Gastrointestinal Stromal Tumor (GIST)

1. Microanatomy of GI tract
2. Incidence and organs affected
3. Pathology
4. Role of immunohistochemistry: Diagnosis and differential
5. The pathology report
6. Parameters for risk and recurrence
7. The molecular analysis and pathologist’s role
8. Summary

Incidence

- Most common mesenchymal GI tumor
- 0.2% of all GI tumors
- 80% of all GI sarcomas
- 5,000 new cases per year in the USA
- Most patients are adults
  - Affects women and men equally

Gross

- Lobulated/multilobulated tumor with smooth edges.
- Marked variability in size (average 10 cm)
- It may extend to mucosa and/or serosa or in both directions.
- It may ulcerate mucosa and bleed
- It may have cystic changes
- Necrosis may be seen.

Sites of Origin

- Omentum
- Mesentery
- Retropertioneum
- GIST
- Extraintestinal (<1%)

CD117

- Origin: Interstitial cell of Cajal
- It coordinates peristalsis as a pacemaker role

Courtesy of Brian Bake, U. Washington

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1. Mucosa
2. Muscularis mucosa
3. Submucosa
4. Muscularis propria
5. Serosa

Courtesy of Douglas Fagel, MD, FACOG, FASGE, AGAF
IMMUNOHISTOCHEMISTRY OF GIST

<table>
<thead>
<tr>
<th>I&amp;H</th>
<th>CD117 (Klt)</th>
<th>CD34</th>
<th>Smooth muscle actin</th>
<th>STAT5 protein</th>
<th>Desmin</th>
<th>Pan-keratin</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>95%</td>
<td>70%</td>
<td>30%</td>
<td>9%</td>
<td>2%</td>
<td>&lt;1%</td>
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DOG1 +
[95% / 40% of KIT neg GIST]

Ckit (CD 117)

GIST DIFFERENTIAL DIAGNOSIS

- Carcinoma
- Melanoma
- Leiomyoma
- Leiomyosarcoma
- Schwannoma
- Fibromatosis

KIT-negative GISTs

HEREDITARY GIST

Role of Pathologist

- Provide diagnosis on the initial biopsy
- On the excisions: Evaluate margins and determine factors that may predict aggressiveness
- Document metastasis
- Select part of tumor and order tests to determine presence of mutations with therapeutic purposes
- Assess response to therapy
Determining Risk of Recurrence

- 10% to 30% of all GISTs behave in a malignant fashion.
  - All GISTs have the potential to become malignant
- GISTs are not classified as benign or malignant at the time of discovery
  - The clinical risk is stratified for each tumor
  - Combination of size, localization and number of mitosis is used to predict malignant potential
- However, there are no histological parameters to predict behavior with certainty
- Necrosis and cellularity may influence behavior

EVALUATION OF RECURRENCE RISK

- MITOSIS-

Pathology Report

- Size
- Sites involved
- Mitotic activity (per 50 fields at high magnification)
- Margins of resection
- Presence of metastasis
  - Intra-abdominal dissemination
  - Liver is a usual site of metastasis
  - Lymph nodes are known for not being involved by GIST

Molecular Analysis

- Tumor proliferates thanks to mutations in the genes for KIT or PDGFR (platelet derived growth factor receptor alpha)
- Both genes codify proteins located on the cell surface
- The mutations cause constant deregulated activation resulting in uncontrolled proliferation
Molecular Heterogeneity – 4q

- 80% of GISTs have a mutation for KIT (CD117)
- 10% of GISTs have it for PDGFRA
- Both are mutually exclusive
- 10% have neither
- V600E BRAF mutation was found within 7% of adult GIST patients that lacked either KIT or PDGFRA mutations.

KIT Receptor Structure

- Extracellular domain (exon 9: 16.2%)
- Membrane Domain (exon 11: 56.1%)
- Tyrosine Kinase I Domain (exon 13/14: 1.2%)
- Tyrosine Kinase II Domain (exon 17: 0.6%)

Clinical Use of the GIST genotype

- Evaluation of the KIT and PDGFRA mutations are useful to:
  - Confirm the diagnosis.
  - Predict response to imatinib (target therapy)
  - Consider the possibility of adjuvant therapy
  - Develop new therapeutic approaches when imatinib fails

Stabilized treatment with imatinib

PET Scan of Abdomen

- Pre-Tx
- Post-Tx (7 days)

80% reduction in SUV (17.2 to 3.4).
Imatinib: Response Prediction by the Kinase Mutation Status in Patients with Advanced Disease

- It controls the disease in 80% of patients.
- Imatinib doses: 400 mg or 800 mg day.
  - KIT mutation exon 9: progression-free survival is longer with 800 mg.
  - KIT mutation exon 11: progression-free survival is not influenced by drug dosage.

Resistance to Imatinib

- It is mainly acquired resistance:
  - occurs after at least 6 months of initial response to the drug.
- Due to secondary mutations.
  - In 45% of patients who initially had it in exon 11:
    - Most of the secondary mutations are in exon 17.
- Sunitinib, which targets KIT, has demonstrated efficacy in patients with GIST after they experience imatinib failure.

Sunitinib

PFS and OS are longer for patients with secondary KIT exon 13 or 14 mutations than for those with exon 17 or 18 mutations.

Pathologist’s handling of the formalin-fixed tissue and paraffin block

- Immunohistochemistry (CD117, CD34, SMA, Des, S100, Pan-K)
- H&E X1
- Examine and mark slide for microdissection
- 10 non-stained slides
- Overlap on the HE and scrape tissue from the non-stained
- Extract DNA for KIT testing (11, 9, 17) (20% of tumor cells)

PCR AMPLIFICATION AND DIRECT SEQUENCING