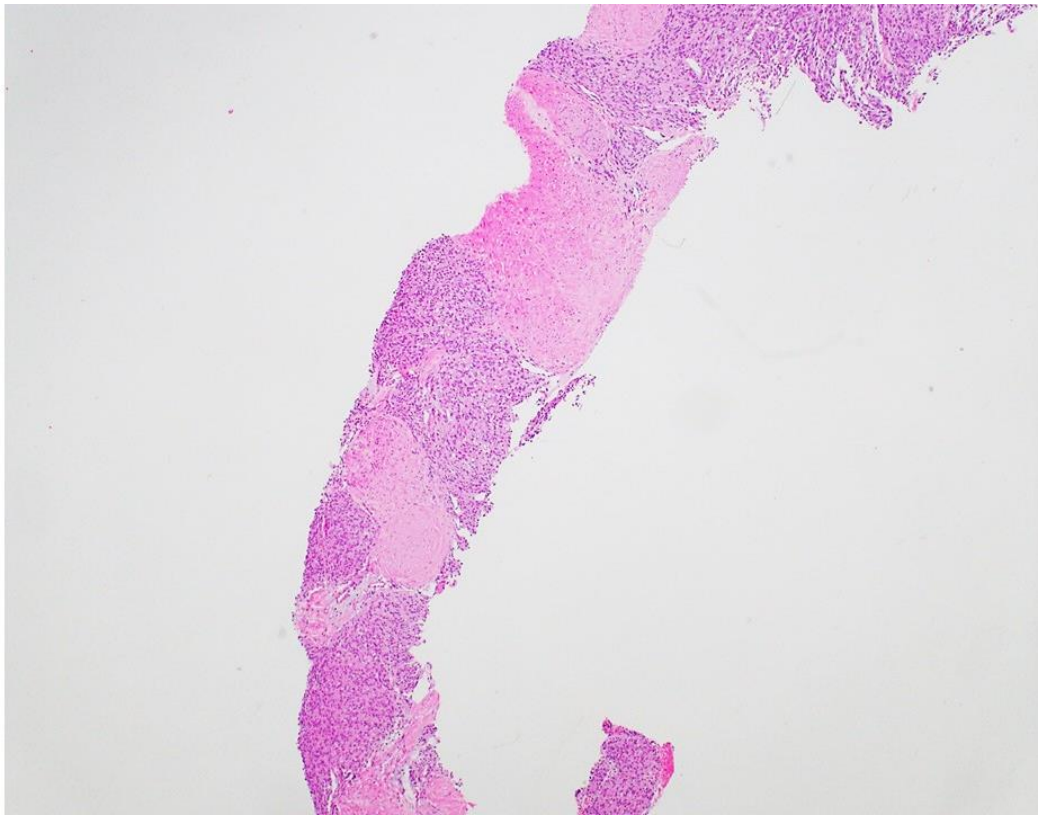
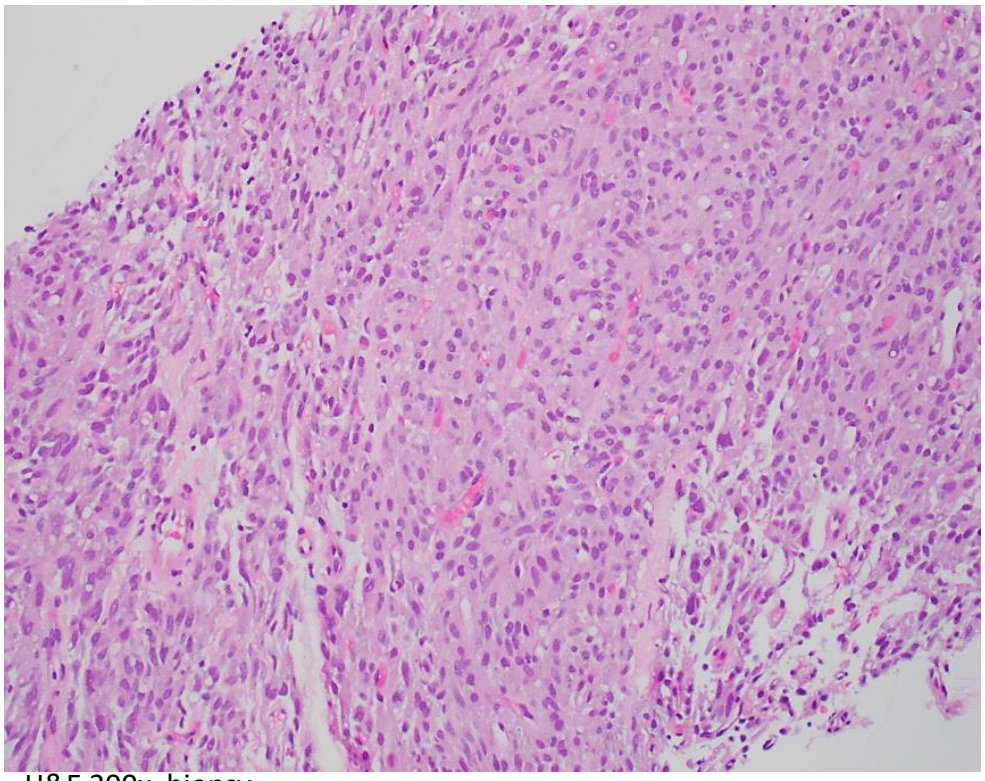
**Clinical History**

A 32-year-old woman presented with severe fatigue, right upper quadrant abdominal pain, and blood in her stool. Laboratory evaluation revealed severe anemia and an endoscopic ultrasound showed four masses in the gastric antrum measuring from 2.5 to 10 cm as well as a 24 cm right lobe liver mass concerning for metastasis. A biopsy of the antral mass was performed with the histologic findings shown in the images below.

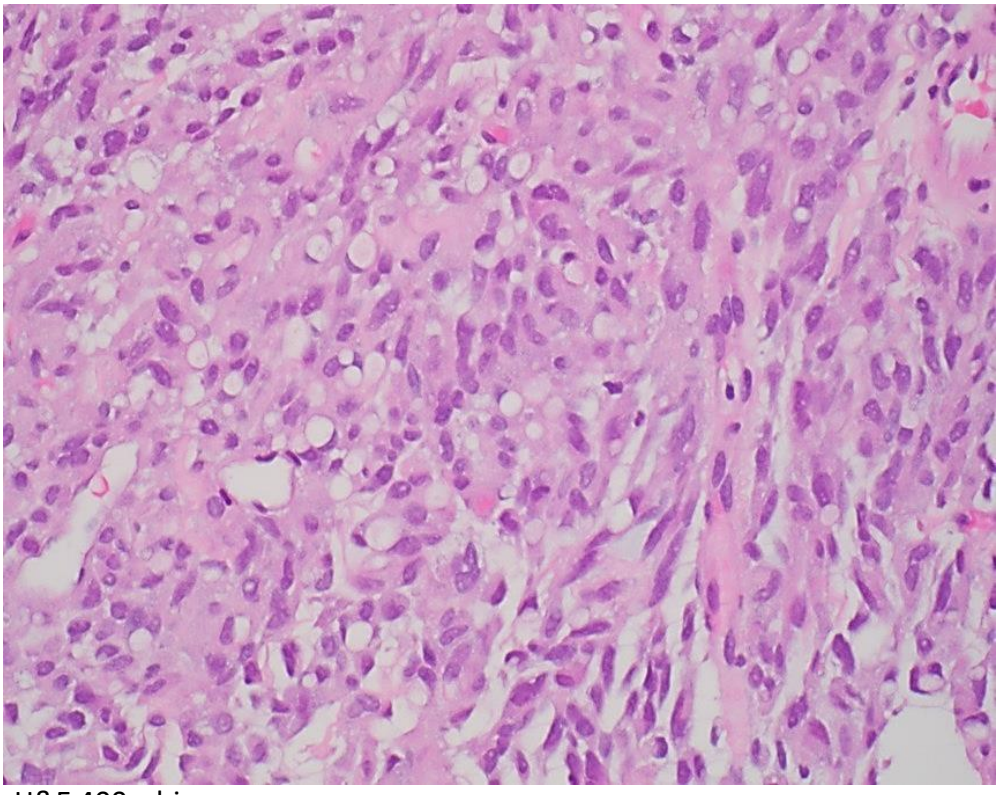
Subsequently the patient underwent a distal gastrectomy and right hepatectomy. An H&E photomicrograph from the gastric resection is also included.



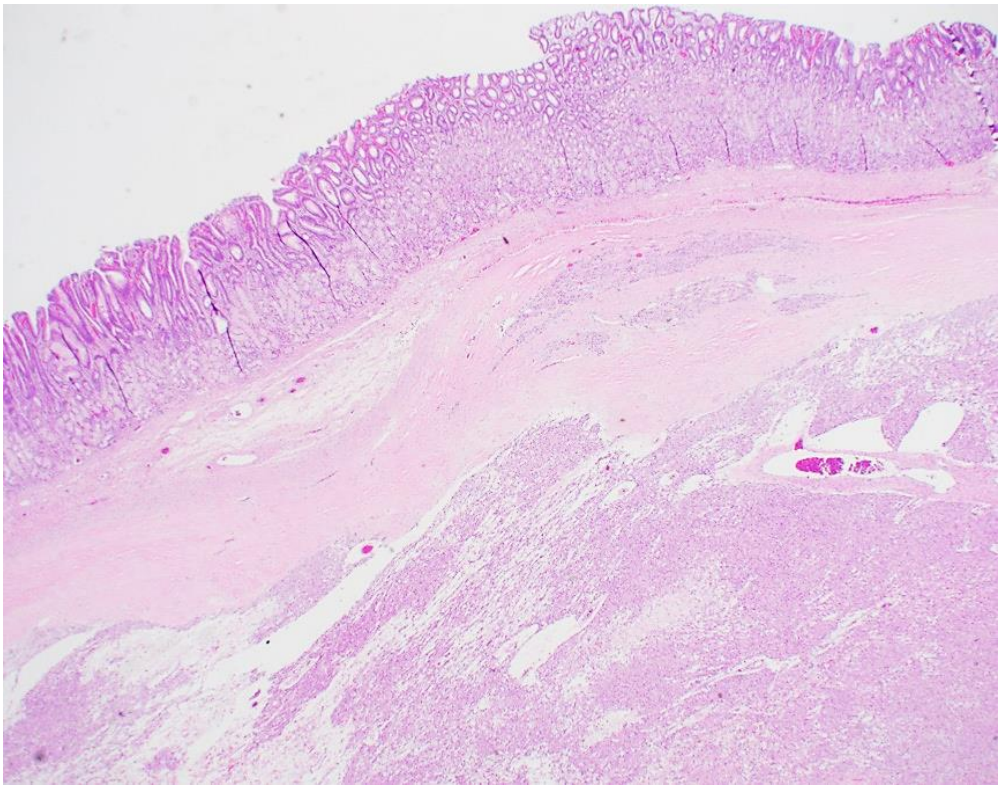
H&E 40x, biopsy



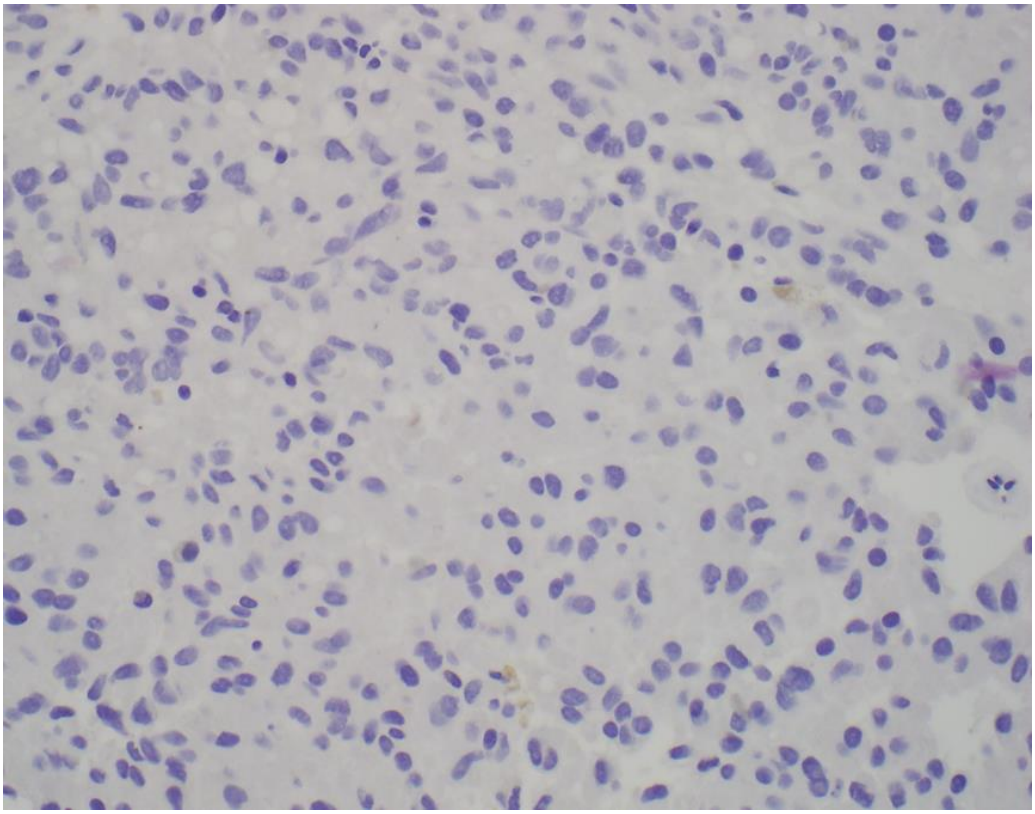
H&E 200x, biopsy



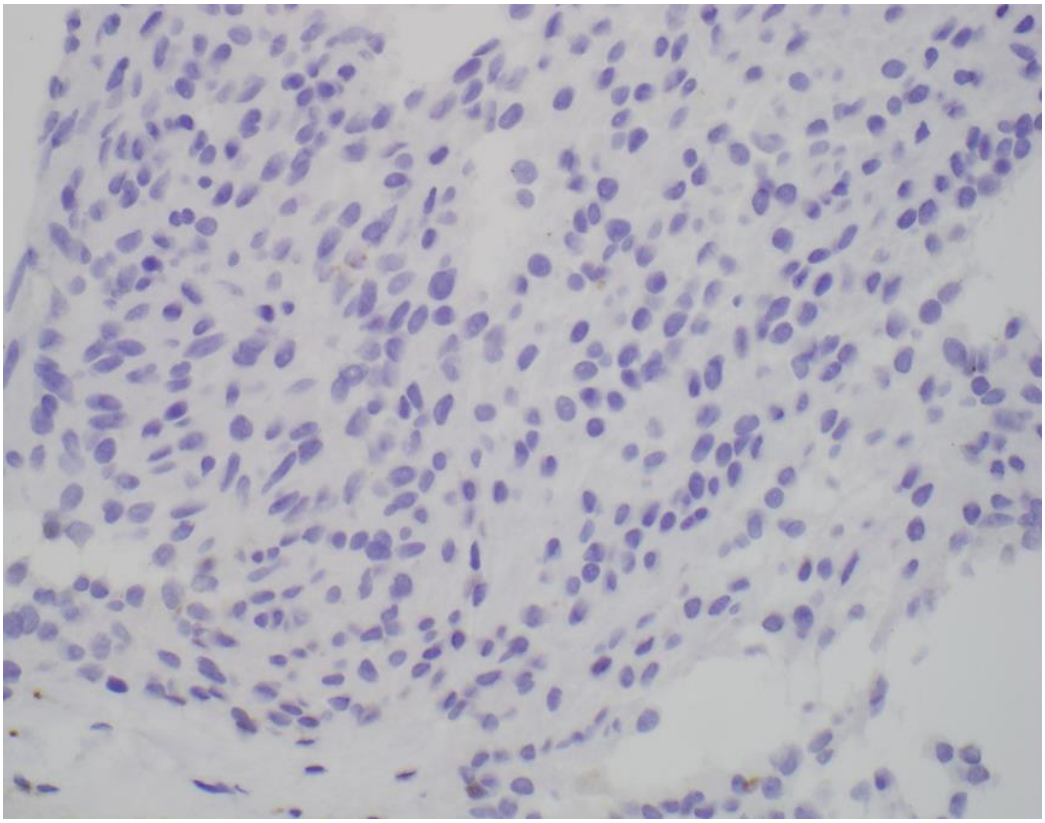
H&E 400x, biopsy



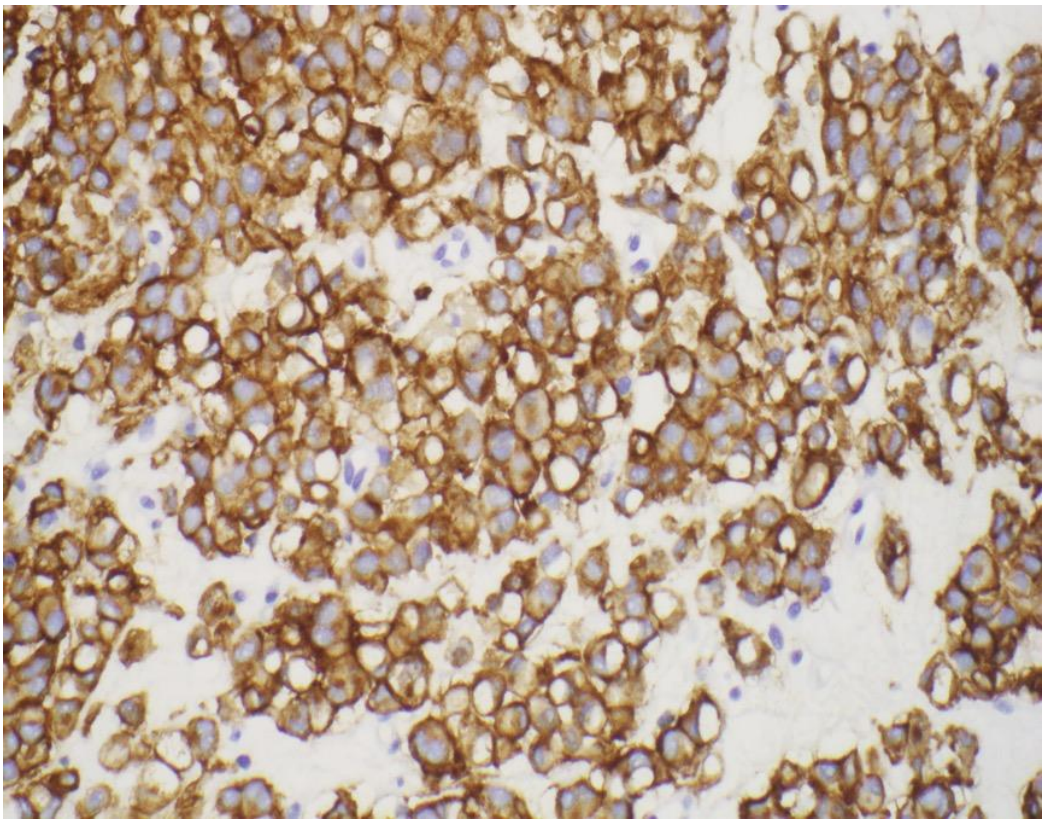
H&E 20x,resection



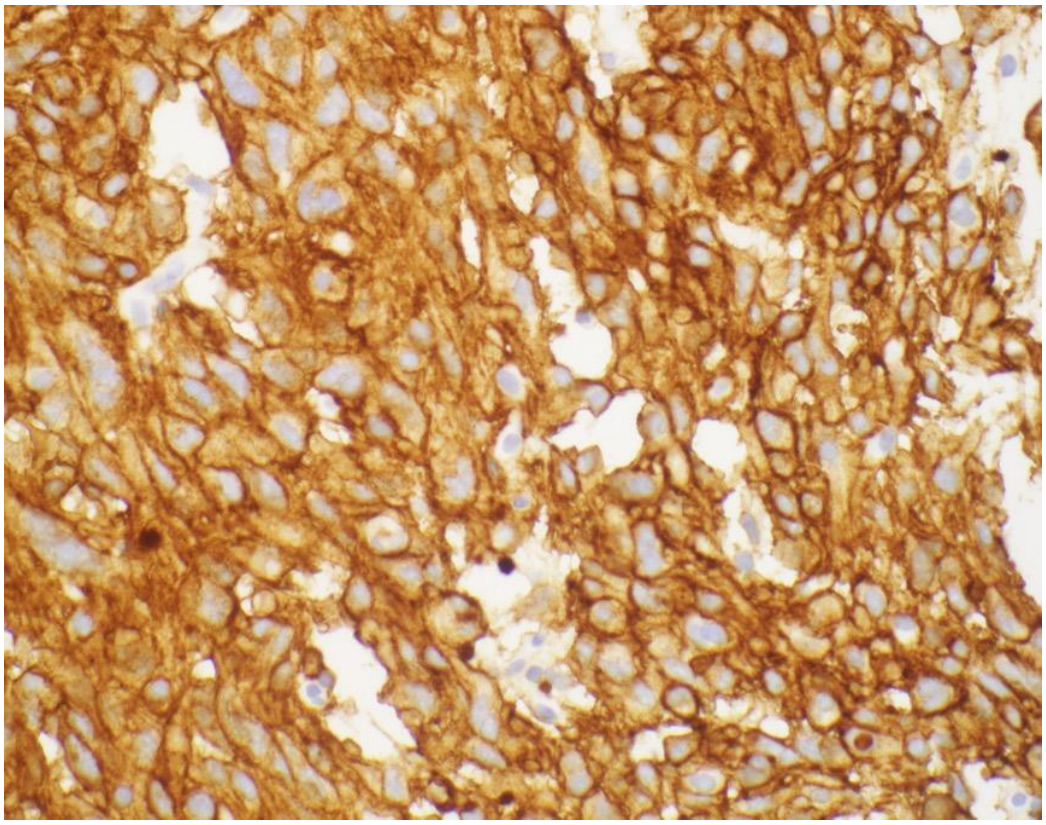
S100 400x



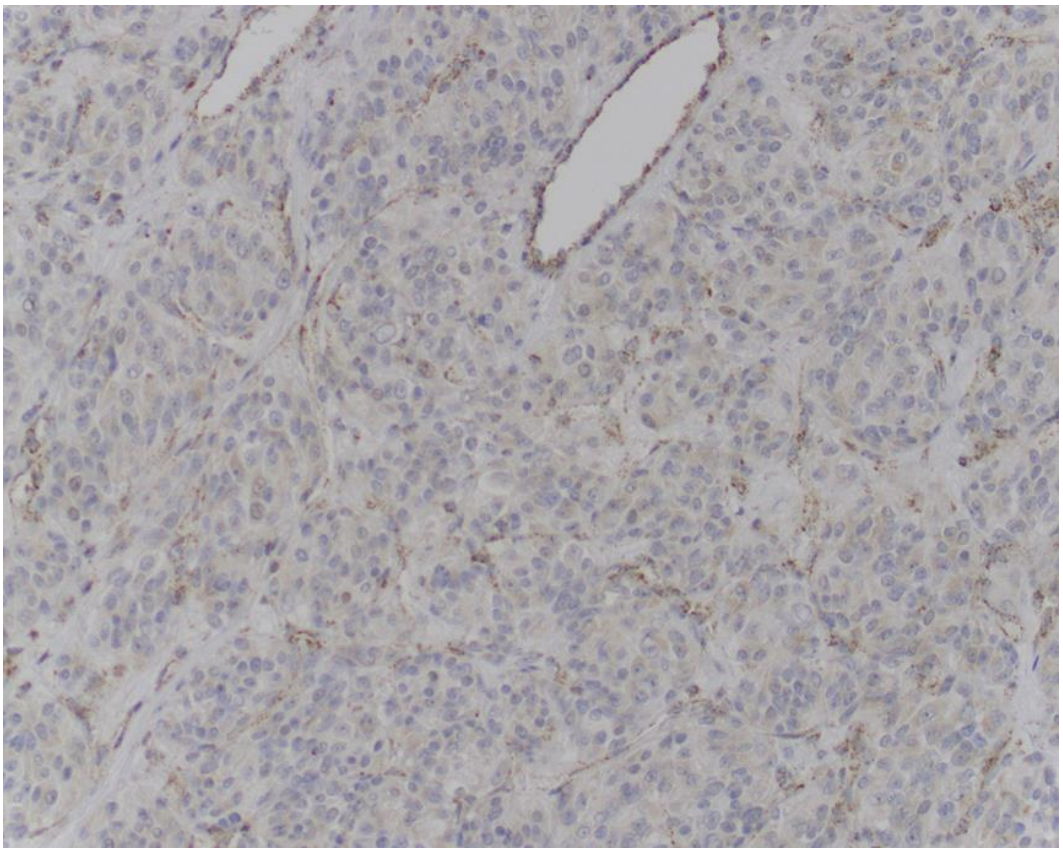
Desmin 400x



CD117 400x



DOG1 400x



SDHB 200x

**What is your diagnosis?**

**A –** KIT mutated gastrointestinal stromal tumor (KIT-mutated GIST)

**B** – SDH deficient gastrointestinal stromal tumor (SDH-deficient GIST)

**C –** Epithelioid leiomyosarcoma

**D -** Gastrointestinal Schwannoma

**E -** Perivascular epithelioid cell tumor (PEComa)

**Correct answer: B - SDH-deficient gastrointestinal stromal tumor (GIST)**

The tumor was multifocal and had a multinodular appearance appreciated both in the biopsy and in subsequent resection. The cells were primarily epithelioid. While the biopsy showed no mitoses, the mitotic rate was 12/5 mm2 on the resection specimen. The tumor was positive for CD117, DOG1, with patchy positivity for CD34 and it was negative for SMA, desmin, S100. An immunostain for SDHB performed on the biopsy and the subsequent resection showed loss of staining. KIT and PDGFRA mutational analysis performed on the biopsy failed to detect any mutations. These findings are diagnostic of SDH-deficient GIST.

SDH-deficient GISTs usually present before the age of 40 years, occur almost exclusively in the stomach (antrum being the most common location), range in size from 1.5 – 12 cm (median 5 cm) and are typically multinodular, plexiform and often divided by fibrous septa. Compared to other GISTs, SDH deficient GISTs have a characteristic epithelioid or mixed spindled/epithelioid appearance, present as multiple tumors, and show lymphovascular involvement with occasional lymph node metastasis [1].

SDH has 4 subunits (A, B, C, and D) but that loss of any of the subunits results in loss of all other as they exist as a complex. Testing for SDHB effectively tests for loss of any of the subunits, and appears to be the most common/available IHC antibody to use. Tumors with loss of SDHB expression by immunohistochemistry can be subdivided into 2 groups: one with SDH gene mutations and a other with loss of SDHB by immunostain without SDH mutations. Those with SDH mutations occur in young adults, are gastric in location, and have a female preponderance (>2:1). Those with loss of SDHB by immunostain without SDH mutations occur in the pediatric age group and young adults, are gastric in location, and occur exclusively in females [2-3].

SDH-deficient GISTs can be seen in association with Carney triad and Carney-Stratakis syndrome. Carney-Stratakis syndrome is hereditary and includes occurrence of GISTs and paragangliomas in the context of SDH germline mutations. Carney triad is not hereditary and involves the occurrence of GISTs, pulmonary chondromas and paragangliomas without SDH mutations [2-3]. Most cases of Carney triad show down-regulation of SDH through site-specific hyper-methylation of the SDHC gene.

SDH deficiency is mutually exclusive with KIT or PDGFRA mutations, although there is a case report that describes KIT mutation in a GIST exhibiting SDH deficiency [4].Mutations in the SDH subunits are also mutually exclusive with mutations in BRAF or NF1. Approximately half of patients with SDH-mutated GISTs have mutations in one of the SDH subunits, with the most common being in SDHA genes.

Conventional risk stratification of GISTs fails to predict disease progression in patients with SDH mutated GISTs [5].

Unlike KIT-mutated GISTs, which are generally responsive to tyrosine kinase inhibitor, SDH-mutated GISTs respond poorly to imatinib because of lack of activating tyrosine kinase mutations [6-7].

Surgery remains the most important form of treatment of non-metastatic GISTs lacking KIT and PDGFRA mutations and is recommended by the National Comprehensive Cancer Network [8].

***Comparison between GISTS with SDH deficiency and GISTs with intact SDH.***

| Feature | **SDH deficient GISTS** | **GISTS with intact SDH** |
|---|---|---|
| Age predilection | Children and young adults | Older adults |
| Gender distribution | F>>M | F = M |
| Anatomic site | Stomach | Entire GI tract |
| Multifocality | Common | Rare |
| Multinodular architecture | Always | Rare |
| Cytomorphology | Epithelioid or mixed | Mixed |
| Prognosis predicted by site, size, mitotic rate | No | Yes |
| Lymph node metastasis | Common | Exceptional |
| Clinical course of metastases | Indolent | Aggressive |
| Sensitive to Imatinib | No | Most cases |
| KIT/PDFGFRA Mutations | None | ~95% |
| SDH mutations (germline) | ~50% | None |
| Syndromic associations | Carney Stratakis syndrome (GISTs and paragangliomas) Carney triad (pulmonary chondromas and paragangliomas) | Neurofibromatosis 1 Familial GIST (germline KIT or PDFGRA mutations) |

**Choice A is incorrect.**

KIT mutated GISTs while being positive for DOG1 and CD117 would have intact SDHB expression by immunohistochemistry. They usually are not multinodular in appearance, have typically spindle cell morphology and are seen in older adults.

GISTS are the most common mesenchymal tumors of the gastrointestinal tract. They are most frequently found in the stomach (50-60%), small intestine (30-35%), and are less common in the colon/rectum (5%) and esophagus (<1%) [6].

KIT-mutant GISTs comprise the vast majority of GISTs. The clinical aggressiveness of KIT-mutant tumors depends on tumor size, mitotic rate, and anatomic site of origin. The most common mutations are in KIT exon 11, which encode portions of the juxtamembrane domain and occur in ~65% to 70% of KIT-associated GISTs. Mutations in exons 9 are seen in 13% of KIT-mutant GISTs, while mutations in exons 13 (1.2%) and 17 (0.6%) are less common. Due to increased sensitivity to imatinib therapy, metastatic GISTs with exon 11 mutations have shown longer overall and event-free survival compared with those with exon 9 mutations in the setting of adjuvant imatinib. Conversely, in cases undergoing second-line treatment with sunitinib, progression-free and overall survival are better for the exon 9 mutant tumors, although exon 11-mutant tumors also show benefit from sunitinib treatment in the form of reduction or stabilization of disease burden. Exon 9 mutant tumors benefit from higher doses of imatinib.

**Choice C is incorrect**

Epithelioid leiomyosarcomas are rare compared to GISTs. Histologically, epithelioid leiomyosarcomas have a greater degree of nuclear pleomorphism and atypia, hyperchromatic nuclei with blunt-ended nuclei, and mitotic activity. In contrast to GISTs, leiomyosarcomas are desmin and SMA positive and are not immunoreactive for CD117 and DOG1.

**Choice D is incorrect**

Gastrointestinal schwannomas are benign peripheral nerve sheath tumors composed of Schwann cells. Similar to GISTs they arise mostly in the stomach and are seen more commonly in women. Histologically, gastrointestinal schwannomas are composed of predominantly interlacing bundles and fascicles of spindle cells with moderate cellularity and mild nuclear atypia with minimal to no mitotic activity. They have characteristic peripheral lymphoid aggregates and are diffusely positive for S100 and SOX10. Schwannomas are SMA, desmin, CD117 and DOG1 negative.

**Choice E is incorrect**

Perivascular epithelioid cell tumors (PEComas) are mesenchymal neoplasms that have a predilection for females (median age 45) and may arise in any site. Histologically, this tumor is composed of nests, trabeculae, or sheets of epithelioid to spindled cells with clear to granular eosinophilic cytoplasm. They express variably co-express smooth muscle and melanocytic markers and may show SMA, desmin, caldesmon, HMB-45, melan-A, and MITF positivity in varying proportions.

**References:**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