Case Presentation

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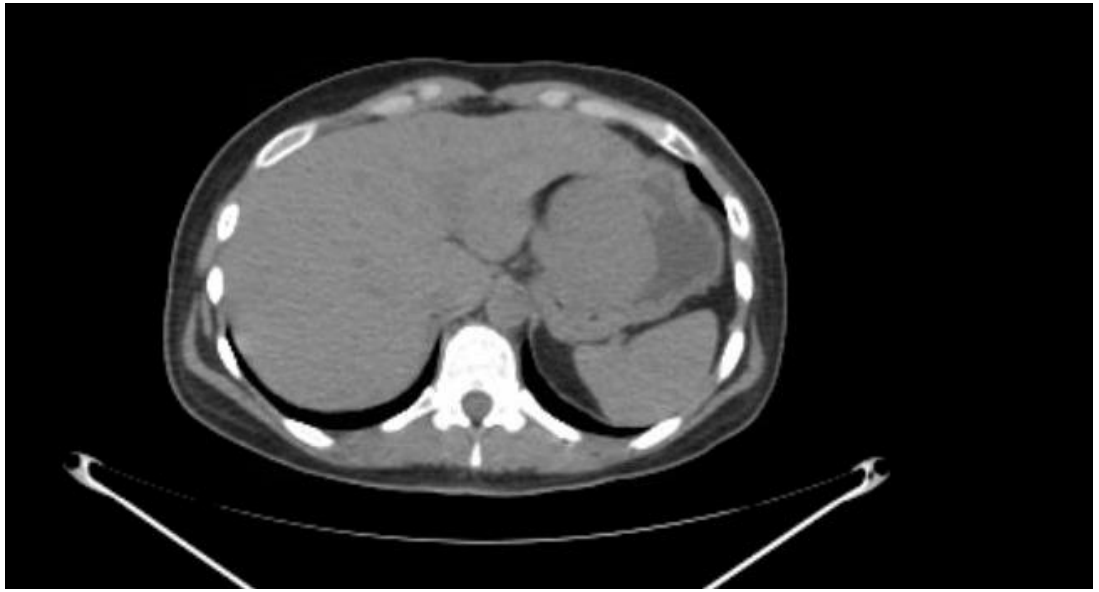
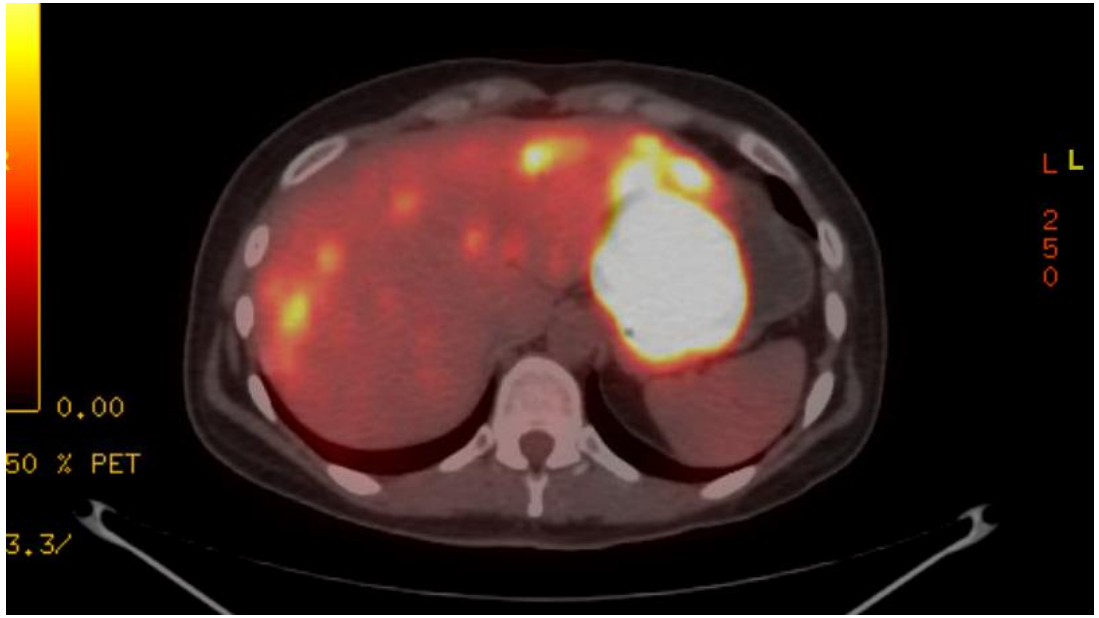
Initial Case Presentation:

- 42 yo female presents with acute onset GI bleeding, severe anemia (Hgb 6), nausea

Endoscopy – large mass protruding from lesser curvature of the stomach

Imaging





Next Steps

- Liver Biopsy – gastrointestinal stromal tumor – pre-molecular testing
- Patient initiated on imatinib
- Continues to be transfusion dependent despite dose escalation of imatinib
- CT remains stable, PET remains active
- Endoscopy confirms gastric mass, with large central ulceration

Surgery

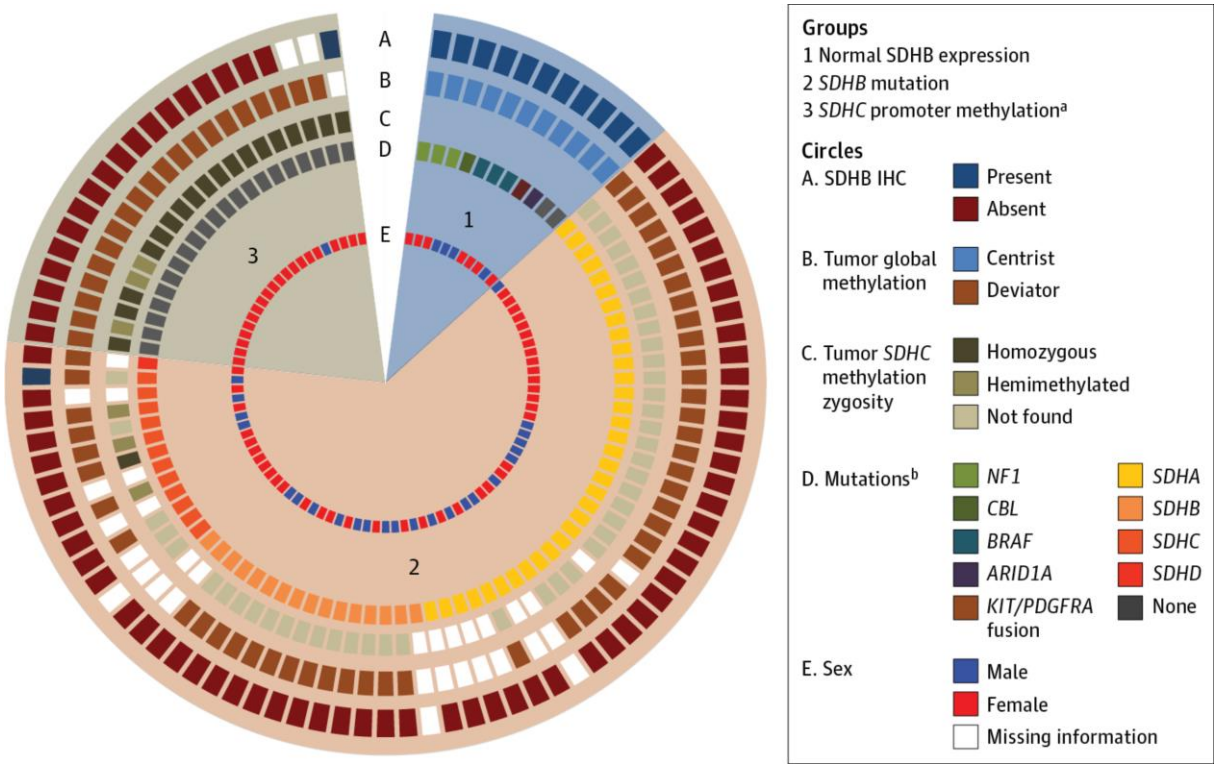
- Extent of surgery – subtotal gastrectomy - resection of mass with goal to control syptoms of bleeding
- Pathology confirms GIST – 4 mitoses/50 HPF
- Specimen included 9 lymph nodes – 4 involved with GIST
- Mutational analysis confirms WT for KIT 11,9, 13,17 and PDGFRa
- Placed on sunitinib

- SDH deficient GIST characterizes a significant subset of patients with previously called “wild-type” GIST

The JAMA Network

From: **Molecular Subtypes of KIT/PDGFRA Wild-Type Gastrointestinal Stromal TumorsA Report From the National Institutes of Health Gastrointestinal Stromal Tumor Clinic**

JAMA Oncol. 2016;2(7):922-928. doi:10.1001/jamaoncol.2016.0256



81% of patients with SDHX mutations in the tumor
also had germline SDHX mutations

Figure Legend:

Immunohistochemical Analysis (IHC) and Genetic Characteristics of Tumors From 95 Patients With KIT/PDGFRA Wild-Type Gastrointestinal Stromal TumorsFive concentric circles depict succinate dehydrogenase (SDH) B expression by IHC (circle A), global tumor DNA methylation (circle B), presence of tumor SDHC promoter methylation including zygosity (circle C), mutations in NF1, BRAF, CBL, ARID1A, KIT/PDGFRA fusion, SDHA, SDHB, SDHC, or SDHD (circle D), and sex (circle E). Tumors are shown in 3 groups: group 1 tumors have normal SDHB expression (n = 11), group 2 tumors have SDHB mutations (n = 63), and group 3 tumors have SDHC promoter methylation (n = 21).

[a]One patient in this group was SDHB positive by IHC.

SDH- Deficient GIST dominants GIST under the age of 20 – but can be seen in the adult age range

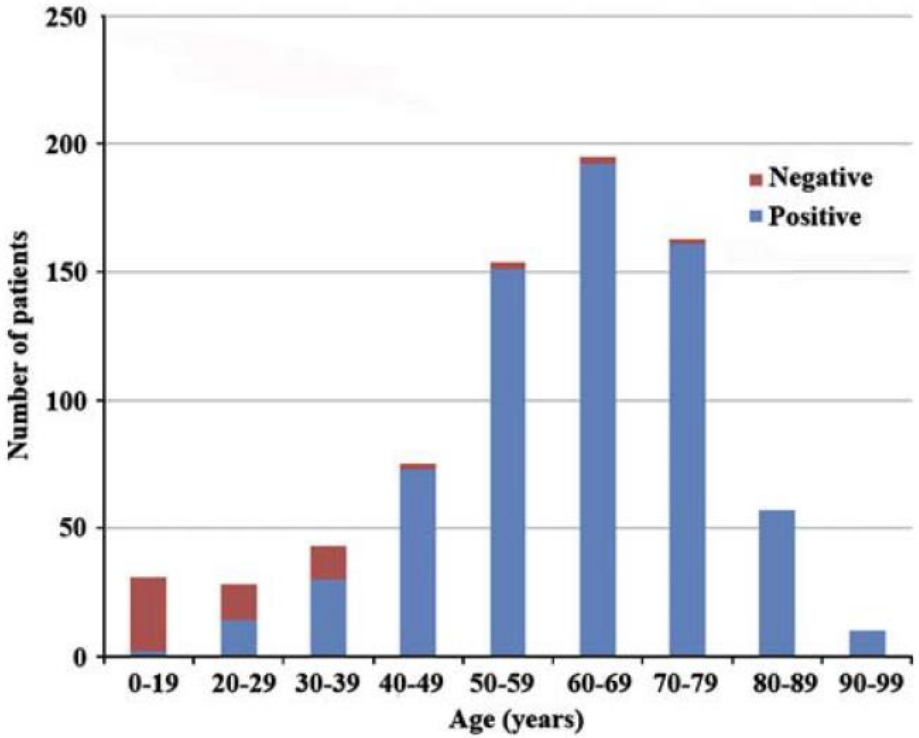


FIGURE 1. Frequency of SDHB-negative and SDHB-positive gastric GISTs as a function of patients' age.

Miettinen et al, AJSP 2011

Additional information – evolution over the next 10 yrs

- Family History of GIST: parent diagnosed with GIST under the age of 40
- SDHB immunohistochemistry (IHC) negative
- Found to have Germline SDH A mutation – confirmed in parent

- Imaging remained stable on sunitinib for 5 years
- Developed cardiomyopathy after 6 yrs– requiring discontinuation of sunitinib
- 2 years later - cardiomyopathy has resolved, GIST remains stable
- What to consider if disease progression?

Treatment options for SDH-Def GIST

- Sunitinib
- Regorafenib
- Pazopanib

    - MOA - ?KIT ?VEGFR

- **A Phase II Trial of the DNA Methyl Transferase Inhibitor, Guadecitabine (SGI-110), in Children and Adults With Wild Type GIST,Pheochromocytoma and Paraganglioma Associated With Succinate Dehydrogenase Deficiency and HLRCC-associated Kidney Cancer**

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