal Recurrent EIMS Treated with Crizotinib

3 months

ALK-Negative Inflammatory Myofibroblastic Tumors?

• Until recently, molecular pathogenesis unknown
• Recent reports identified fusions involving receptor tyrosine kinase genes other than ALK
Inflammatory Myofibroblastic Tumors Harbor Multiple Potentially Actionable Kinase Fusions

Christine M. Lovly1, Abha Gupta2, Doron Lipson3, Geoff Otto3, Tina Brennan3, Catherine T. Chung4, Scott C. Borinstein2, Jeffrey S. Ross3, Philip J. Stephens3, Vincent A. Miller3, and Cheryl M. Coffin7

Cancer Discovery 2014;4:889-895.

Molecular Characterization of Inflammatory Myofibroblastic Tumors With Frequent ALK and ROS1 Gene Fusions and Rare Novel RET Rearrangement

Cristina R. Antonescu, MD,* Albert J.H. Suurmeijer, MD,† Lei Zhang, MSc,* Yun-Shao Sung, MSc,* Achim A. Jungbluth, MD,* William D. Travis, MD,* Hikmat Al-Ahmadi, MD,* Christopher D.M. Fletcher, MD,‡ and Rita Alaggio, MD§

Am J Surg Pathol • Volume 39, Number 7, July 2015
Inflammatory Myofibroblastic Tumor

TFG-ROS1
Inflammatory Myofibroblastic Tumor

ROS1 - 6q22
3' (c)
5' (t)
ALK, ROS1 and NTRK3 gene rearrangements in inflammatory myofibroblastic tumours

Hidetaka Yamamoto, Akihiko Yoshida, Kenichi Taguchi, Kenichi Kohashi, Yui Hatana, Atsushi Yamashita, Daisuke Mori & Yoshinao Oda

ETV6-NTRK3 Is Expressed in a Subset of ALK-Negative Inflammatory Myofibroblastic Tumors

Ali H. Alassiri, MD, Rola H. Ali, MD, Yaoqing Shen, PhD, Amy Lum, BSc, Caron Strahlendorf, MD, Rebecca Deyell, MD, Rod Rashek, MD, Poul H. Sorensen, MD, PhD, Janessa Laskin, MD, Marco Marra, PhD, Stephen Yip, MD, PhD, Cheng-Han Lee, MD, PhD, and Tony L. Ng, MD, PhD

Am J Surg Pathol • Volume 40, Number 8, August 2016
Gastrointestinal Neuroectodermal Tumor

- Also known as clear cell sarcoma-like tumor
- ~50 reported cases, increasingly recognized
- Young to middle-aged adults
- Mean age 40 years
- Small bowel (70%), stomach, colon
- Large infiltrative masses
- May be mistaken for GIST
- Aggressive sarcoma
- Lymph node and liver metastases
Ileum

Gastrointestinal Neuroectodermal Tumor

Courtesy of Mee Joo, MD
Gastrointestinal Neuroectodermal Tumor
Gastrointestinal Neuroectodermal Tumor
Gastrointestinal Neuroectodermal Tumor

Jejunum
Ileum

Gastrointestinal Neuroectodermal Tumor
Gastrointestinal Neuroectodermal Tumor: Immunophenotype and Molecular Genetics

- Diffuse strong reactivity for S100 protein and SOX10
- Lacks melanocytic markers (HMB-45, melan A, MiTF)
- t(12;22) with \( \text{ATF1-EWSR1} \) or t(2;22) with \( \text{CREB1-EWSR1} \)
EWS-CREB1: A Recurrent Variant Fusion in Clear Cell Sarcoma—Association with Gastrointestinal Location and Absence of Melanocytic Differentiation

Cristina R. Antonescu,1 Khedoudja Nafa,1 Neil H. Segal,2 Paola Dal Cin,3 and Marc Ladanyi1


Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract

David L. Stockman, MD,* Markku Miettinen, MD,† Saul Suster, MD,* Dominic Spagnolo, MBBS, FRCPath, MD,‡§ Hugo Dominguez-Malagon, MD,|| Jason L. Hornick, MD, PhD,¶ Volkan Adsay, MD,§ Pauline M. Chou, MD, PhD,** Benhur Amanuel, MBBS, FRCPath,‡§ Peter VanTuinen, PhD,* and Eduardo V. Zambrano, MD*
Gastrointestinal Neuroectodermal Tumor
Metastatic Gastrointestinal Neuroectodermal Tumor

Lymph node
PEComa

- Family of related mesenchymal lesions:
  - Angiomyolipoma (AML)
  - Lymphangiomyomatosis (LAM)
  - PEComa NOS
- All share distinctive cell type: “perivascular epithelioid cell” (PEC)
- Evidence of myogenic (smooth muscle) and melanocytic differentiation
- No known normal tissue counterpart
PEComa: Clinical Features

- Female predominance (5:1 overall, but no gender predilection in GI tract)
- Middle-aged adults
- Rarely associated with TSC (unlike AML and LAM)
- Most common sites: abdomen/pelvis, retroperitoneum, visceral sites (especially GI tract and uterus)
- Minority (25%) in somatic soft tissue and skin
PEComa
PEComa: Immunophenotype

- Mixed melanocytic/myogenic phenotype
- Nearly all HMB-45 positive
- Most positive for MiTF
- SMA most sensitive myogenic marker
- Some lack smooth muscle markers (especially epithelioid/clear cell)
- Focal S100 protein in 10-20%
- TFE3 positive in 10-15%
PEComa

HMB-45

Melan A
PEComa: Criteria for Malignancy

- Features associated with malignant behavior in GI tract:
  - Mitotic activity ($\geq 2$ per 10 HPF)
  - Marked nuclear atypia
  - Diffuse pleomorphism
Colon Malignant PEComa

Courtesy of Joon Choi, MD
Malignant PEComa
Malignant PEComa
Metastatic Malignant PEComa
Metastatic Malignant PEComa
Metastatic Malignant PEComa
**PEComa: Molecular Findings**

- Frequent deletions of *TSC2* at 16p13
- Activation of mTOR (mammalian target of rapamycin) signaling pathway
- Therapeutic implications for patients with clinically aggressive PEComas
- mTOR inhibitors
- Small subset with *TFE3* rearrangement
Dichotomy of Genetic Abnormalities in PEComas With Therapeutic Implications

Narasimhan P. Agaram, MBBS,* Yun-Shao Sung, MS,* Lei Zhang, MD, MS,* Chun-Liang Chen, MS,* Hsiao-Wei Chen, MS,* Samuel Singer, MD,† Mark A. Dickson, MD,‡ Michael F. Berger, PhD,*§ and Cristina R. Antonescu, MD*

Am J Surg Pathol • Volume 39, Number 6, June 2015
Malignant PEComa treated with sirolimus

9 months

Courtesy of Andrew Wagner, MD, PhD
Practice points

• Not all GI mesenchymal tumors are GIST

• Critical distinctions owing to marked differences in behavior and treatment

• After first considering GIST, ask yourself if there are any distinctive histologic features that might suggest an alternative diagnosis

• Order IHC based on differential diagnosis
THANK YOU