Gastrointestinal Stromal Tumors (GIST)

- Mesenchymal tumors of the
  - GI tract wall
  - mesentery
  - omentum
  - retroperitoneum
- Previously thought to be smooth muscle tumors known as leiomyomas and leiomyosarcomas
DEFINITION

Mesenchymal tumors characterized by almost universal expression of the c-kit proto-oncogene protein

Davila RE et al, Gastrointest Endosc 2003; 58: 80-88

**c-kit proto-oncogene**

- Located on the long arm of chromosome 4
- Encodes a 145 kD transmembrane receptor with internal tyrosine kinase activity
- CD117 is an antigen on the extracellular portion
c-kit Receptor

- Binds a ligand known as **stem cell factor which is a growth factor**
- Binding results in:
  - gene transcription
  - cell division
  - chemotaxis
  - actin reorganization
  - **cell growth**

GIST Pathogenesis

Thought to arise from the development of several **gain-of-function** mutations in the c-kit proto-oncogene
Mutations result in constitutive activation of the c-kit receptor without ligand

GISTS and Genetic Mutations

- > 80% have activating c-kit mutations
- 5-7% have activating mutations of PDGFRA
  (another tyrosine kinase receptor similar to c-kit)
- c-kit and PDGFRA mutations are mutually exclusive
- 10-15% are negative for c-kit and PDGFRA mutations and are called wild-type
GIST can be differentiated from other mesenchymal tumors based on immunohistochemical staining.

95% of all GIST stain positive for CD117 → Hallmark of GIST diagnosis.
GIST Immunohistochemistry

- Overall, 60% to 70% stain positive for CD34
  - Sialylated transmembrane glycoprotein and hematopoietic progenitor cell antigen found in mesenchymal cells
- Usually negative for smooth muscle actin (SMA)
  - Although small subset of small intestinal GIST are positive for SMA
- Negative for desmin (rarely positive)
- Negative for S100 protein (rarely positive)

<table>
<thead>
<tr>
<th></th>
<th>GIST</th>
<th>Leiomyomas</th>
<th>Schwannomas</th>
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<tbody>
<tr>
<td>CD117</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>(&gt;95%)</td>
<td></td>
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<tr>
<td>CD34</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td>(60%-70%)</td>
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<tr>
<td>SMA</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<td></td>
<td>(usually)</td>
<td></td>
<td></td>
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<tr>
<td>Desmin</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>S100</td>
<td>-</td>
<td>-</td>
<td>+</td>
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Proposed Cellular Origin of GIST - Interstitial Cells of Cajal (ICC)

- A complex network of cells within the muscle layer of the GI tract
- Serve as a pacemaker that regulates gut motility
- Their development is dependent on normal c-kit activity
- Have identical immunohistochemical staining for CD117, CD34 and other antigens
- GIST originate from the ICC or a pluripotential stem cell that later differentiates into the ICC


Epidemiology

- Estimated incidence is 4,000 to 6,000 cases per year in the US
- Annual incidence of 11-14 cases per million
- Peak occurrence in the 5th and 6th decades
- Rare in patients < 40 years of age
- Extremely rare in children
- No gender or ethnic predominance
Hereditary Forms of GIST

• Familial GIST
  – Several reported families
  – Individuals have TNTC tumors
  – Germline activating mutations of c-kit or PDGFRA
  – Autosomal dominant
• Neurofibromatosis Type I
  – 7% lifetime risk
  – Small intestinal tumors > stomach tumors
  – Majority are CD117 negative

Clinical Presentation

• 10%-30% of GIST are incidentally found in totally asymptomatic patients
<table>
<thead>
<tr>
<th>Location</th>
<th>Frequency</th>
<th>Location Details</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>Rare</td>
<td></td>
<td>Dysphagia, Mediastinal mass on XRAY</td>
</tr>
<tr>
<td>Stomach</td>
<td>60-70%</td>
<td>Fundus &gt; Antrum or Body</td>
<td>GI bleed / Anemia, Abdominal Pain</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>20-30%</td>
<td>Jejunum &gt; Ileum &gt; Duodenum</td>
<td>GI bleed / Anemia, Abdominal pain, Palpable mass on PE, SBO / Intussusception, Jaundice</td>
</tr>
<tr>
<td>Colon</td>
<td>Rare</td>
<td>Rectum &gt; Colon</td>
<td>GI bleed / Rectal bleeding, Change in bowel habits, Abdominal pain, Palpable mass</td>
</tr>
<tr>
<td>Gallbladder/</td>
<td>Rare</td>
<td></td>
<td>Cholecystitis / Appendicitis</td>
</tr>
<tr>
<td>Appendix</td>
<td></td>
<td></td>
<td>Perforated tumors: abscess/ascites</td>
</tr>
<tr>
<td>Mesentery/</td>
<td>Rare</td>
<td></td>
<td>Abdominal Pain</td>
</tr>
<tr>
<td>Omentum/</td>
<td></td>
<td></td>
<td>Palpable mass on PE</td>
</tr>
<tr>
<td>Peritoneum</td>
<td></td>
<td></td>
<td>Perforated tumors: abscess/ascites</td>
</tr>
</tbody>
</table>

81 yo woman presenting with pneumonia found to have a retrocardiac mass on Chest CT
67 yo man with intermittent melena, 20 lbs weight loss, and iron deficiency anemia

42 yo man with 2 wk history of melena presents with syncope and hematochezia
Histopathology

- 70% to 80% of GIST are the spindle cell type
- 20% to 30% of GIST are the epithelial type
- <10% of GIST have a mixed type (epithelial and spindle cell)
ALL GIST HAVE MALIGNANT POTENTIAL!

THE TERM “BENIGN” SHOULD NOT BE ASCRIBED TO GIST

Tumor Behavior

• Malignant behavior is defined by:
  ▪ metastasis to other organs
    ➢ Liver (>50%)
    ➢ Mesentery/Omentum/Peritoneum
    ➢ Lungs (<10%)
    ➢ Bone (<10%)
  ▪ OR direct invasion to adjacent organs
• GIST rarely metastasize to lymph nodes
Risk of Malignant Behavior

- Determined by:
  - Tumor size
  - Mitotic index (number of mitoses seen per 50 HPF)
  - Tumor location

2001 NIH GIST Workshop Guidelines for Predicting Malignant Behavior

<table>
<thead>
<tr>
<th>Size, mm</th>
<th>Mitotic index, per 50 HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low risk</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Low risk</td>
<td>20–50</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>≤50</td>
</tr>
<tr>
<td></td>
<td>50–100m</td>
</tr>
<tr>
<td>High risk</td>
<td>&gt;50</td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
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</tbody>
</table>

HPF, High-power field.

* Small bowel GIST appear to have higher risk of malignant behavior even when small (<50mm)
Diagnostic Evaluation

- Radiologic imaging can be used to:
  - Determine tumor size and location
  - Rule out metastatic disease
- CT is the preferred modality with diagnostic yield of 74%
- CT cannot distinguish from other GI tract tumors or determine layer of origin
- PET may be used in the initial evaluation:
  - To completely rule out metastases
  - To establish a baseline prior to initiating therapy
Endoscopy

Characteristic appearance:

- Subepithelial lesion with normal overlying mucosa
- May have central ulceration or umbilication

Endoscopy

- Endoscopic biopsies are limited due to inability to reach beyond the normal overlying mucosa and submucosa
- Forceps biopsies of subepithelial lesions using a stacked technique has a low yield of 42% with a 2.8% risk of bleeding

Hunt GC et al. Gastrointest Endosc 2003; 57: 68-72
Endoscopic Ultrasound

- Is indicated in the evaluation of submucosal lesions of the GI tract
- Can determine layer of origin
- Can rule out other diagnoses
- Usual features include hypoechoic mass with smooth borders arising from the muscularis propria
- EUS findings alone are helpful for making the diagnosis of GIST
- Sensitivity – 65% - 95%
- Specificity – 72% - 92%

Location of GIST in GI Tract Wall

- mucosa
- submucosa
- muscularis propria
- adventitia/serosa
- Adjacent Organ
EUS Findings Suggestive of Malignant GIST

- Tumor size > 4 cm
- Irregular border
- Echogenic foci
- Cystic spaces

Presence of 2/3 features: sensitivity of 80-100% for malignancy

Chak A et al, Gastrointest Endosc 1997; 45: 468-73
**EUS-guided FNA**

- Should be performed to obtain a tissue diagnosis
- CD117 staining of EUS-FNA specimens is important in making the diagnosis
- Systematic review of clinical diagnosis of GIST – 46 studies, 4,534 patients
  - yield of EUS alone: 68.7% (40% - 100%)
  - yield of EUS + FNA: 84% (73.8% - 100%)


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**EUS-guided Core Biopsy**

- Performed with the 19-gauge Tru-cut needle
- Yields a core tissue specimen
- Theoretically useful in obtaining mitotic index and therefore, determining malignant risk
- Diagnostic yield is 80%
- Highest yield in gastric tumors on the lesser curve
- Associated with high failure rate and septic complications
- Should be considered when FNA is non-diagnostic
MANAGEMENT

Surgery

• Is the mainstay of treatment
• Is recommended for localized tumors ≥ 2cm without evidence of metastasis
• Goal is to achieve complete resection
• Wide resection of uninvolved tissue is not necessary
• Lymphadenectomy is not necessary since nodal metastases are rare
• Laparoscopic wedge resection of gastric GIST has been shown to be safe and effective
• Following complete resection, surveillance CT scan should be performed every 3-6 months for 5 yrs, then annually

National Comprehensive Cancer Network Clinical Practice Guidelines & European Society for Medical Oncology Recommendations
Small Incidental GIST & EUS Surveillance

- Lesions < 2cm have a low risk of malignant behavior
- Surveillance with EUS can be done in tumors < 2cm, specially stomach GIST
- EUS surveillance every 6-12 months can be considered
  - Should refer to surgery if there is:
    - Interval growth
    - Patient becomes symptomatic
    - Development of high-risk features (cysts, ulceration, or irregular margin)

National Comprehensive Cancer Network Clinical Practice Guidelines

Endoscopic Resection of GIST

- Can be performed in small lesions located within the muscularis mucosa or submucosa
- Has been described in lesions arising from the muscularis propria including use of
  - band ligation
  - needle knife
  - endoscopic enucleation using insulated-tip electrosurgical knife
  - combined endoscopic and laparoscopic approach
- Variable complication rates and limited follow-up
Medical Management - Imatinib

- A selective inhibitor of several tyrosine kinases including c-kit and PDGFRA
- FDA approved in 2002 for the treatment of unresectable and metastatic GIST
- Optimal dose: 400 mg PO daily
Imatinib in the Management of Advanced Disease

- Advanced disease is defined as:
  - Tumors that are metastatic
  - Locally invasive tumors
- Monitoring of treatment response with CT scan every 3 months
- Median progression-free survival of 20-26 months
- Disease progression can be managed with
  - Dose escalation
  - Alternative tyrosine kinase inhibitor, sunitinib

Adjuvant Imatinib

- Indicated in completely resected tumors with high risk features:
  - Ruptured tumor
  - Gastric tumors >5cm, >5 mitosis/50 HPF
  - Small intestinal tumors ≥2cm, >5 mitosis/50 HPF
- Dose - 400mg QD for minimum of 3 years
- Overall 3 year survival > 95%
- Recurrence free survival at 3 years > 60%
Neoadjuvant Imatinib

• Should be considered for:
  – Potentially resectable tumors with significant perioperative morbidity
  – Borderline resectable tumors
  – Potentially resectable tumors requiring extensive organ disruption
• Goal is to reduce tumor size to facilitate surgery
• Still under study in several clinical trials
• Unclear duration of treatment - 3-6 mo

Conclusions

• GIST are mesenchymal tumors of the GI tract and other intraabdominal sites
• Development of gain-of-function mutations in the c-kit proto-oncogene is important in GIST oncogenesis
• Immunohistochemical analysis with CD117 staining is key for diagnosis
• Endoscopic ultrasound with FNA is currently the most important method of diagnosis
Conclusions

- Surgery is the mainstay of treatment for localized tumors without metastases
- Further studies are needed to determine the role of endoscopic resection of GISTs
- Treatment with imatinib leads to prolonged progression free survival in advanced metastatic or unresectable disease
- Recommend multidisciplinary approach to patient and consider referral to expert centers with possible inclusion into clinical trials