An unusual cause of upper gastrointestinal bleeding : duodenal GIST. A case report and literature review

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Abstract

A duodenal GIST is an unusual cause of upper gastrointestinal bleeding. Duodenal GISTs are rare and constitute 5% of all GISTs. A significant percentage of duodenal GISTs are located in the third and fourth portion of the duodenum and may not be detected on routine upper endoscopy. Push enteroscopy is necessary to locate these lesions. It is extremely important to differentiate a duodenal GIST from other submucosal tumors like leiomyomas, leiomyosarcomas or leiomyoblastomas which may present in a similar manner, because the treatment and prognosis differ significantly. Appropriate histological and immunohistiochemical staining is required to confirm the diagnosis. Surgical resection is the treatment of choice and may involve limited resection or a pancreaticoduodenectomy. Adjuvant therapy with Imatinib has been shown to prolong survival in patients with GIST in general. (Acta gastroenterol. belg., **2011**, 74, **347-351**).

Introduction

Gastrointestinal stromal tumors (GIST) are the most frequent mesenchymal tumors within the gastrointestinal tract (1-3) and can occur anywhere in the gastrointestinal tract from the lower esophagus to anus. Stomach (60%) and small bowel (35%) are the most frequent sites of occurrence (2). Within the small bowel, the jejunum and ileum tend to be more commonly involved than the duodenum. Duodenal GISTs are rare and constitute 5% of all GISTs (2,4). It is extremely important to differentiate this tumor from other submucosal tumors like leiomyomas, leiomyosarcomas or leiomyoblastomas which may present in a similar manner, because the treatment and prognosis differs significantly. In one study, 46 (45.5%) of the 101 duodenal GISTs whose location was specified, were found to involve the third and fourth portion of the duodenum (5). Here we report a case of a young female patient who presented with gastrointestinal bleeding and was found to have an inconclusive esophagogastroduodenoscopy (EGD). A push enteroscopy done subsequently revealed a bleeding submucosal tumor in the third portion of the duodenum that was later confirmed to be a duodenal GIST.

Case report

The patient was a 33 year-old Asian female who came to the emergency department with the chief complaint of dizziness and dark stools for one week. She denied hematemesis, abdominal pain, nausea or altered bowel movements. There was no history of weight loss or a family history of cancer. Past medical history was significant for chronic hepatitis B and migraine headaches for which she had been taking ibuprofen intermittently.

Examination revealed a pale appearing young female in no acute distress. She was mildly hypotensive (90/55 mm of Hg) and tachycardic (102/minute). The abdomen was soft, non tender and no masses were palpable. She had black stool on rectal examination that was strongly positive for occult blood. Her hemoglobin on admission was 4 g/dl (normal 12-16 g/dl) with normocytic red blood cells, normal platelets and a normal coagulation profile. Iron and ferritin were normal. The total iron binding capacity was low.

The patient was hemodynamically resuscitated and placed on intravenous proton pump inhibitors. An esphagogastroduodenoscopy (EGD) done the next day was unremarkable. Subsequently she underwent a push enteroscopy that revealed a fungating, soft tissue mass in the third portion of duodenum at 60 cm from the incisors (Fig. 1). Biopsy of the lesion resulted in brisk bleeding that ceased spontaneously. The bowel mucosa adjacent to the mass was injected with India ink for subsequent surgical identification. The endoscopic biopsy revealed a spindle cell neoplasm with immunohistochemical staining being positive for CD 117, Smooth Muscle Actin (SMA) and CD 34 (Fig. 2). A diagnosis of GIST was made.

The patient underwent limited resection of the tumor as the periampullary area was spared. On gross examination the lesion measured $3.5 \times 2.1 \times 2.0$ cm. The resection margins were negative for tumor. The neoplasm had a spindle cell morphology. The cells were minimally pleomorphic ; mitotic rate was one mitotic figure per 50 high power fields. No tumor necrosis was seen. The patient did well post operatively and was discharged from the hospital.

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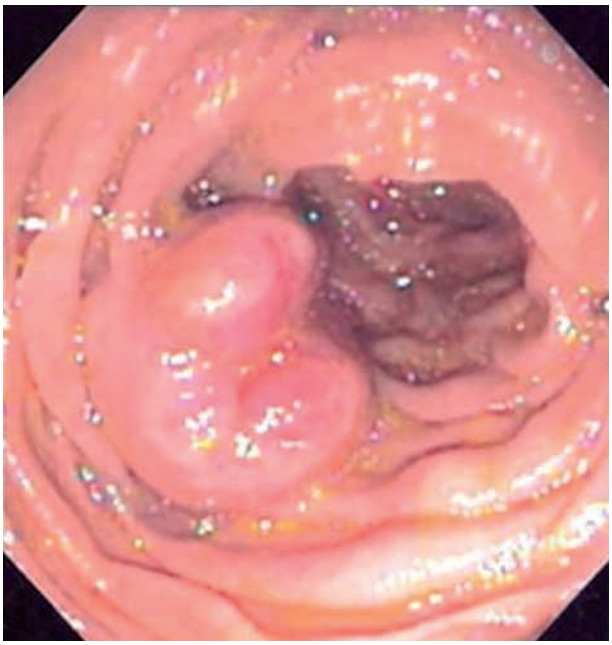

Fig. 1. — Endoscopic appearance of duodenal GIST in our patient.

Discussion

Gastrointestinal stromal tumors are defined as specific, Kit or PDGFRA mutation-driven mesenchymal tumors of the gastrointestinal tract (6). They are believed to originate from interstitial cells of Cajal (6). Knowledge of the molecular pathogenesis of GISTs has helped distinguish these tumors from a variety of other tumors especially leiomyomas, leiomyoblastomas, and leiomyosarcomas (6). This distinction is important in the management of gastrointestinal stromal tumors.

The annual incidence of GIST has been estimated in population-based studies at 14.5 per million in Sweden (6) and 11 per million in Iceland (6). Data from epidemiologic studies and GIST therapeutic trials indicate that the annual incidence in the United States is between 4500 to 6000 cases (roughly 10 to 20 cases per million population per year) (7,8,9). Kawanowa et al indicated that the frequency of incidentally detected subcentimeter GIST may be much higher (10). There is no clear sex predilection, but malignant GIST may be slightly more common in men (11). Duodenal GISTS may present anywhere from 40 to 80 years of age with the mean age of presentation being 57 years (2). Rarely, duodenal GIST may be seen in the pediatric population. A case of duodenal GIST in a 7 year old boy has been reported (12).

The most common presentation of duodenal GIST is gastrointestinal bleeding (50%) similar to other small bowel GISTs. This is in contrast to gastric GISTs which are often found incidentally on routine endoscopy. Our patient presented with melena. A duodenal GIST may sometimes present as an abdominal mass (40%) or with abdominal pain (20%). A GIST arising from the C loop of the duodenum may mimic a pancreatic head tumor (13,14). Rarely a GIST may arise from a duodenal diverticulum (15). A routine EGD may not locate the lesion as 45% of duodenal GISTs are known to involve the third and fourth portion of the duodenum (5). A push enteroscopy maybe required as in our case. The endoscopic appearance of a duodenal GIST is that of a submucosal tumor. Duodenal and small bowel GISTs (6.0-6.3 cm) are usually larger than gastric GISTs (median size of 3.0 cm) (2). It is important to note that non-GIST submucosal tumors tend to be smaller in size than GISTs (2.5 cm *vs.* 8.5 cm respectively) (2). The diagnostic yield of endoscopic biopsies is poor being in the range of 17-42% (16,17). In our case we were able to obtain a positive biopsy because the lesion was ulcerated.

A sub mucosal lesion found at endoscopy usually needs further characterization by EUS. GIST tumors usually arise from the fourth layer (muscularis propria) and are hypoechoic. A malignant pattern maybe suggested by the presence of an irregular extra luminal margin, cystic spaces and lymph nodes (18). While the gross sonographic picture cannot distinguish a GIST from either a leiomyoma or leiomyosarcoma, fine needle aspiration done along with EUS will help confirm the diagnosis. In our patient we did not proceed with further work-up like EUS and capsule endoscopy as our endoscopic biopsy was successful in making the diagnosis. Capsule endoscopy may be useful in detecting GIST beyond the reach of the endoscope.

Tissue sampling via EUS can be obtained by fine needle aspiration (FNA). The sensitivity of FNA in making a diagnosis of GIST is around 80%. The National Comprehensive Cancer Network and the American Gastroenterological Association, both indicate that EUS guided sampling of GIST tumors is the preferred method of sampling (18).

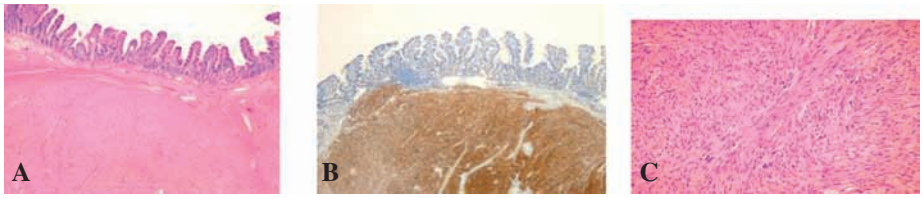

Fig. 2. — Microscopic imaging of the duodenal GIST ; A. Circumscribed cellular submucosal lesion. Mucosa is unremarkable (H&E, 20×) ; B. Strong positive staining of the submucosal lesion for CD117 (20×) ; C. Minimally pleomorphic population of spindle cells in fascicular pattern (H&E, 100×).

Small intestinal GISTs can be subdivided morphologically into spindle cell and epitheloid stromal tumors. Nearly half of them (40%-50%) in addition contain microscopically distinctive eosinophilic, periodic acid-Schiff-positive aggregates of extracellular collagen fibers, called skeinoid fibers. Skeinoid fibers are commonly seen in the nonmalignant cases and have been found to be a marker of favourable prognosis (19,20). The epitheliod pattern in small intestinal GISTs is associated with more aggressive behavior. A major defining immunohistochemical characteristic of GIST tumors is positivity for the Kit (CD117) receptor tyrosine kinase. In one study by Miettienen *et al.* (20), CD117 (KIT) positivity was documented in all 109 (100% of cases) duodenal GISTs. Although Kit positivity is highly suggestive of GIST, other tumors like metastatic melanoma, seminoma and mastocytoma may express KIT positivity. Therefore appropriate clinicopathological correlation is required to make a final diagnosis (5). Another commonly manifested antigen is CD34 which was present in 54% of duodenal GISTs in one study (5). Smooth muscle antigen positivity may be found but to a lesser degree (39%). None of the 109 cases of duodenal GISTs tested positive for desmin or keratin in the study by Miettenen *et al.* (20). In contrast smooth muscle tumors are typically desmin and SMA positive, and CD34 and CD117 negative thereby differentiating the two (Table 1).

Approximately 80% of GISTs have KIT gene mutations. Most gene mutations in GISTs affect exon 11 m and result in spontaneous receptor dimerization and receptor activation. However, in some cases, a mutation is present in exon 9, 13, or 17, with a different structural biological mechanism that results in uncontrolled KIT signaling (6). Approximately, 10-15% of GISTs lack mutations in either the KIT gene or PDGFRA, and their molecular pathogenesis remains unknown (6).

The most important determinants of prognosis in GIST are tumor size and mitotic activity, the latter typically expressed as number of mitoses per 50 HPF (6). Small intestinal GISTs have a more aggressive behavior than gastric GISTs with comparable size and mitosis parameters, especially for tumors less than 5 cm in size (6). The reason for the greater biologic potential of small intestinal versus gastric GISTs is unknown. For clinicopathological comparison Miettienen *et al.* (5) divided all duodenal GISTs (n = 135) into 6 groups based on tumor size and mitotic rate (Table 2). Group 1 tumors (< 2 cm, < = 5/50HPF) are considered benign with excellent 5 yr (> 94%) survival and no recurrence. In contrast, nearly 86% of patients in group 6 (> 5 cm, > 5 mitosis/50HPF) died of the disease within 21 months (5).

Table 1. — **Showing immunohistochemical characteristics of GIST, Leiomyoma and Leiomyosarcoma**

Tumor	CD 117	CD 34	Smooth Muscle Actin	Desmin
GIST	+++	++	+/-	---
Leiomyoma	–	–	++	++
Leiomyosarcoma	–	–	++	++

Table 2. — **Classification of Duodenal GIST (adapted from Miettenen *et al.*)**

	Tumor size	Mitotic rate
Group 1	< or = 2 cm	< or = 5 mitoses/50 HPF
Group 2	> 2 cm but < 5 cm	< or = 5 mitoses/50 HPF
Group 3	> 5 cm	< or + 5mitoses/50 HPF
Group 4	< or = 2 cm	> or = 5 mitoses/50 HPF
Group 5	> 2 cm but < 5 cm	> or = 5 mitoses/50 HPF
Group 6	> 5 cm	> or = 5 mitoses/50 HPF

All GISTs regardless of size have a malignant potential and should be ideally resected. However this may not be practically feasible especially with regard to GISTs found incidentally at endoscopy. The American Gastroenterological Association recommends removal of all GISTs > 3 cms as well as those with concerning EUS features. The National Comprehensive Cancer Network uses a cut-off mark of 2 cms (18). Surgery remains the current standard of therapy. Surgical options for duodenal GISTs include limited tumor resection (LR) or pancreaticoduodenectomy (PD). The decision to perform one over the other is guided by the size of the tumor, local invasion and proximity to the ampulla. Also some investigators feel that in view of the negligible submucosal spread and lymphatic involvement seen with GIST, limited resection is adequate. Goh *et al.* (2) compared the outcome of LR and PD in 15 patients with duodenal GISTS and found no difference in the morbidity, recurrence rate or diseases specific survival. LR was associated with a shorter operation time. They concluded that LR is a viable treatment option for suspected duodenal GIST. Winfield *et al.* (4) reported on 8 patients with duodenal GISTs. Five of these patients underwent pancreatoduodenectomy, 2 had partial duodenal resection and one had exploratory celiotomy. Of the 5 patients undergoing PD, one died postoperatively, one had recurrence of the diseases, while three remained without evidence of diseases at 1 month, 6 months and 12 months respectively. Of the two patients with partial resection, one had no evidence of disease at 6 months and other had no evidence of disease at 5 years. Endoscopic resection of small GISTs has been reported, but because of the risk of positive margins and tumor spillage, its role remains controversial (21).

A preliminary report from American College of Surgeons Oncology Group (ACOSOG) trial suggest that adjuvant Imatinib 400 mg given daily for a minimum of one year for patients with resected GIST 3 cm in size or greater resulted in a better progression free survival or recurrence rate at 14 months (22). Response to chemotherapy may depend on certain molecular characteristics

of the tumor. Patients with exon 11 mutations are more likely to respond to Imatinib than are those with other or no mutations. The phase II clinical trial conducted in United States and Finland, the Australasian phase III trial, and a North American trial have shown that patients with a KIT 11 mutation had the best objective response to Imatinib therapy in the setting of metastatic disease (23). In the adjuvant setting as well patients with exon 11 mutation have a better survival benefit with imatinib therapy (24). The risk of progression is low for KIT exon 11 mutation than for KIT exon 9 mutations. KIT exon 17 and PDGFRA exon 18 mutations are refractory to Imatinib therapy. In patients with no mutation found in KIT or PDGFR, the likelihood of benefit to Imitanib is 25% to 40% and these patients also have a higher risk for progression of the diseases (20). For patients with non-metastatic but unresectable GISTs, initiation of imatinib therapy is within scope of the FDA indication. Cases of successful down staging of duodenal and rectal GIST with neo-adjuvant Imatinib and subsequent surgical resection have been described (25,26,27). Sunitinib Malate is a small-molecule receptor tyrosine kinase inhibitor that is FDA-approved for Imatinib-refractory or -intolerant in GIST (28).

The risk of malignancy in tumors < 2 or 3 cms is small and EUS surveillance maybe appropriate in these patients. The optimal frequency of follow-up and risk associated with this strategy remains uncertain. Yearly follow-up seems to be an acceptable routine (18). Monitoring with EUS may also be an option for asymptomatic elderly patients who have multiple co-morbidities and are high risk surgical candidates regardless of the size of the tumor, especially if no malignant features are present.

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