A Few Observations on Gastrointestinal Stromal Tumors and Their Differential Diagnosis

E. Montgomery

A 9cm mass was excised from the jejunal wall and mesentery of a 33 year old woman.
This must be a GIST since it is associated with the small bowel but the mitoses don’t match the large size.
Diagnosis: Mesenteric Fibromatosis
Mesenteric Fibromatoses

• May be a component of Gardner syndrome (FAP)

• Virtually all familial fibromatoses have associated FAP gene mutations
Fibromatoses - Clinical

• 2-4 individuals per million per year.
• In children, equal gender incidence, mostly extra-abdominal.
• Puberty – age 40 usu in females [estrogen driven] and in abdominal wall.
• Older adults – mostly extra-abdominal – equal gender incidence.
• Associated with FAP and APC gene alterations.

Fibromatosis of Shoulder
In Young Woman

Imaging Study of
Fibromatosis in
Elderly Man
Features of Fibromatoses

• Sweeping Fascicles of Fibroblasts
• Infiltrative Growth Pattern
• Characteristic Vascular Pattern
**β catenin in Fibromatoses**

- Accumulates in nucleus
- NOT detected in GISTs
Small Intestine – Malignant Stromal Tumor

CD117/c-kit, Gastrointestinal Stromal Tumor
STI571 (Gleevec, Imatinib)

- Effective against GIST based on CD117 expression
- Dako antibody partnered with Novartis
- 75% of fibromatosis reactive using Dako c-kit antibody early on (using antigen retrieval)

CD117 in DESMOIDS

- Yantiss et al (2000) - 75%
- Hornick & Fletcher (2002) - 5%
- Barisella et al (2002) - 81%
- Montgomery et al (2002) - 60%
- NOW – not such a problem
Beta Catenin Staining
– Mesenteric Fibromatosis

Beta-Catenin in GIST
– No Nuclear staining
GIST

Stromal tumors of GI tract
of spindle or epithelioid morphology, which
are immunohistochemically positive for
kit (CD117)

Identical tumors arise in
omentum, mesentery, retroperitoneum
bladder, gall bladder

GIST

- 5-10% of all sarcomas
- 4,500/yr in US
- 1% of GI malignancy
- M > F >50 yrs
- Pain, bleeding, mass
- Incidental
- Metastasis
GIST: Distribution %

- Esophagus  rare
- Stomach  60
- Small intestine  35
  - duodenum  15
  - jejunum  35
  - ileum  45
- Colorectal  <5
- Extra GI  <5

Emory et al, AJSP 1999; 23: 82

Spindle cell GIST
CD34, Epithelioid GIST
GIST: Associations

- Familial, multiple germline c-kit mutation (11)
- NF-1
  - NF-1 product/c-kit interaction [lack kit mutations but stain with kit antibodies]
- Carney’s triad
  - Epithelioid GIST
  - Paraganglioma
  - Pulmonary chondroma

Family of KIT wild type GISTS – All Stain With KIT/DOG1

- NF1-associated
- Succinate dehydrogenase deficient ones:
  - About 7% of all GISTS
  - Mostly pediatric
  - Always gastric to date
  - Often epithelioid with plexiform growth
  - Associated with Carney triad, Carney-Stratakis syndrome (GISTs and paraganglioma)
GISTS – What Is Important in 2011

• Location, Location, and Location
• Size and mitotic counts
• Morphology
• CD117/c-kit/DOG1 staining
• CD117 Negative Examples

Location – Very Simply

• Esophagus – Majority of mesenchymal tumors in eso are leiomyomas – the eso GISTs are usually malignant
• Stomach – Most common site for GISTS, they are usually benign.
• Small bowel and colon and extra-intestinal – more aggressive.
Consensus Paper

• **Hum Pathol 2002; 33: 459**
  - Very low risk - < 2cm, <5/50 mits
  - Low risk – 2-5 cm, <5/50 mits
  - Intermediate risk- <5 cm, 6-10/50 mits OR >5cm, <5/50 mits
  - High risk - >5 cm, >5/50 mits OR >10 cm, any mitotic rate, OR any size and >10/50 mits
  - Trouble with this is that it ignores site

Features Seen In Benign Gastric Stromal Tumors

• Abundant collagen.
• Abundant vacuoles.
• Not much cell overlap.
What is Done Now to Prognosticate

• The AJCC GIST staging, TNM staging, NCCN 2007 system are all based on work by Miettinen

• Now a nomogram has been developed (Am J Surg Pathol 2011; 35:1646)

• Let’s look at the important key studies

Large AFIP Study of Gastric GIST


• 1869 cases originally classified as smooth muscle tumors of the stomach

• 1765 (94%) of these were GISTs.

• Slight male predominance (55%); median age of 63 years. Only 2.7% of tumors before age 21 years and 9.1% before 40 years.

• 0.5 to 44 cm (median, 6.0 cm); 12% incidentally detected.
Gastric GISTS, Outcome – About 20% Died

<table>
<thead>
<tr>
<th>Size Mits/50hpf</th>
<th>Outcome (% Mets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 cm &lt;5mits/50</td>
<td>2-3%</td>
</tr>
<tr>
<td>&gt;10 cm &gt;5mits/50</td>
<td>86%</td>
</tr>
<tr>
<td>&gt;10 cm &lt;5mits/50</td>
<td>11%</td>
</tr>
<tr>
<td>&lt;5 cm &gt;5mits/50</td>
<td>15%</td>
</tr>
</tbody>
</table>

AFIP Gastric GIST Study

• Unfavorable factors: Tumor location in fundus or gastroesophageal junction, coagulative necrosis, ulceration, and mucosal invasion (P <0.001).
• Favorable: Tumor location in antrum (P <0.001).
<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Size</th>
<th>Mitoses/ 50 hpf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>No larger than 2 cm</td>
<td>No more than 5/50</td>
</tr>
<tr>
<td>Probably benign</td>
<td>&gt;2, ≤ 5 cm</td>
<td>No more than 5/50</td>
</tr>
<tr>
<td></td>
<td>&gt;5, ≥ 10 cm</td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>No larger than 2 cm</td>
<td>No more than 5/50</td>
</tr>
<tr>
<td>Low Moderate Malignant</td>
<td>&gt;10 cm</td>
<td>No more than 5/50</td>
</tr>
<tr>
<td>Potential</td>
<td>&gt;2, ≤ 5 cm</td>
<td>&gt;5/50</td>
</tr>
<tr>
<td>High Malignant Potential</td>
<td>&gt;5, ≥ 10 cm</td>
<td>&gt;5/50</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm</td>
<td></td>
</tr>
</tbody>
</table>

Large AFIP Study of Small Intestinal GISTs

- 1091 tumors originally classified as smooth muscle tumors of the small intestine (including jejunum or ileum, excluding duodenum)
- 906 (83%) were GISTs.
AFIP Study of Small Intestinal GISTs

- 55:45 male-to-female ratio
- Median age 59 years (range, 13-94 years). 0.6% before age 21; 13.6% before 40.
- 0.3 to 40 cm (median, 7.0 cm) and most commonly presented with GI bleeding or acute abdomen; 18% were incidentally detected.

Small Intestinal GISTs - About 40% Died

<table>
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<tr>
<th>Size</th>
<th>Mits/50</th>
<th>% Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cm</td>
<td>&lt;5mits/50</td>
<td>2-3%</td>
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<tr>
<td>&gt;10 cm</td>
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<td>86%</td>
</tr>
<tr>
<td>&gt; 10 cm&lt;5mits/50</td>
<td>&gt;50%</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 cm &gt;5mits/50</td>
<td>&gt;50%</td>
<td></td>
</tr>
<tr>
<td>5-10 cm &gt;5 mits/50</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>
AFIP Study of Small Intestinal GISTs

• Skeinoid fibers were present in 44% of cases, and their presence was associated with a favorable course.

• Most epithelioid tumors were malignant, and this morphology sometimes emerged from less cellular and less mitotically active spindle cell tumors, suggesting that it represented a transformation.
### Skeinoid Fibers

### Table: Tumor Parameters and Patients With Progressive Disease During Follow-Up

<table>
<thead>
<tr>
<th>Group</th>
<th>Size, cm</th>
<th>Mitotic Rate per 50 HPFs</th>
<th>Gastric GISTs</th>
<th>Small Intestinal GISTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≤2</td>
<td>≤5</td>
<td>0 Very low if any</td>
<td>0 Very low if any</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2 ≤5</td>
<td>≤5</td>
<td>1.9 Low</td>
<td>4.3 Low</td>
</tr>
<tr>
<td>3a</td>
<td>&gt;5 ≤10</td>
<td>≤5</td>
<td>3.6 Low</td>
<td>24 Intermediate</td>
</tr>
<tr>
<td>3b</td>
<td>&gt;10</td>
<td>≤5</td>
<td>12 Intermediate</td>
<td>32 High</td>
</tr>
<tr>
<td>4</td>
<td>≤2</td>
<td>&gt;5</td>
<td>0 Low†</td>
<td>30 High</td>
</tr>
<tr>
<td>5</td>
<td>&gt;2 ≤5</td>
<td>&gt;5</td>
<td>16 Intermediate</td>
<td>73 High</td>
</tr>
<tr>
<td>6a</td>
<td>&gt;5 ≤10</td>
<td>&gt;5</td>
<td>35 High</td>
<td>85 High</td>
</tr>
<tr>
<td>6b</td>
<td>&gt;10</td>
<td>&gt;5</td>
<td>86 High</td>
<td>96 High</td>
</tr>
</tbody>
</table>

* Note: significantly worse prognosis in small intestinal GISTs. Based on data from Miettinen et al.\(^2\) HPFs indicates high-power fields.† Denotes tumor categories with very small numbers of cases insufficient for prediction of malignant potential.
What if There is No CD117?

- About 2-9% of GISTs are Ckit negative and lack kit mutations
- A percentage of such cases have PDGFRA mutations [Science 2003; 299:708]
- Diagnosis should be with caution
- DOG1 now resolves many cases


Requests For Mutation Analysis

- Most common mutation in kit [exon 11] responsive to imatinib
- Patients with KIT exon 9 mutations may need higher dose imatinib or newer compounds [eg, sunitinib]
- Most common of the PDGFRA receptor mutations in NOT responsive

The testing costs about $1,500.00
Who Needs Mutational Analysis

• Not all GISTs require mutational analysis—this technique is best reserved for those in patients with;
• Advanced disease (i.e. recurrent or metastatic tumors) in patients being treated with tyrosine kinase inhibitors
• Patients who have developed tyrosine kinase inhibitor resistance.
• http://www.amptestdirectory.org

CD117 is Not Specific for GIST:

<table>
<thead>
<tr>
<th>GIST</th>
<th>Small cell ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatofibrosarcoma</td>
<td>ALCL</td>
</tr>
<tr>
<td>Solitary fibrous tumor</td>
<td>R-S cells</td>
</tr>
<tr>
<td>WD liposarcoma</td>
<td>AML</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Seminoma</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>Glioma</td>
</tr>
<tr>
<td>Angiosarcoma, KS</td>
<td>Endometrial ca</td>
</tr>
<tr>
<td>Melanoma/CCS</td>
<td></td>
</tr>
<tr>
<td>Myofibroblasts/Fibromatosis</td>
<td></td>
</tr>
</tbody>
</table>
Spindle Cell Neoplasms of The GI Tract Are not all GISTS

Stromal tumor – per the surgeon
Colon resection, immunosuppressed patient
Anal epithelioid lesion

CD117
Immuno Tip

• About 30-40% of melanomas label with CD117/kit be careful not to call them epithelioid GIST
Another Immuno Tip

• About 10% of epithelioid GISTS stain with MELAN-A [but not HMB45 and MART]

• In our hands these expressed CD34 [most melanomas do not] and lacked S100 [most melanomas have S100].
Differential Diagnosis of Spindle Cell GIT Tumors

- Smooth muscle tumors
- Inflammatory myofibroblastic tumor
- Schwannomas
- Glomus Tumor
- Solitary Fibrous Tumor
- Spindle cell carcinoma
- Mesothelioma
- Dedifferentiated Liposarcoma

The Secret

- Diagnosing GIT mesenchymal tumors is really about knowing which tumors live in which layers
- For example, inflammatory fibroid polyp (with PDGFRA mutations) is in the submucosa whereas GIST (also with PDGFRA mutations) is in the muscularis propria
Layers – Centered in:

**Mucosa**
- Some nerve sheath tumors
- “Benign fibroblastic polyp”/perineurioma
- Incidental leiomyomas of muscularis mucosae
- Synovial sarcoma [super rare]
- Mucosal melanoma [anus, esophagus]

**Submucosa**
- Inflammatory fibroid polyp
- Some benign nerve sheath tumors
- Gangliocytic paraganglioma

Layers – Centered in:

**Muscularis propria**
- GIST
- GIT schwannoma [with lymphoid cuff]
- Esophageal leiomyomas
- GIT glomus tumors
- Ganglioneuromatosis
- GIT tract clear cell sarcoma

**Mesentery**
- Desmoid/ fibromatosis
- Inflammatory myofibroblastic tumor
- Sclerosing mesenteritis
- Mesenteric myositis ossificans
Layers

**Whenever it wants to**

- Metastatic MELANOMA
- Some sarcomatoid carcinomas [such as renal cell ca]

Layers: Mucosa
“Schwann Cell Hamartoma”

Benign fibroblastic polyps of the colon/perineurioma

- Incidental - detected in adult patients undergoing screening colonoscopy.
- Mean age in the reported series 61.5 years.
- Small polyps at endoscopy (size range, 0.2 – 1.5 cm).
- Lamina propria - Some intimately admixed with hyperpastic polyps.
- “Vimentin-only” lesions, lacking CD31, S-100, CD117/c-kit, Bcl-2, and desmin.
- A few have focal SMA and CD34.
- Similar lesions with EMA/ glut1/ claudin 1 can be regarded as “perineurioma”
Benign fibroblastic polyp/perineurioma associated with hyperplastic polyp – “stromal epithelial interactions”?
Something Submucosal
Inflammatory Fibroid Polyp (IFP)

- First described by J Vaněk
- 6 lesions, all in stomach (antrum/pylorus-5)


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IFP

- Present term coined in early 1950’s

IFP- Other terms

- Gastric submucosal granuloma with eosinophilic infiltration
- Eosinophilic granuloma
- Granuloblastoma
- Neurofibroma
- Hemangiopericytoma

IFP Location

- Vast majority in stomach
- 3-4% of all gastric polyps
- Usually in adults (60-80yrs)
IFP- Endoscopic Appearance

- Smooth submucosal lesions
- Surface ulceration/erosion in about 1/3 of cases
- Presentation is site specific
IFP – Loads of eosinophils
IFP- Pathogenesis

• Used to be considered reactive
• Now we know there are mutations in PDGFRA [exon 18, gastric, exon 12, small bowel] and protein expression
• One family with these tumors in 3 generations of women (“Devon polyposis”)
• Diploid flow cytometry.
• Japanese examples associated with gastric ca (not western ones, coincidence?)
IFP Pearls

- Gastric ones involve the mucosa (and the submucosa), as do colonic ones.
- The small bowel ones are submucosal lesions that ulcerate, but that tend not to infiltrate mucosa. They have less prominent perivascular “onion skinning”

IFP- Immunohistochemistry

- Fibroblastic/myofibroblastic
- Variable actin, negative S100
- Consistent CD34 (less striking in large tumors)
- NO CD117/c-kit, +PDGRFA
- ? Dendritic – cyclin D1, fascin