Wild-type GIST: A Rare Cause of Gastrointestinal Bleed

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BACKGROUND

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal neoplasms that represent 1-2% of primary gastrointestinal (GI) cancers.[1-2] GISTs can occur anywhere along the GI tract; therefore, clinical presentation varies based on location of the tumor. Patients can present with GI bleeding, obstruction and/or abdominal pain; however, others are asymptomatic and the tumors are discovered incidentally.[1,3]

Surgical resection is the primary curative treatment.[1,4] However, neoadjuvant and adjuvant tyrosine kinase inhibitors (TKIs) may be considered in those with a mutation in the *KIT* or platelet-derived growth factor alpha (*PDGFRA*) gene.[5-9] For GISTs without a *KIT* or *PDGFRA* mutation, also referred to as wild-type GISTs, the benefits of TKIs are unclear.

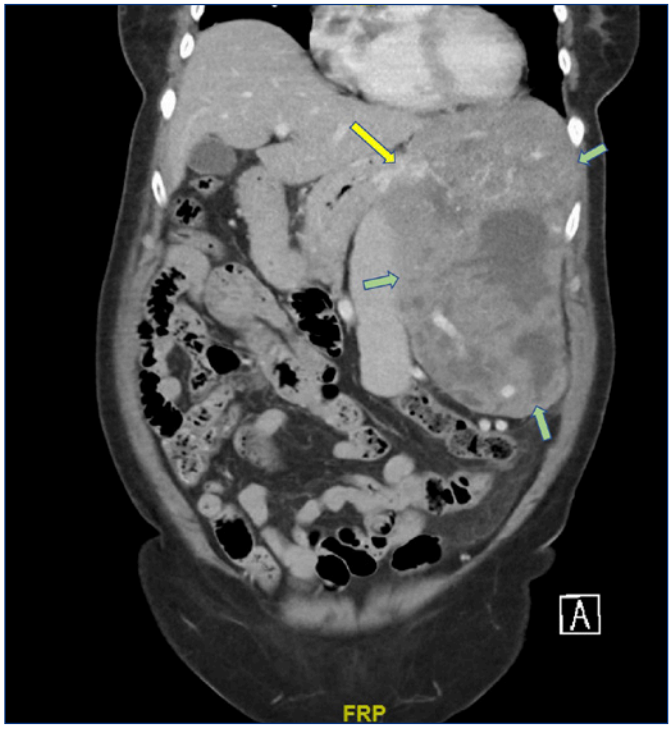
CASE SUMMARY

The patient is a 74-year-old woman with a past medical history of irritable bowel syndrome, mitral valve prolapse, diabetes, hypertension, and hyperlipidemia who presented with melena, non-bloody, non-bilious emesis, and abdominal pain.

Physical exam was notable for abdominal distension, dullness to percussion of the left half of the abdomen, and left upper quadrant tenderness. Admission labs were notable for a hemoglobin of 6.9 g/dL, white blood count of 5.2*10^9/L, and platelets of 254*10^9/L. Serum electrolytes and creatinine were within normal limits and BUN was elevated at 32 mg/dL. A computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast revealed a large heterogenous mass in the left upper quadrant measuring 20.2 x 12.8 x 22.0 cm with a vascular pedicle arising from the greater curvature of the stomach. The spleen and left adrenal gland were also encased, with possible direct invasion.

The patient received a blood transfusion and was started on a proton pump inhibitor given presumed upper GI tract bleeding. Carcinoembryonic antigen and cancer antigen 19-9 tumor markers were negative. Upper endoscopy revealed vascular congestion in the gastric body but no evidence of mass or bleeding. Interventional radiology guided biopsy was positive for DOG-1 and CD117 (KIT) expression, which confirmed the diagnosis of GIST. Mitotic figures numbered up to 3 per 50 HPFs. Next-generation sequencing was negative for mutations in twenty-one genes, including *KIT* and *PDGFRA*. Additional chest imaging did not show metastatic disease.

Figure 1. Coronal CT abdomen showing heterogenous mass measuring 20.2 x 12.8 x 22.0 cm (green arrows) with a vascular pedicle arising from the greater curvature of the stomach (yellow arrow). The spleen and left adrenal were also encased with possible direct invasion.



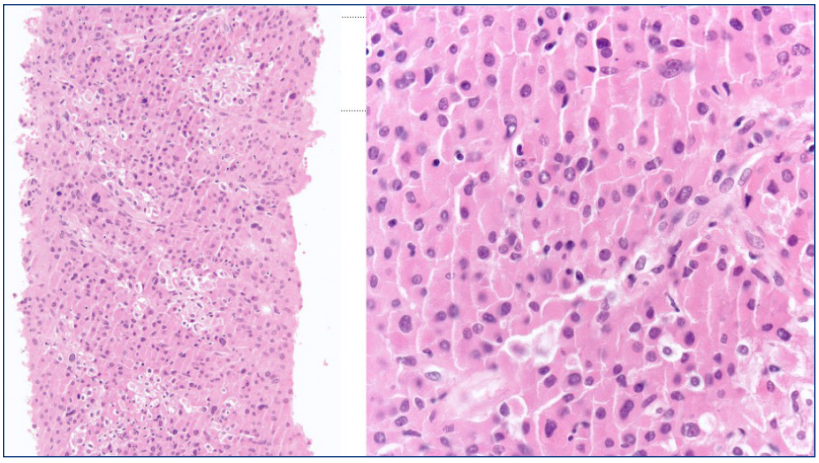
The patient completed a course of neoadjuvant imatinib, a TKI. Post-treatment CT scan demonstrated significant interval decrease in tumor size, measuring 15 x 7.5 x 13 cm. The patient is currently continuing imatinib with plans for future surgical resection.

DISCUSSION

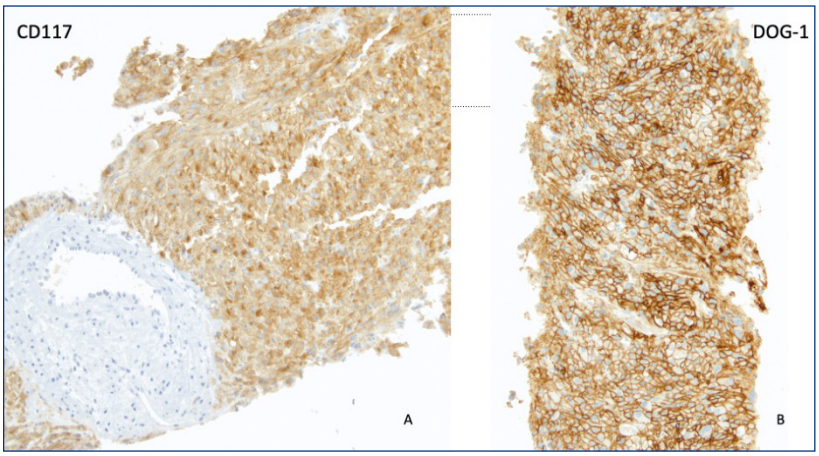
Imaging of GISTs can reveal a heterogenous mass, often with different degrees of necrosis and cystic changes with possible enteric fistulation and calcification.[10] These rare tumors often reach large sizes before symptoms like GI bleeding appear, seen in about 30% of cases.[3] Confirmatory diagnosis is made from biopsy with immunohistochemical expression of KIT or DOG-1.[1, 11-12]

Roughly 60% of patients are cured by surgery.[13] However,

Figures 2A, B. Biopsy sample of GIST tumor, epithelioid variant. The rounded nuclei with abundant cytoplasm is epithelioid morphology. Pleomorphism is more common in epithelioid GIST compared to other types.



Figures 3A, B. Confirmatory IHC expression of CD117 (KIT) and DOG-1. In Figure 3A, a large vessel in the lower left is included for contrast, as it does not express CD117.



in this case, due to the tumor's size and invasion into neighboring organs, upfront resection was not feasible. For patients with high tumor burden or high risk of recurrence, TKIs can be used to selectively inhibit receptor tyrosine kinases like KIT and PDGFRA.[5-9,14-15] Interestingly, although 95% of GISTs over-express KIT, only 80% of GISTs contain *KIT* gene mutations.[1] The second most common oncogenic drivers are *PDGFRA* mutations, seen in about 5–10% of tumors.[9,16] Wild-type GISTs make up 10–15% of GISTs.[17]

Given the lack of mutation in the targeted receptor gene in wild-type GISTs, treatment of these tumors with TKIs is controversial.[1,17-24] Some research suggests that alternative genes may be targeted.[9, 24-25] Additionally, although surgery is the only curative treatment, wild-type GISTs have a greater propensity to progress or recur despite complete surgical resection.[4,26] Additional research is needed to further elucidate treatment options for wild-type GISTs and their unique molecular features.

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