Mesenchymal Tumors of the Esophagus

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KINGS COUNTY HOSPITAL CENTER
SURGERY GRAND ROUNDS 5/2/2013
55M presented to KCHC ED on 11/10/12 with epigastric pain, chest pain, dysphagia, inability to tolerate solid food intake and weight loss (30lb) for 1 month

- PMH: esophageal ulcers 20y ago
- PSH: none
- Meds: Prilosec PRN
- All: NKDA
- SH: tobacco (quit 8 years ago, 3ppd for many years), alcohol occasionally, no illicit drugs
Case Report

- **PE:**
  - NAD
  - VS- 99.7 126/86 74
  - HEENT- NCAT, no lymphadenopathy
  - Chest- CTA b/l, RRR
  - Abd- soft, nt, nd, no scars
  - Ext- warm, FROMx4

- **Labs:**
  - CBC- 10/44/12/349
  - Comp- 141/4.1/100/27/18/0.8/108
  - LFT- 6.9/4.0/16/11/87/0.5
  - PT/PTT- 20.8/11
CT chest/abdomen:
- 7.8 x 4.3 x 7.9 cm midesophageal mass starting at level of the carina
- Near complete obstruction of esophagus
- Right paratracheal lymph node 1.3 cm
Case Report

- **EGD:**
  - Large subepithelial mass at 30 cm

- **EUS:**
  - Heterogenous/hypoechoic mass with anechoic spaces
  - Submucosal with infiltration of muscularis propria

- **Pathology:**
  - Suggestive of smooth muscle tumor (FNA)
Operation:
- Right thoracotomy, mobilization of thoracic esophagus
- Exploratory laparotomy, mobilization of stomach and transection of proximal stomach, creating tubular gastric conduit
- Left neck incision, mobilization of cervical esophagus, transection of esophagus and esophago-gastric anastomosis
Case Report

- **Postop Course:**
  - POD#1-5: Extubated on the table, NPO, on TPN in SICU
  - POD#6: Transferred to floor
  - POD#9: Gastrografin swallow
  - POD#10-13: diet advanced
  - POD#14: discharged home

- **Pathology:**
  - 8cm leiomyoma with stromal myxoid degeneration
  - Margins negative
  - 0/34 LN
Mesenchymal Tumors of the GI tract

- Subepithelial tumors arising from mesenchymal cells
- Mesenchymal tumors comprise 1% of primary GI neoplasms
- Esophageal cancer 50 times more common

Types:
- **GIST**
  - Interstitial cells of Cajal (GI Pacemaker cells)
  - Characterized by c-kit mutation and KIT overexpression (95%)
- **Sarcomas**
  - Lipomas
  - Liposarcomas
  - Leiomyomas
  - Leiomyosarcomas
  - Desmoid tumors
  - Schwannomas
  - Peripheral nerve sheath tumors
Mesenchymal Tumors of the Esophagus

- Mid to distal third of esophagus
- Usually small and asymptomatic, but can grow to enormous size and produce dysphagia
- Rounded submucosal lesion with intact overlying mucosa, ulceration and bleeding uncommon
- Types:
  - Gastrointestinal stromal tumors (GIST)
  - Leiomyomas
  - Leiomyosarcomas
**Diagnosis**

- **Endoscopy**
  - submucosal protuberant lesions

- **EUS/FNA**
  - Hypoechoic lesions originating from the muscularis propria or muscularis mucosa
    - *FNA for immunohistochemistry*

- **PET**
  - *GIST shows increased FDG uptake*
Histological Diagnosis

- GIST, leiomyoma and leiomyosarcoma share similar histologic findings on H&E staining
- Immunohistochemical required to distinguish between these tumors:
  - GIST: positive for KIT, DOG-1 (95%), CD34 (65%), smooth muscle actin (50%)
  - Leiomyoma: positive for smooth muscle actin (95%), desmin (95%), negative for KIT, DOG-1
- FNA >80% accurate
Majority of mesenchymal tumors of the esophagus are leiomyomas (60%)

- Benign tumor
- Male preference
- Histologic distinction difficult between well-differentiated leiomyosarcoma and leiomyoma

**Treatment:**
- Lesions < 2cm can be observed with serial EUS or endoscopically resected
- Lesions > 2cm should be surgically resected (local resection vs esophagectomy depending on size)
Leiomyosarcoma

- Very rare
- Slow growing, malignant tumor
- Treatment: esophagectomy
- 5-year survival rate 58.3% after esophagectomy in a case series of 12 patients
GIST

- Annual incidence 4000-6000 new cases (7-20 cases per million)
- No predilection for either sex
- Mean age at diagnosis: 63y
- Location:
  - Stomach 40-60%
  - Jejunum/ileum 25-30%
  - Duodenum 5%
  - Colorectum 5-15%
  - Esophagus 1%
  - Retroperitoneum, mesentry, omentum
- Frequently metastasize to liver and peritoneum and rarely to regional lymph nodes
- Despite complete resection, only 50% of patients remain recurrence-free for 5 or more years
• Presence of activating mutations in the KIT gene (c-kit) or PDGFRA and overexpression of KIT protein (CD 117)
• Transmembrane tyrosine kinase receptor, activation initiates an intracellular signaling cascade that influences a variety of cellular functions that include proliferation, differentiation, and adhesion
• 75% of KIT gene mutations affect exon 11, less frequently affected are exon 9, 13, and 17
• 10% of adult GISTs lack mutations in either the KIT gene or PDGFRA, some of which have mutations in genes that encode subunits of the enzyme succinate dehydrogenase (SDH)
<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>(no tumor-related mortality)</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 cm, &lt; 5 mitoses/50 HPF</td>
</tr>
<tr>
<td>Probably benign</td>
<td>(&lt;3% with progressive disease)</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm but ≤5 cm, &lt; 5 mitoses/50 HPF</td>
</tr>
<tr>
<td>Uncertain or low</td>
<td>malignant potential</td>
</tr>
<tr>
<td></td>
<td>&lt; 2 cm, &gt;5 mitoses/50 HPF</td>
</tr>
<tr>
<td>Low to mod.</td>
<td>malignant potential (12%-15%</td>
</tr>
<tr>
<td></td>
<td>tumor-related mortality)</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm, &lt; 5 mitoses/HPF</td>
</tr>
<tr>
<td></td>
<td>&gt;2 cm but ≤5 cm, &gt;5 mitoses/50 HPF</td>
</tr>
<tr>
<td>High malignant</td>
<td>potential (49%-86% tumor-related</td>
</tr>
<tr>
<td></td>
<td>mortality)</td>
</tr>
<tr>
<td></td>
<td>&gt;5 cm but ≤10 cm, &gt;5 mitoses/50 HPF</td>
</tr>
<tr>
<td></td>
<td>&gt;10 cm, &gt;5 mitoses/50 HPF</td>
</tr>
</tbody>
</table>

Adopted by NCCN for gastric GISTs
Surgical Treatment: General Principles

- Complete gross resection with an intact pseudocapsule
- Segmental resection of the stomach or intestine with negative resection margins (1 to 2 cm)
- Necessity of achieving negative microscopic margins is uncertain with large (>10 cm) GISTs
- Routine lymphadenectomy is unnecessary
- Tumor should be handled carefully to avoid rupture, which markedly increases the risk of a disease recurrence
More difficult to manage than are GISTs arising in serosa-lined intraabdominal organs because of the lack of tumor confinement by serosal layer

- Local resection of small tumors if negative resection margins can be achieved, esophagectomy for tumors < 2 cm
- Open en bloc esophagectomy for esophageal GISTs
- Transhiatal esophagectomy is not recommended because of risk of violation and rupture of tumor
### Outcome

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Gastric</th>
<th>Jejunum/ileum</th>
<th>Duodenum</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2 to 5</td>
<td>98.1%</td>
<td>95.7%</td>
<td>91.7%</td>
<td>91.5%</td>
</tr>
<tr>
<td>5 to 10</td>
<td>96.4%</td>
<td>76%</td>
<td>66%</td>
<td>43%</td>
</tr>
<tr>
<td>&gt;10</td>
<td>88%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High Grade</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>100%</td>
<td>50%</td>
<td>–</td>
<td>46%</td>
</tr>
<tr>
<td>2 to 5</td>
<td>84%</td>
<td>27%</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>5 to 10</td>
<td>45%</td>
<td>15%</td>
<td>14%</td>
<td>29%</td>
</tr>
<tr>
<td>10</td>
<td>14%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers.

Case series of 4 cases at single center and 33 cases from the National Cancer Database

5 year survival 14% in SEER database, patients undergoing resection have better outcomes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>15 (45)</td>
</tr>
<tr>
<td>RT alone</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Surgery + chemo</td>
<td>2 (6)</td>
</tr>
<tr>
<td>RT + chemo</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Imatinib alone</td>
<td>3 (9)</td>
</tr>
<tr>
<td>No therapy</td>
<td>7 (21)</td>
</tr>
</tbody>
</table>

Esophageal GIST

- Case series of 7 patients with esophageal GIST who underwent surgical resection 2001-2003
- 2 patients with recurrence requiring esophagectomy after resection
- 2 patients with metastatic disease on TKI

Table 1. Patient Characteristics and Treatment History

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
</tr>
<tr>
<td>Median Age, years (range)</td>
<td>46.4 (39–68)</td>
</tr>
<tr>
<td>Primary presenting symptom</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3</td>
</tr>
<tr>
<td>Location of lesions</td>
<td></td>
</tr>
<tr>
<td>Distal esophagus</td>
<td>7</td>
</tr>
<tr>
<td>Median size of lesion, cm (range) (longest diameter)</td>
<td>6.3 (4–17)</td>
</tr>
<tr>
<td>Surgical procedures</td>
<td></td>
</tr>
<tr>
<td>Enucleation by VATS</td>
<td>3</td>
</tr>
<tr>
<td>Enucleation by thoracotomy</td>
<td>2</td>
</tr>
<tr>
<td>Esophagectomy</td>
<td>2</td>
</tr>
<tr>
<td>Median follow-up period, years (range)</td>
<td>4.4 (2.2–7.0)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>2</td>
</tr>
</tbody>
</table>

VATS = video-assisted thoracoscopic surgery.

Adjuvant Therapy: TKI

- Small molecule tyrosine kinase inhibitors imatinib/sunitinib
- Block signaling via KIT and PDGFRA by binding to the adenosine triphosphate-binding pocket required for phosphorylation and activation of the receptor
- Inhibition of tumor proliferation
- Median survival of patients with advanced GIST increased from approximately 20 to 60 months following introduction of imatinib
- NCCN guidelines recommend adjuvant imatinib for at least 36 months for patients with high risk GIST (tumor >5 cm in size with high mitotic rate [>5 mitoses/50 HPF] or a risk of recurrence that is >50 percent)
SSG XVIII trial

- Randomized controlled trial
- 400 patients with high-risk resected GIST
- 12 vs 36 months of 400mg imatinib
- primary endpoint was RFS
- At a median follow-up of 54 months, prolonged treatment was associated with a significant improvement in RFS
- 5-year RFS 66% vs 48%
- overall survival 92% vs 82%
- questions remain as to whether treatment should be continued for longer than 3 years, as within 6 to 12 months of discontinuing adjuvant imatinib, rates of disease recurrence were similarly increased

Joensuu et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor. JAMA 2012;307(12):1265-72
Neoadjuvant Therapy

- Unresectable or borderline resectable primary tumor
- Potentially resectable tumor that requires extensive organ disruption
- Local recurrence of locally advanced disease
- Limited amount of potentially resectable metastatic disease
- Goal of treatment is a reduction in tumor size that may facilitate complete surgical resection and/or increase the likelihood of organ preservation
- Phase 2 trial for neoadjuvant imatinib 6-12 weeks, radiologic response < 10%, stable disease 80-90%

Esophageal mesenchymal tumors are a rare disease, leiomyomas are most common.

Tumors < 2 cm which are not FDG avid can be observed or enucleated endoscopically.

Treatment for esophageal mesenchymal tumors > 2 cm is complete surgical resection, enucleation or esophagectomy depending on tumor size.

Segmental resection of esophageal GISTs is unadvisable due to poor tumor integrity and lack of serosa.

No large numbers reported for esophageal GIST but recurrence and mortality is high (5 year survival 14%).

Adjuvant therapy with imatinib based on risk stratification.
References

- Sabiston Textbook of Surgery, 19th ed
- Cameron: Current Surgical Therapy, 10th ed
- UpToDate: www.uptodate.com
- Joensuu et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor. JAMA 2012;307(12):1265-72
With regards to GISTs, which of the following statements is incorrect?

A. Combination of cellular morphology and KIT immunohistochemistry are required for diagnosis

B. After the small intestine, the stomach is the second most common locations

C. The majority of GISTs have an activating mutation in the KIT oncogene

D. GISTs are usually resistant to conventional chemotherapy and radiation therapy

E. Complete surgical resection is standard of care
A 55 year old man is evaluated for dysphagia and chest pain. A barium esophagram shows a 3 cm smooth filling defect in the distal end of the esophagus. Which of the following is true of his condition?

A. Cystic transformation or central necrosis is often associated with this condition
B. Patients often have hematemesis or anemia because of ulceration
C. EUS will show a hypoechoic mass in the submucosa
D. Endoscopic biopsy should be performed to rule out malignancy
E. Esophagectomy is recommended for all lesions