Mesenchymal lesions of the gastrointestinal tract
Approach to diagnosis and an update

Shefali Chopra, M.D.
Keck Medical center, University of Southern California
• Approach to a spindle cell tumor

• Some newer described entities

• Genotyping in desmoid fibromatosis

• GISTs

• Malignant Gastrointestinal Neuroectodermal Tumors
Spindle cell tumor
Immunostain panel

- CD34
- KIT(CD117)
- DOG 1
- S100
- SMA
- Desmin
- Pancytokeratin
DOG1/TMEM16A

- DOG 1 stains about a third of the KIT negative GISTs
- Utility in identification of PDFR a mutant GISTs
- DOG 1 and CD117 each stain >95% of GISTs and between them serve to mark essentially all cases.
Schwannoma
Microcystic/Reticular Schwannoma: A Distinct Variant With Predilection for Visceral Locations

Bernadette Liegl, MD,* † Michael W. Bennett, MB, BCh, BAO, MRCPI,* and Christopher D.M. Fletcher, MD, FRCPATH*
Reticular microcystic schwannoma

• Rare variant of schwannoma with distinctive predilection for gastrointestinal tract
• Occurs in elderly patients (peak incidence 6th decade) with female predominance
• Striking microcystic and reticular lesional growth
• S100 +; GFAP+/-
• Benign
Case 2

- 63 year old male with 3 cm mobile polyp in the mid esophagus
Diagnosis

- Schwannoma with degenerative change
Case 3

- 43 year old man with 1.5 cm polyp in the proximal esophagus
MDM2 FISH
MDM2:CEN12 – 3.9
? Diagnosis
Polypoid fibroadipose tumors of the esophagus: ‘giant fibrovascular polyp’ or liposarcoma? A clinicopathological and molecular cytogenetic study of 13 cases

Rondell P Graham¹,²,⁴, Saba Yasir¹,⁴, Karen J Fritchie¹, Michelle D Reid³, Patricia T Greipp² and Andrew L Folpe¹

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• 13 cases, 5 of which were diagnosed as giant fibrovascular polyp, 4 as well differentiated LPS, 3 as dedifferentiated and one lipoma

• All tumors presented as pedunculated polypoid masses
• Microscopically the tumors were centered in the subepithelial stroma and were lined by intact squamous mucosa
• Close examination revealed slightly enlarged, hyperchromatic stromal cells – somewhat subtle
• MDM2 amplified in 13 of 13 cases
• The morphological features of esophageal well differentiated seem typically to be less impressive than their soft tissue or retroperitoneal counterparts

• High risk for local recurrence and/or dedifferentiation

• Diagnosis of giant fibrovascular polyp should be made with caution in the esophagus
Esophageal well-differentiated liposarcomas are quite rare, with fewer than 50 reported cases.

The natural history of esophageal liposarcomas, many of which have presented as large polypoid masses is potential for local recurrence and dedifferentiation, and eventual metastatic risk in dedifferentiated tumors.
Case 4: 31 year old male with a 3.2 cm gastric tumor
Diagnosis ?
Plexiform Angiomyxoid Myofibroblastic Tumor of the Stomach

Yoshihisa Takahashi, MD,* Seiichiro Shimizu, MD,† Tsuyoshi Ishida, MD,‡ Kiyoshi Aita, BS,* Suzuko Toida, PhD,* Toshio Fukusato, MD,* and Shigeo Mori, MD*
• Few cases reported
• Elderly patients with gastrointestinal hemorrhage due to mucosal ulceration
• GI tract
• Striking plexiform growth pattern
• Cytologically bland spindle cells set in intercellular myxoid matrix
• Rich capillary network
• Variable expression of myogenic markers
- EM: myofibroblastic differentiation
- No mutations in the KIT and PDFGRA genes reported
- Benign
- Gastric bleeding potentially represents a life threatening condition
Plexiform Fibromyxoma
A Distinctive Benign Gastric Antral Neoplasm Not to be Confused With a Myxoid GIST

Markku Miettinen, MD,* Hala R. Makhlof, MD,† Leslie H. Sobin, MD,†
and Jerzy Lasota, MD*

Am J Surg Pathol • Volume 33, Number 11, November 2009

- Adults
- 12 cases
- Gastric antrum
- Benign
Recurrent \textit{MALAT1–GLI1} oncogenic fusion and \textit{GLI1} up-regulation define a subset of plexiform fibromyxoma

Lien Spans, Christopher DM Fletcher, Cristina R Antonescu, Alexandre Rouquette, Jean-Michel Coindre, Raf Scioto and Maria Debiec-Rychter
A Distinctive Novel Epitheliomesenchymal Biphasic Tumor of the Stomach in Young Adults ("Gastroblastoma")
A Series of 3 Cases

Markku Miettinen, MD,* Nancy Dow, MD,† Jerzy Lasota, MD,* and Leslie H. Sobin, MD†
• Occurrence in young adults
• Relatively large size
• Low grade features with low mitotic activity
• Indolent clinical course
Gastroblastoma harbors a recurrent somatic MALAT1–GLI1 fusion gene

Rondell P Graham¹,², Asha A Nair³, Jaime I Davila³, Long Jin², Jin Jen⁴, William R Sukov², Tsung-Teh Wu¹, Henry D Appelman⁵, Jorge Torres-Mora¹, Kyle D Perry¹, Lizhi Zhang¹, Sara M Kloft-Nelson⁴, Ryan A Knudson⁴, Patricia T Greipp² and Andrew L Folpe¹

Table 1: Summary of the clinical characteristics of the cases of gastroblastoma

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Specimen type</th>
<th>Tumor size (cm)</th>
<th>Metastases</th>
<th>Follow-up (mos)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>M</td>
<td>Resection</td>
<td>3.8</td>
<td>Lymph node, liver, peritoneum</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>M</td>
<td>Resection</td>
<td></td>
<td>No</td>
<td>12</td>
<td>ANED</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>M</td>
<td>Resection</td>
<td>9.0</td>
<td>No</td>
<td>93</td>
<td>ANED</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>F</td>
<td>Needle Bx</td>
<td>4.0</td>
<td>Liver</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 2: Summary of the immunohistochemical results of the cases of gastroblastoma

<table>
<thead>
<tr>
<th>Case</th>
<th>Positive immunohistochemistry results</th>
<th>Negative immunohistochemistry results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AE1/AE3&lt;sup&gt;e&lt;/sup&gt;, CD56&lt;sup&gt;e&lt;/sup&gt;, NSE&lt;sup&gt;e&lt;/sup&gt;, low Ki-67 (~10%)</td>
<td>Chromogranin, synaptophysin, CEA, TTF-1,PLAP, CD30, AFP, HCG, Chromogranin, synaptophysin, KIT, DOG1, desmin, S100, melan-A, SOX10, TLE-1, CD99, keratin 5/6</td>
</tr>
<tr>
<td>2</td>
<td>AE1/AE3&lt;sup&gt;e&lt;/sup&gt;, patchy SMA&lt;sup&gt;s&lt;/sup&gt;</td>
<td>Chromogranin, synaptophysin, NSE, desmin, SMA, calretinin, inhibin, KRT 34/E12, CD34</td>
</tr>
<tr>
<td>3</td>
<td>AE1/AE3&lt;sup&gt;e&lt;/sup&gt;, focal CD10&lt;sup&gt;e&lt;/sup&gt;, KIT, CD56&lt;sup&gt;e&lt;/sup&gt;, vimentin&lt;sup&gt;s&lt;/sup&gt;</td>
<td>Chromogranin, synaptophysin, NSE, desmin, SMA, calretinin, inhibin, KRT 34/E12, CD34</td>
</tr>
<tr>
<td>4</td>
<td>Patchy OSCAR&lt;sup&gt;e&lt;/sup&gt;, low Ki-67 (~10%), vimentin&lt;sup&gt;s&lt;/sup&gt;</td>
<td>KRT 34/E12, KRT7, KRT 20, CDX2, chromogranin, synaptophysin, CD34, CD99, KIT, DOG1, calretinin, WT1, SMA, desmin, EMA, MOC31, melan-A, HMB-45, pCEA</td>
</tr>
</tbody>
</table>
The structure of the MALAT1–GLI1 fusion gene reported in the subset of plexiform fibromyxoma is the same as that seen in gastroblastoma.

The fusion gene is believed to have the same functional consequence in both tumor types where it is present.
• Plexiform fibromyxoma is clinically benign and lacks biphasic morphology, quite different from gastroblastoma.

• MALAT1–GLI1 fusions in both of these tumors represents example of identical genetic events in unrelated neoplasms
Case 5: 41 year old female with an abdominal wall mass
Diagnosis ?
Desmoid Fibromatosis

- Desmoid tumors are extremely rare - incidence 4 per million per year in the United States.
- Although desmoids have a benign histologic appearance and lack the ability to metastasize, they invade locally—often aggressively—and recur repeatedly.
• Can occur infrequently as part of familial syndromes like familial adenomatous polyposis (FAP) and familial infiltrative fibromatosis and are caused by germline mutation of the adenomatous polyposis gene (APC)
• Most desmoids are sporadic and have the CTNNB1 gene mutations in 87% of cases
Tumorigenesis and Neoplastic Progression

Specific Mutations in the \(\beta\)-Catenin Gene (\(CTNNB1\)) Correlate with Local Recurrence in Sporadic Desmoid Tumors

Alexander J.F. Lazar,*† Daniel Tuvin,*‡ Shohrae Hajbashli,*§ Sultan Habeeb,‖ Svetlana Bolshakov,*‡ Empar Mayordomo-Aranda,‖ Carla L. Wameke,‖ Dolores Lopez-Terrada,‖ Raphael E. Pollock,*‡ and Dina Lev*§

From the Sarcoma Research Center,* and Departments of Pathology,*‡ Surgical Oncology,* Cancer Biology,* and Division of Quantitative Sciences,* The University of Texas MD Anderson Cancer Center, Houston; and the Department of Pathology,‖ Texas Children’s Hospital and Baylor College of Medicine, Houston, Texas
Sequencing desmoids for β-catenin mutations identified three specific point mutations in two different codons of *CTNNB1* (exon 3)

- ACC to GCC in codon 41 (41A), resulting in the replacement of threonine by alanine (59%)
- TCT to TTT in codon 45 (45F), resulting in the replacement of serine by phenylalanine (33%)
- TCT to CCT in codon 45 (45P), resulting in the replacement of serine with proline (8%)
• CTNNB1 45F Mutations Significantly Correlate with Increased Desmoid Tumor Recurrence

• Desmoids bearing the 41A CTNNB1 gene mutation exhibited a more intense β-catenin nuclear expression compared to 45F CTNNB1-mutated desmoids
Gastrointestinal stromal tumors

• Most common mesenchymal tumors of the GI tract
• 0.2% of all GI tumors and 80% of all sarcomas
• Up to 5000 new cases/year in the USA
• Annual incidence 7-19 cases/million
GIST - Anatomic location

- Esophagus (<1%)
- Stomach (60%)
- Duodenum (5%)
- Colorectum (4%)
- Jejunum and ileum (30%)
- Appendix (<1%)

Extragastrointestinal -1% or less Omentum/mesentry
NF1

- In the setting of *NF1* mutations patients are more likely to develop multiple independent GISTs
- Rare sporadic *NF1* – mutant GISTS
- They are 1-2% of the GISTs and approximately 4-6% of small intestinal GISTs
- Important as these quadruple negative (KIT, PDGFR a, BRAF and SDHA-D) GISTs might be first presentation of NF1.
BRAF – 3.5 to 13% of GISTS lacking *KIT* and *PDGFRα*

• V600E mutation causes a conformational change in BRAF that favors an activated state and results in unabated progrowth intracellular RAS signaling

• Can occur exclusive of *KIT/ PDGFRα* mutations

• Important to distinguish because of their potential susceptibility to BRAF inhibitors.

• Predilection for the small bowel
Case 6

• 18 year old with gastric tumor
• 10 cm in greatest dimension
• Mitotic rate 6/50 hpf
Diagnosis ?
Gastrointestinal Stromal Tumors of the Stomach in Children and Young Adults
A Clinicopathologic, Immunohistochemical, and Molecular Genetic Study of 44 Cases With Long-Term Follow-Up and Review of the Literature
Markku Miettinen, MD,* Jerzy Lasota, MD,* and Leslie H. Sobin, MD†

Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD
Barbara Pasini1,16, Sarah R McWhinney2,16, Thalia Bel3, Ludmila Matyakhina3, Sotirios Stergiopoulos4, Michael Muchow5, Sostisatos A Boikos5, Barbara Ferrando1, Karel Pacak4, Guillaume Assie5,14, Eric Baudin6, Agnes Chompret7, Jay W Ellison8, Jean-Jacques Briere9,10, Pierre Rustin9,10, Anne-Paulie Gimenez-Roqueplo11,12,13,16, Charis Eng9,14,16, J Aidan Carney15,16 and Constantine A Stratakis*1,16

Succinate Dehydrogenase-Deficient GISTs: A Clinicopathologic, Immunohistochemical, and Molecular Genetic Study of 66 Gastric GISTs With Predilection to Young Age
Markku Miettinen, MD,* † Zeng-Feng Wang, PhD,* Maarit Sarlomo-Rikala, MD,‡ Czeslaw Osuch, MD,§ Piotr Rutkowski, MD,‡ and Jerzy Lasota, MD*
• A small subset of gastric gastrointestinal stromal tumors (7-10%) have loss of function of succinate dehydrogenase complex of the inner mitochondrial membrane

• Loss of function is signaled by immunohistochemical loss of SDH subunit B

• SDH deficient GISTs comprise a great majority of gastric GISTS in children and young adults
<table>
<thead>
<tr>
<th>Feature</th>
<th>SDH deficient GISTS</th>
<th>GISTS with intact SDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age predilection</td>
<td>Children and young adults</td>
<td>Older adults</td>
</tr>
<tr>
<td>Gender distribution</td>
<td>F&gt;&gt;M</td>
<td>F = M</td>
</tr>
<tr>
<td>Anatomic site</td>
<td>Stomach</td>
<td>Entire GI tract</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Multinodular architecture</td>
<td>Always</td>
<td>Rare</td>
</tr>
<tr>
<td>Cytomorphology</td>
<td>Epithelioid</td>
<td>Mixed</td>
</tr>
<tr>
<td>Prognosis predicted by site, size and mitotic rate</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>Common</td>
<td>Exceptional</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>Clinical course of metastasis</td>
<td>Indolent</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Sensitive to Imatinib</td>
<td>No</td>
<td>Most cases</td>
</tr>
<tr>
<td>KIT/PDGFGRa Mutations</td>
<td>None</td>
<td>~95%</td>
</tr>
<tr>
<td>SDHx mutations (germline)</td>
<td>~50%</td>
<td>None</td>
</tr>
<tr>
<td>Syndromic associations</td>
<td>Carney Stratakis syndrome (GISTs +paragangliomas) Carney triad (pulmonary chondromas and or paragangliomas)</td>
<td>Neurofibromatosis 1 Familial GIST (germline KIT or PDGFRA mutations)</td>
</tr>
</tbody>
</table>
• SDHB stain can classify a GIST as SDH deficient it does not tell which subunit.
• Adding a SDHA immunostain can help predict that a mutation is present in the hard to sequence SDHA subunit
• Primary resistance to Imatinib
• Anecdotal responses to Sunitinib have been reported.
• Absence of SDH complex drives increased vascular endothelial growth factor and IGFR receptor signaling pathway accounting for efficacy of Sunitinib which has inhibitory effects on both VEGFR and IGF1R
Syndromic GISTs

- Familial GIST
- Germline mutations of KIT/PDGFRA
- Develop GISTs with 100% penetrance
- NF Type 1
Prognosis in GIST

• GIST as a paradigm for personalized medicine
• Areas of importance
• To determine who should receive follow up for patients with resectable localized disease
• To determine who should receive adjuvant therapy for patients with resectable localized disease
• To determine the type of targeted therapy for treatment of metastatic disease
Prognostic Biomarkers in GIST

- Tumor size > 5 cm with mitotic rate > 5/5mm
- Tumor size > 10 cm
- Mitotic rate > 10/5mm
- Tumor location
- Tumor rupture either before or during surgery is an important negative prognostic factor
- Incomplete resection especially in rectum associated with a higher risk of recurrence
<table>
<thead>
<tr>
<th>Tumor Parameters</th>
<th>Risk for Progressive Disease* (%), Based on Site of Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Stomach</td>
</tr>
<tr>
<td>Mitotic Rate</td>
<td>Size</td>
</tr>
<tr>
<td>≤ 5 per 50 HPF</td>
<td>≤ 2 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 2, ≤ 5 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 5, ≤ 10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
</tr>
<tr>
<td>&gt; 5 per 50 HPF</td>
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<tr>
<td></td>
<td>&gt; 5, ≤ 10 cm</td>
</tr>
<tr>
<td></td>
<td>&gt; 10 cm</td>
</tr>
</tbody>
</table>

Data are based on long-term follow-up of 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal GISTs.
Abbreviations: GIST, gastrointestinal stromal tumor; HPF, high-power field.
*Defined as metastasis or tumor-related death.
†Denotes small numbers of cases.
Adapted from Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Sem Diagn Pathol 2006;23:70–83.
Precursor lesions

- Microscopic foci of KIT-positive spindle cell hyperplasia (1–10mm) are commonly found in patients with germline *KIT* or *PDGFRA* mutations or *NF1* mutations. They have also been described adjacent to sporadic GISTs.
- They are common incidental findings in gastroesophageal resections (9%–35%).
- These lesions have been variably designated as sporadic Cajal cell hyperplasia, microscopic GISTs, GIST tumorlets, or “seedling” GISTs.
Although nearly 85% of incidental microscopic lesions harbor *KIT* mutations, based on statistics, only a small proportion (<1%) progress to clinically significant GISTs.

These microscopic lesions require additional genetic events to transform into clinically significant neoplasms.
GIST Progression

- ICC Cells
- Micro-GIST
- Low risk GIST
- Malignant GIST

- KIT or PDGFRA mutation
- Loss of 14q, 22q
- Loss of 1p p16, p53

>10 Million
~5,000 / yr
~2,000 / yr
### GIST Normogram

**NCCN Task Force Report**

<table>
<thead>
<tr>
<th>Points</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
<th>100</th>
</tr>
</thead>
</table>

#### Size (cm)

- 0
- 5
- 10
- 15
- 25
- 35
- 45
- 50
- 60
- 70
- 80
- 90
- 100

#### Mitotic index

- < 5/50 HPF
- ≥ 5/50 HPF

#### Site

- Colon/Rectum
- Stomach/Other
- Small Intestine

#### Total Points

- 0
- 20
- 40
- 60
- 80
- 100
- 120
- 140
- 160
- 180
- 200

#### Prob. of 2 year RFS

- 90
- 80
- 70
- 60
- 50
- 40
- 30
- 20
- 10

#### Prob. of 5 year RFS

- 90
- 80
- 70
- 60
- 50
- 40
- 30
- 20
- 10

**Figure 4** Nomogram for predicting probabilities of 2- and 5-year recurrence-free survival. Points are assigned for size, mitotic index, and site of origin by drawing a line upward from the corresponding values to the “Points” line. The sum of these 3 points, plotted on the “Total Points” line, corresponds to predictions of 2- and 5-year recurrence-free survival.

Abbreviations: HPF, high-power field; RFS, recurrence-free survival.

Who should be followed clinically?

- GIST < 2 cm with < 5 mitosis/ 50 HPFs do not need follow-up
- Intermediate to high risk GIST require follow-up
Who should receive adjuvant therapy?

- FDA in January 2012 approved longer adjuvant use of imatinib (Gleevec) in patients with intermediate/high risk GIST
- It was initially shown that 12 months of imatinib after primary resection of a GIST significantly delayed disease recurrence versus a placebo
- A subsequent trial proved that 36 months of adjuvant imatinib was superior to 12 months
Primary imatinib resistance

• Seen in at least 10% of GIST
• Tumors that progress within 3-6 months of initiating therapy
• KIT WT
• KIT exon 9 mutations
• Most common PDGFRA mutant (exon 18-D842V) – Crenolanib is a TKI that has activity versus D842V in vitro and is now being tested in a clinical trial
Should we treat according to KIT/PDGFRα Genotype?

- Imatinib and Sunitinib appear to have different efficacies in GIST of different genotype
- KIT exon 9 mutants may respond better to imatinib 800mg/d or sunitinib
- KIT WT may respond better to sunitinib
- Current recommendations are imatinib 400mg/d followed by imatinib 800mg/d followed by sunitinib
Imitanib- Delayed/Secondary resistance

- Characterized by patients who show partial response or at least stable disease and then go on to develop disease progression
- Usually happens within 2 years of initiation of therapy
- The resistance mutations are distributed non-randomly in exon 17 and 13/14 representing the second kinase domain activation loop and first kinase domain ATP binding pocket
- Two of the most common mutations, V654A and T6701 are resistant to imatinib
- There is significant heterogeneity of resistance across different lesions and also within different areas of the same lesion
Sunitinib malate

- Tyrosine kinase receptor that targets KIT, PDGFR
- The most common secondary mutations (V654 A and T6701) are sensitive to sunitinib
- FDA approved for GIST patients who have failed or are intolerant of imatinib
- More recently FDA has approved regorafenib for third line of treatment for patients resistant to imatinib and sunitinib
Responses to TKI therapy

• Even long term TKI treatment fails to eradicate GIST cells resulting in disease persistence
Treatment related changes

- Hypocellularity
- Myxoid stroma
- Fibrosis/ Hyalinization
- Necrosis
- Nest of tumor cells always virtually present
- Report as percentage of viable tumor
Rhabdomyosarcomatous Differentiation in Gastrointestinal Stromal Tumors After Tyrosine Kinase Inhibitor Therapy

A Novel Form of Tumor Progression

Bernadette Liegl, MD,* † Jason L. Hornick, MD, PhD,* Cristina R. Antonescu, MD, ‡ Christopher L. Corless, MD,§ and Christopher D. M. Fletcher, MD, FRCPath*

Am J Surg Pathol • Volume 33, Number 2, February 2009
• Besides rhabdomyoblastic cartilaginous and osseous differentiation have been observed in cases of treated GISTs.
• In rare cases GISTs may progress to high grade anaplastic sarcomas that lose CD117 expression. This has observed in both imatinib treated and TKI - naive GISTs.
• Even cytokeratins can be expressed
Case 7

• 70 year old man with 6.5 cm pancreatic/duodenal tumor
• A small number of primary gastrointestinal clear cell sarcomas have been reported
• Many of these lacked evidence of melanocytic differentiation and thus were called clear cell sarcoma - like tumors of the gastrointestinal tract
Diagnosis ?
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, FRCPA, MD,‡§ Hugo Dominguez-Malagon, MD,||
Jason L. Hornick, MD, PhD,¶ Volkan Adsay, MD,# Pauline M. Chou, MD, PhD,**
Benhur Amanuel, MBBS, FRCPA,‡§ Peter VanTuinen, PhD,* and Eduardo V. Zambrano, MD*

Am J Surg Pathol • Volume 36, Number 6, June 2012
• Mean age 42 years (17-60 years)
• 8 male and 8 female
• 7 patients had liver and 11 lymph node metastasis at time of diagnosis
• 12 patients had clinical followup and 6 died within 3 to 106 months
• 10 in small intestine, 4 in stomach and 2 in colon
• Tumor size 2.4-15 cm
• Majority had extensive tumor necrosis
Immunohistochemical findings

- S100 and SOX 10 positive
- Melanocytic (HMB 45, Melan A, tyrosinase and MiTF) and GIST (CD117, DOG 1, CD34) markers negative
- Synaptophysin and CD56 variably positive
- CD99 and epithelial markers negative
- MIB 1: 22-34%
Ultra structural findings and molecular findings

• None of the tumors showed evidence of myoid or melanocytic differentiation
• 12 cases positive for EWSR1 break apart FISH of the 14 cases studied
• 6 showed rearrangement of ATF1, 3 of CREB1, 2 no rearrangement of either ATF1 or CREB1 genes and one case was not evaluated
• How to approach a spindle cell tumor – useful immunostains
• Newer described benign entities like Microcystic schwannoma, plexiform angiomyxoid myofibroblastic tumor and gastroblastoma
• Desmoids – TCT to TTT codon 45(45F) replacement of serine by phenyalanine correlates with increased desmoid tumor recurrence
• GISTs including genotyping, prognosis, adjuvant therapy, utility of genotyping for therapy, imatinib resistance –primary and secondary
• SDH mutated GIST
• Malignant gastrointestinal neuroectodermal tumors with reappraisal of clear cell sarcoma like tumors of the gastrointestinal tract
Questions ?