A 50 year-old Caucasian gentleman presented with melena. Identification of multiple gastric submucosal masses and a family history of gastrointestinal stromal tumors had important clinical implications for both the patient and his asymptomatic children.

Case

A 50 year-old Caucasian gentleman with a history of gastroesophageal reflux, diabetes mellitus and basal cell carcinomas presented with melena over the past few weeks. He denied nausea, vomiting and abdominal pain.

His vitals and abdominal exam were unremarkable. Digital rectal exam revealed black, tarry stool. Hemoglobin on admission was 6.3 g/dL. Computed tomography (CT) scan revealed two infiltrating masses in the proximal stomach (Images 1 and 2).

After resuscitation, an upper endoscopy noted a large submucosal mass in the fundus and two smaller submucosal masses along the angularis. Subsequent endoscopic ultrasound described the masses as lacking a defined capsule and having irregular extension into the gastric wall with isoechoic and heterogenous areas. Fine needle aspiration revealed spindle cell tumors (CD117 positive/DOG1 negative/SMA negative cells with < 2 mitoses per 20 high powered field) (Images 3 and 4). Upon further questioning he reported that multiple first- and second-degree relatives have been diagnosed with gastrointestinal stromal tumors (GISTs).

His disease was thought to be locally advanced and he was started on neo-adjuvant imantinib. Total gastrectomy was performed several months later; small ileal and jejunal tumors, not previously seen by CT, were identified intraoperatively and resected. These additional lesions were GISTs as well, and he was placed on long-term maintenance imantinib.

A detailed family history revealed that his father, brother, paternal aunt and multiple cousins on the paternal side had previously been diagnosed with GISTs, the youngest at age 25 and the oldest at age 57. The patient underwent genetic testing, revealing him to be heterozygous for a three nucleotide deletion on exon 11 of KIT mRNA.

After his diagnosis with the germline KIT mutation, his two adult children (son and daughter) were tested and both were positive. His asymptomatic daughter was found to have a 3 cm jejunal mass on screening CT enterography and resection is planned. His son is scheduled for an EGD, colonoscopy and CT enterography.

Discussion

GISTs are rare tumors, most commonly due to sporadic mutations of the KIT gene. The annual incidence of GISTs is estimated at 10 - 20 per 1,000,000. The median age of diagnosis is 50 years of age and some literature suggests a male predisposition. Presentations may include gastrointestinal bleeding, abdominal pain and gastrointestinal outlet obstruction. GISTs may occur
Familial Multifocal Gastrointestinal Stromal Tumor

in the stomach (60 - 70%), small intestine (20 - 30%), colon/rectum (5%) and esophagus (<5%).

GISTs usually present as solitary tumors with local or locally advanced disease. Only 10% of cases are metastatic upon initial diagnosis. Multifocal disease can also be due to multiple primary tumors. The occurrence of multiple primary GISTs in adults is rare but may be under appreciated. It is almost exclusively seen in familial GIST disorders or other specific syndromes, such as Carney’s triad or type 1 neurofibromatosis.

Familial GISTs are part of a rare autosomal dominant disorder of unknown incidence. It is due to inherited germline mutations of the KIT gene in 80% of cases and mutations of the PDGFRA gene in 10% of cases. Given how rare familial GISTs are, guidelines do not discuss when to screen for germline mutations, nor how/when to evaluate asymptomatic family members with the mutation. Finally, case reports have described an association between familial GISTs and other manifestations of the KIT gene mutations, including gastrointestinal dysmotility, cutaneous hyperpigmentation, urticaria pigmentosa, systemic hypercellularity and hypocellularity. No marked necrosis, increased mitoses, or atypical mitoses identified.
m mastocytosis and melanoma. The link between these disorders may be explained by a common progenitor cell that requires KIT activation to differentiate into interstitial cells of Cajal, gastrointestinal smooth muscle, melanocytes and mast cells.4,8

CONCLUSIONS

• When a patient is found to have multifocal GISTs or a family history of gastrointestinal stromal tumors in multiple family members, consider genetic testing for a familial GIST mutation.

• For patients with a germline KIT mutations, periodic GI tract surveillance, including dedicated small bowel imaging, seems reasonable. Our patient’s asymptomatic daughter underwent a CT enterography that identified a GIST, allowing for pre-symptomatic surgical resection.

• Furthermore, an annual dermatologic evaluation may be prudent. Our patient’s daughter was found to have a dysplastic nevus.

References


Answers to this month’s crossword puzzle: