A 43 year old male presents with abdominal complaints. An axial CT reveals ....
Diagnosis: Gastrointestinal Stromal Tumor

Location: stomach
Size: 12 cm
Mitotic count: 10 mitoses / 50 high power fields
Risk Assessment: High risk of aggressive behavior
Mutation status: ?

C-kit
Gastrointestinal Stromal Tumors (GIST) Understanding Pathology and the Role of Mutations in Treatment

What is a GIST
How is it going to behave
What is the science of GIST
Why did I get a GIST
Who gets a GIST
Gastrointestinal Stromal Tumors

Definition
Epidemiology
Pathology
Molecular pathology
    oncogenic mutations
Prognostic Features
A malignant tumor/neoplasm
- has the biological capacity to metastasize
Classified according to the normal tissues of the body
Epithelium – carcinoma
Melanocytes - melanoma
Immune cells – lymphoma/leukemia/myeloma
Connective tissue - sarcoma
Gastrointestinal Stromal Tumor

Definition: A mesenchymal neoplasm whose line of differentiation recapitulates the cells of Cajal and has a broad spectrum of biological behavior.
Gastrointestinal Stromal Tumors

Epidemiology

1% GI malignancies
3,300-6,000 new clinically significant cases/year in U.S.
11-20 per million persons
10-30% behave clinically malignant
<1% familial
Gastrointestinal Stromal Tumors

Gender: M:F = 1:2
Gastrointestinal Stromal Tumors

Clinical Findings
Depends on size, location and invasion of other organs
Abdominal mass, GI bleeding, pain, anorexia, perforation, fever
Site specific
Incidental finding
Gastrointestinal Stromal Tumors
Gastrointestinal Stromal Tumors
Gastrointestinal Stromal Tumors
Gastrointestinal Stromal Tumors
<table>
<thead>
<tr>
<th>Tumor Feature</th>
<th>Risk of Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mitoses</strong></td>
<td><strong>Stomach</strong></td>
</tr>
<tr>
<td>&lt;5/50 hpf</td>
<td>very low (0%)</td>
</tr>
<tr>
<td>&gt;2≤5</td>
<td>very low (1.9%)</td>
</tr>
<tr>
<td>&gt;5≤10</td>
<td>low (3.6%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>mod (12%)</td>
</tr>
<tr>
<td>≥5/50 hpf</td>
<td>very low (0%)</td>
</tr>
<tr>
<td>&gt;2≤5</td>
<td>mod (16%)</td>
</tr>
<tr>
<td>&gt;5≤10</td>
<td>high (55%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>high (86%)</td>
</tr>
<tr>
<td><strong>Size (cm)</strong></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>very low (0%)</td>
</tr>
<tr>
<td>&gt;2≤5</td>
<td>low (8.3%)</td>
</tr>
<tr>
<td>&gt;5≤10</td>
<td>high (34%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>high (52%)</td>
</tr>
<tr>
<td>≥5/50 hpf</td>
<td>very low (0%)</td>
</tr>
<tr>
<td>&gt;2≤5</td>
<td>high (50%)</td>
</tr>
<tr>
<td>&gt;5≤10</td>
<td>high (86%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>high (90%)</td>
</tr>
</tbody>
</table>

*J Surgical Oncology 2011;104:865-873*
Gastrointestinal Stromal Tumors

Immunohistochemical profile

C-Kit: 85-100%
DOG-1: 85-100%
CD 34: 30-100%
Gastrointestinal Stromal Tumors

C-kit
Gastrointestinal Stromal Tumors

Terminology

Gastrointestinal stromal tumor; Mazur 1983

Interstitial Cells of Cajal

Described > 100 yrs ago
Located throughout GI tract
Function as ‘pacemaker’ and mediator of neuro transmission
C-Kit vital to development and function
C-KIT

Protein – cell surface receptor - tyrosine kinase
Chromosome 4, Development of heme stem cells, germ cells, mast cells, melanocytes, interstitial cells of Cajal
Cell survival
Cell proliferation
Cell adhesion
Cell differentiation and maturation
Gastrointestinal Stromal Tumor

Genetic disease - caused by mutations
Molecular Classification of GIST

- CKIT: 75-80%
- PDGFRA: 5-8%
- BRAF: 6%
- SDH-A,B,C,D: 2%
- HRAS: <1%
- NF1: 5-8%
Gastrointestinal Stromal Tumors

C-Kit Mutations
Described 1998
Located on chromosome 4
Found in 75-80% of GIST
Mutations activate the tyrosine kinase receptor

PDGFRα Mutations
Located on chromosome 4
Found in 5-8% of GIST
Mutations activate tyrosine kinase receptor
Gastrointestinal Stromal Tumors

Inactive KIT or PDGFRA

Active KIT or PDGFRA

Ligand binding

Oncogenic mutations

Signalling

Exon 9 (11%)

Exon 11 (67.5%)

Exon 13 (0.9%)

Exon 17 (0.5%)
Gastrointestinal Stromal Tumors

- Kit mutations - worse prognosis than PDGFRα mutations
  - deletions in exon 11 - most aggressive
  - Exon 9 mutations associated with intestinal location and more aggressive course

- PDGFRα exon 14 and 18 mutations - gastric origin, epithelioid morphology and favorable outcome

Arch Pathol 2011;135:1298-1310.
C-Kit and PDGFRa Negative GIST Account for 12% of GIST

epithelioid/stomach

BRAF
NRAS
HRAS

NF1

loss of function mutation
– succinate dehydrogenase & IGFR amplification
Progression of Molecular Aberrations in GIST

Additional CKIT and PDGFRα mutations

Resistance to Drugs

Benign

CKIT
PDGFRα
BRAF
SDH

Chromosome 14, 14q Loss or monosomy
Chromosome 8q 17q Gains
Chromosome 1p, 9p, 11p 10, 13q, 15q, 22q Loss

Malignant
GIST – Treatment Effect
Gastrointestinal Stromal Tumors

**Outcome**

- Local recurrence 44-66%
- Spread along serosal surfaces
- Deposits in liver
- 5 yr survival 38-65%
- 60% develop metastases
- (18% have metastases at presentation)
Gastrointestinal Stromal Tumors

Summary

GIST is the most common mesenchymal tumor of the bowel and recapitulates the cells of Cajal.

GIST have the potential to be biologically aggressive – risk stratification based on size, mitotic rate, and location.

GIST is associated with mutations (KIT, PDGFRα, SDH, BRAF) and there is a relationship between mutation and biological behavior and response to therapy. Additional mutations are responsible for acquired resistance to therapy.
Gastrointestinal Stromal Tumors

Etiology
Unknown – vast majority are sporadic; rarely a complication of prior radiation
Associated with syndromes: Carney’s triad, Carney-Stratakis syndrome, von Recklinghausen’s disease type 1
Familial forms
<table>
<thead>
<tr>
<th>Genetic type</th>
<th>Relative frequency</th>
<th>Anatomic distribution</th>
<th>Germline examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KIT mutation (relative frequency 75–80%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 8</td>
<td>Rare</td>
<td>Small bowel</td>
<td>One kindred</td>
</tr>
<tr>
<td>Exon 9 insertion AY502-503</td>
<td>10%</td>
<td>Small bowel and colon</td>
<td>None</td>
</tr>
<tr>
<td>Exon 11 (deletions, single nucleotide substitutions and insertions)</td>
<td>67%</td>
<td>All sites</td>
<td>Several kindreds</td>
</tr>
<tr>
<td>Exon 13 K642E</td>
<td>1%</td>
<td>All sites</td>
<td>Two kindreds</td>
</tr>
<tr>
<td>Exon 17 D820Y, N822K and Y823D</td>
<td>1%</td>
<td>All sites</td>
<td>Five kindreds</td>
</tr>
<tr>
<td><strong>PDGFRA mutation (relative frequency 5–8%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 12 (such as V561D)</td>
<td>1%</td>
<td>All sites</td>
<td>Two kindreds</td>
</tr>
<tr>
<td>Exon 14 N659K</td>
<td>&lt;1%</td>
<td>Stomach</td>
<td>None</td>
</tr>
<tr>
<td>Exon 18 D842V</td>
<td>5%</td>
<td>Stomach, mesentery and omentum</td>
<td>None</td>
</tr>
<tr>
<td>Exon 18 (such as deletion of amino acids IMHD 842–846)</td>
<td>1%</td>
<td>All sites</td>
<td>One kindred</td>
</tr>
<tr>
<td><strong>KIT and PDGFRA wild-type (relative frequency 12–15%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>~7–15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDHA, SDHB, SDHC and SDHD mutations</td>
<td>~2%</td>
<td>Stomach and small bowel</td>
<td>Carney–Stratakis</td>
</tr>
<tr>
<td>HRAS and NRAS mutation</td>
<td>&lt;1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporadic paediatric GISTs</td>
<td>~1%</td>
<td>Stomach</td>
<td>Not heritable</td>
</tr>
<tr>
<td>GISTs as part of the Carney triad</td>
<td>~1%</td>
<td>Stomach</td>
<td>Not heritable</td>
</tr>
<tr>
<td>NF1-related</td>
<td>Rare</td>
<td>Small bowel</td>
<td>Numerous</td>
</tr>
</tbody>
</table>

GIST, gastrointestinal stromal tumour; NF1, neurofibromatosis type I; PDGFRA, platelet-derived growth factor receptor-α; SDH, succinate dehydrogenase.
C-Kit
## GI Stromal Tumors

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% cases</th>
<th>Imat. Resp</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT exon 11</td>
<td>70%</td>
<td>85%</td>
</tr>
<tr>
<td>KIT exon 9</td>
<td>15%</td>
<td>45%</td>
</tr>
<tr>
<td>KIT exon 13</td>
<td>&lt;5%</td>
<td>few</td>
</tr>
<tr>
<td>KIT exon 17</td>
<td>&lt;5%</td>
<td>few</td>
</tr>
<tr>
<td>PDGRA d842</td>
<td>4%</td>
<td>none</td>
</tr>
<tr>
<td>PDGFRA other</td>
<td>1%</td>
<td>few</td>
</tr>
<tr>
<td>No KIT/ PDGFRA</td>
<td>5-10%</td>
<td>little</td>
</tr>
</tbody>
</table>
GI Stromal Tumors

Treatment

Complete resection; Conventional chemotherapy fails

Imatinib - inhibitor of c-Kit

most effective

Mechanism of Action of Gleevec™

Gleevec is not entirely selective for Bcr-Abl; it also inhibits c-Kit and PDGF-R.
Metastatic GIST Before and After Imatinib

Baseline Pre-Imatinib

7 July 2000

Avid PET Uptake

1 Month on Imatinib

7 August 2000

No PET Uptake

Courtesy of George D. Demetri, MD.
GI Stromal Tumors

Differential Diagnosis

- Fibromatosis
- Leiomyoma, leiomyosarcoma
- Schwannoma
- Inflammatory fibroid polyp
Interstitial Cells of Cajal
GI Stromal Tumors

GIST recapitulates cells of Cajal
Similar ultrastructural features and immunophenotype as cells of Cajal
Similar distribution as cells of Cajal
Both express c-Kit
IG Stromal Tumors

Other Prognostic Features

Proliferation markers
Ki-67, PCNA

Flow Cytometry
aneuploidy
Kit monomer
Activated Kit
Mutated Kit

Stem Cell Factor
Stem Cell Factor
GI Stromal Tumors

Morphologic Prognostic Features

Location, size, mitotic activity and invasion of other organs

Good features: stomach, $\leq 5$cm, $\leq 1$ mitosis/50 hpf, non-invasive
Gleevec is not entirely selective for Bcr-Abl; it also inhibits c-Kit and PDGF-R.
GIST Treated with Imatinib

Pre-treatment

Post-treatment
Gleevec Trials

- Partial response 59%
- Stabilization 28%
- Progression 13%
- If no ckit mutation, 8x more likely to have progression (44%) vs Exon 11 mutation (5%)
Special Groups of GIST

Children
usually female, usually have epithelioid morphology

Familial GIST- inherited mutation in exon 11 Kit gene

ICC hyperplasia & multiple GIST, hyperpigmentation

Type 1 von Recklinghausen’s Disease
arise in background of diffuse hyperplasia of ICC, multiple, lack mutation in KIT + PDGFA

have inactivating mutation of NF1 gene producing dysfunctional protein neurofibromin

Carny’s triad – gastric GIST, pulmonary chondroma, paraganglioma, no Kit or PDGF mutations
GI Stromal Tumors

**Etiology**

- unknown
- rare complication of radiation
- associated with Carney’s triad, von Reckinghausens disease, type 1, and intestinal neuronal dysplasia
C-Kit Negative GIST

Epithelioid morphology
PDGFR-alpha mutations
Originate in omentum/peritoneum
Many are responsive to Imatinib
Imatinib mesylate (Gleevec)

**MECHANISM:**
Binds to ATP binding pocket of C-KIT kinase domain and inhibits receptor phosphorylation

**TOXICITY:**
Mild anemia, nausea, diarrhea, muscle cramps hepatorenal failure (rare)