



ORIGINAL ARTICLE

DIAGNOSIS AND TREATMENT OF GASTROINTESTINAL STROMAL TUMORS: AN ELEVEN-YEAR EXPERIENCE AT A TERTIARY-CARE HOSPITAL

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Abstract

Aim of the study: Is to review the clinical characteristics, pathologic features, and surgical management of gastrointestinal stromal tumors (GISTs) treated at a single tertiary hospital.

Methods: From 2002 to 2012, 25 patients treated by surgical excision of GISTs. Data on patients' age, sex, tumor location, tumor size, presenting symptoms, type of surgery and complications were collected.

Results: In the first 5 years of this study, only six cases of GISTs were diagnosed. Mean patients' age was 53.9 years. The male/ female ratio was 15/10. Sixteen cases (64%) were gastric GISTs, eight cases (32%) were small bowel GISTs. The most common presenting symptoms were GIT bleeding (32%) and abdominal pain (32%). Surgical resection included partial gastrectomy in 15 patients (60%), segmental jejunum-ileal resection in 6 patients (24%). GIST of the Meckel's diverticulum was reported in one patient and treated by ileal resection. One patient underwent wedge resection of the duodenum with Roux-en-Y duodenojejunostomy. Gastrectomy combined with colectomy was done in one case.

Conclusion: There is modest increase in GISTs diagnosed over the last several years due to improved diagnostic criteria. GISTs occur most frequently in the stomach followed by the small intestine, and may be found in rare sites as Meckel's diverticulum and duodenum. Surgical treatment is usually partial or segmental resection; however, larger tumors may require en bloc resection of adjacent organs.

Keywords: Tumor, Stromal, Gastrointestinal, GIST.

INTRODUCTION

In 1983, Mazur and Clark introduced the term "stromal tumor".⁽¹⁾ In 1998, Hirota and co-workers reported that gastrointestinal stromal tumors (GISTs) contained activating c-kit mutations, which play a central role in its pathogenesis.⁽²⁾ GISTs are rare mesenchymal tumors of the gastrointestinal tract (GIT), comprising approximately 1% of all gastrointestinal cancer. GISTs are a distinct disease entity based on their molecular

pathogenesis, immunohistochemical staining, and responsiveness to targeted therapy.⁽³⁾ Historically, these tumors were often classified as gastrointestinal smooth muscle tumors or neural tumors.⁽⁴⁻⁶⁾

The oncogenic drivers for GISTs are tyrosine kinase enzymes (KIT) and, to a lesser degree, platelet-derived growth factor receptor alpha (PDGFRA), both of which become constitutively activated following certain primary mutations. These mutations are mostly in the

c- KIT gene and rarely in PDGFRA.⁽⁷⁾ GISTs are thought to arise from interstitial cells of Cajal or a stem cell-like subset of KIT-positive spindle cells around the myenteric plexus.^(2,8) Interstitial cells of Cajal are normally part of the autonomic nervous system of the intestine and serve a pacemaker function in controlling motility.⁽⁸⁾

This study was designed to review the clinical characteristics, pathologic features, and surgical management of GISTs treated at a tertiary- care hospital.

PATIENTS AND METHODS

This study represents a retrospective analysis of patients with GISTs managed at surgery department- Assiut University Hospital in the period from 2002 to 2012.

Medical history, physical examination, laboratory studies (complete blood count, liver and kidney function tests) chest radiogram, transabdominal ultrasonography (US) and abdominopelvic computerized tomography (CT) scan were performed for all patients. US (Fig. 1) were employed in the detection, differential diagnosis of GISTs as well as their metastasis to the liver. CT scan (Figs. 1-3) is helpful in defining the endoluminal and exophytic extent of tumor as well as surgical planning and follow-up of patients with GISTs. Upper or lower GIT endoscopies were performed when indicated (Fig. 3).

Endoscopic biopsy should be performed only in the presence of mucosal ulceration. CT or ultrasound guided biopsy was not done for operable disease as it may cause tumor rupture, hemorrhage and peritoneal

seedling with negative impact on final outcome. Definite diagnosis and consideration for inclusion in adjuvant therapy by specific molecular inhibitor was delayed until after appropriate resection and full diagnostic evaluation of the excised tumor.

The surgical management varied according to the site of the tumor (Figs. 4-6). GISTs tend to protrude from the tissue of origin to surrounding structures or into the peritoneal cavity. Gastric GISTs commonly demonstrated extension into the gastrohepatic ligament, the gastrosplenic ligament, and the peritoneal cavity (Fig.4,6). The surgical strategy was complete surgical removal of the tumor (R0). The consistency of the tumors may be solid and fleshy, partially cystic, or cystic. Intraoperatively, meticulous surgical dissection was needed for large fragile tumor with intra-tumoral hemorrhage or necrosis to avoid rupture. The pathologists reviewed all postoperative specimens for histopathological diagnosis and evaluation of morphological and immuno-histochemical characteristics (Figs.7,8). According to Miettinen et al ⁹, the tumors were classified into probably malignant, probably benign or uncertain or low malignancy potential (Table 1). The adjuvant therapy after resection of primary GISTs by tyrosine kinase inhibitors (imatinib mesylate) was given to immunohistologically proven GISTs. Imatinib therapy was also used to treat recurrent GISTs.

Patients and tumor characteristics were evaluated. Data on patients' age, sex, tumor location, tumor size, presenting symptoms, type of surgery and complications were collected and analyzed. Tumor size was defined as the largest diameter of the tumor in any dimension.

Table 1. Malignancy potential of GISTs ⁹

Probably benign:

Intestinal tumors: Maximum diameter ≤ 2 cm *and* no more than 5 mitoses per 50 HPFs*

Gastric tumors: Maximum diameter ≤ 5 cm *and* no more than 5 mitoses per 50 HPFs

Probably malignant:

Intestinal tumors: Maximum diameter > 5 cm *or* more than 5 mitoses per 50 HPFs

Gastric tumors: Maximum diameter > 10 cm *or* more than 5 mitoses per 50 HPFs

Uncertain or low malignant potential:

Intestinal tumors: Maximum diameter > 2 cm but ≤ 5 cm *and* no more than 5 mitoses per 50 HPFs

Gastric tumors: Maximum diameter > 5 cm *and* ≤ 10 cm *and* no more than 5 mitoses per 50 HPFs

*HPFs: High power fields.

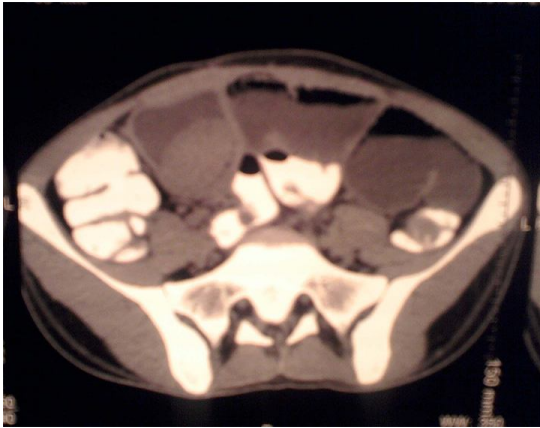


Fig 1. CT scan with contrast enema showing evidence of dilated intestinal loops in a case of ileal stromal tumor complicated by ileo-ileal intussusception (left). Abdominal US of the previous case showing pseudokidney sign characteristic of intussusception (right).

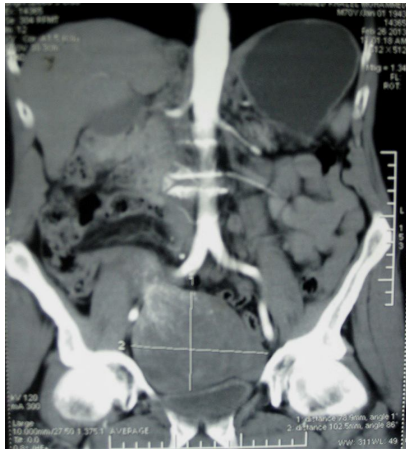


Fig 2. CT scan of pedunculated gastric stromal tumor comes out as solid ovoid mass 10x12 cm in the pelvis compressing the urinary bladder (left). CT arteriogram of the previous case showing that the lesion receives its arterial supply from the right gastroepiploic artery entering through the pedicle with strong arterial blush (right).

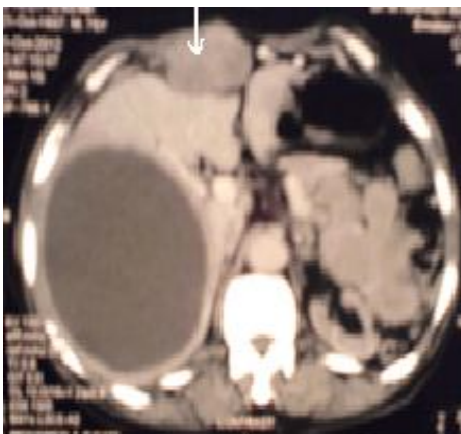


Fig 3. CT scan showing peritoneal deposit (arrow) caused by locoregional recurrence of GIST with an associated liver cyst (left). Endoscopic view of sharply demarcated gastric stromal tumor in a patient presented by dyspepsia (right).

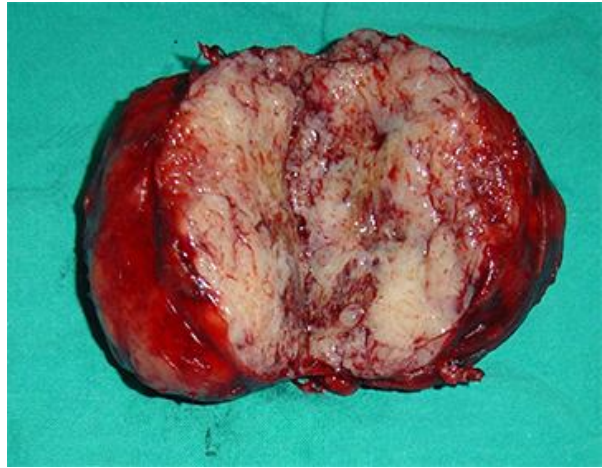
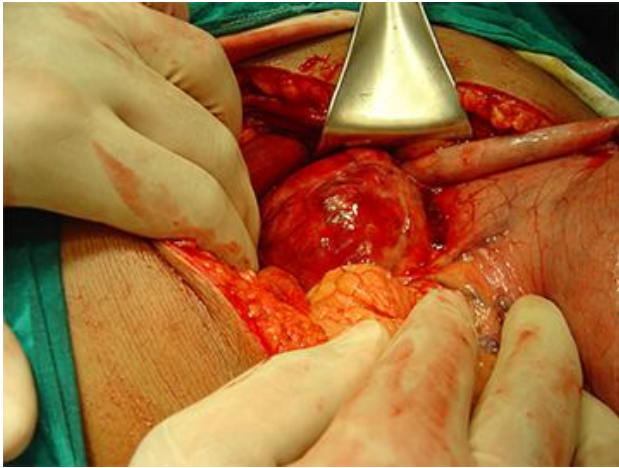


Fig 4. Exophytic stromal tumor of the stomach protruded to the lesser omentum: intra-operative view (left) and postoperative specimen showing tan white, solid and fleshy cut surface with occasional areas of hemorrhage (right).

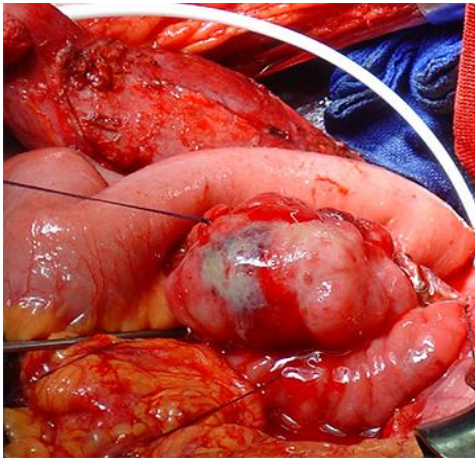


Fig 5. Stromal tumor of the duodenum: intra-operative view (left) and postoperative specimen (right).



Fig 6. Pedunculated stromal tumor with narrow pedicle originating from the distal part of the greater curve of the stomach: intra-operative view (left) and postoperative specimen (right).

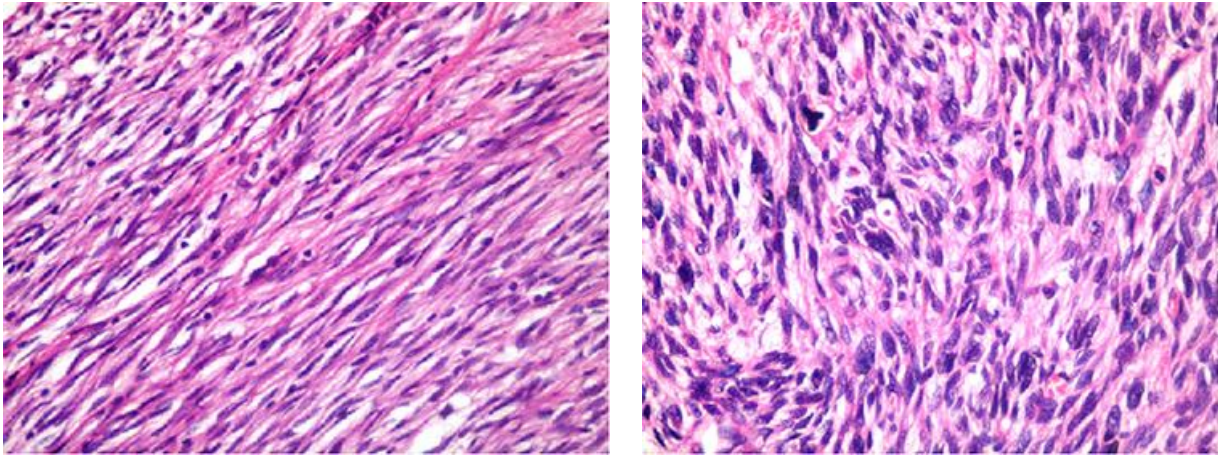


Fig 7. High power views of hematoxylin-eosin-stained sections (x400). Benign GIST with moderate cellularity showing spindle cells with little pleomorphism and no mitosis (left). Malignant GIST with pleomorphic spindle cells and numerous mitotic figures (right).

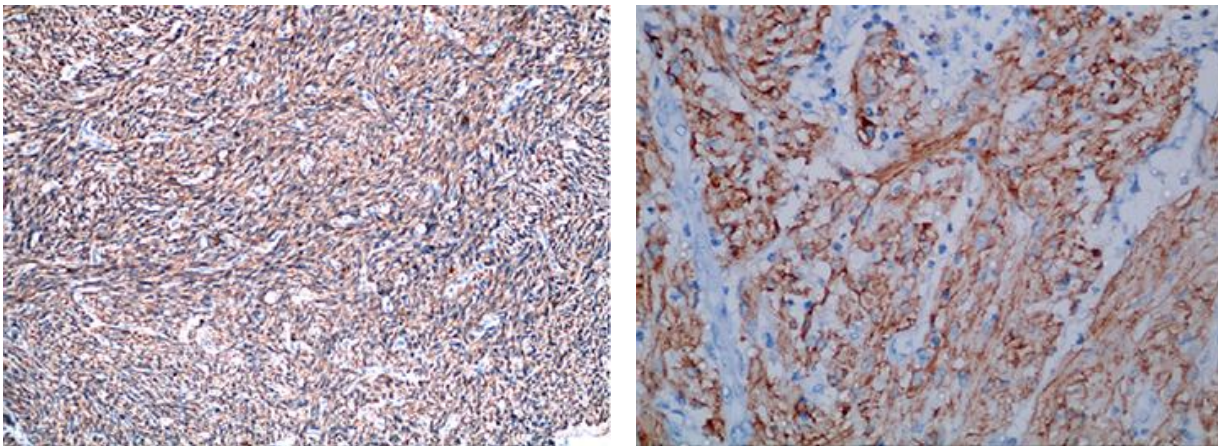


Fig 8. Immuno-histochemical staining. Spindle cell GIST showing cytoplasmic staining pattern of c-Kit (x 100) (left). Epithelioid GIST showing membranous staining pattern of c-kit (x400)(right).

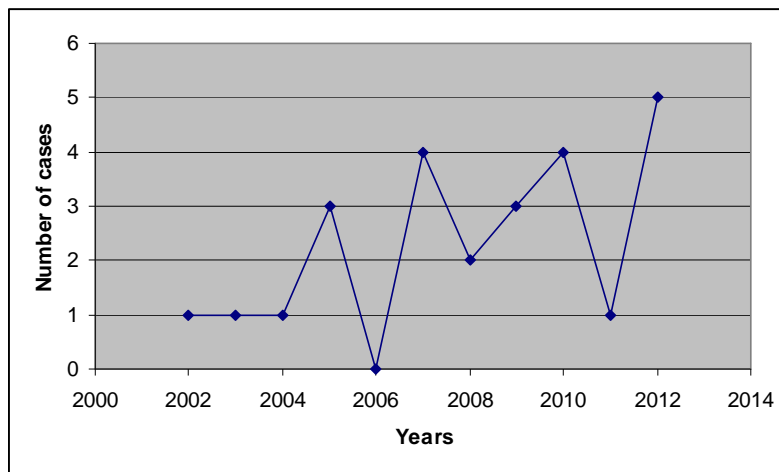


Fig 9. Annual distribution of patients included in this study.

RESULTS

This study included 25 consecutive patients treated by surgical excision for lesions that proved postoperatively to be GISTs. In the first 5 years of this study, only six cases of GISTs were diagnosed (Fig. 9). Mean patients' age was 53.9 years (range between 17 and 75). Only 4 cases (16%) were diagnosed before the age of 40 years. The male/ female ratio was 15/10. Sixteen cases (64%) were gastric GISTs, eight cases (32%) were small bowel GISTs [jejuno-ileal (6), duodenum (1), and Mickel's diverticulum (1)] and GIST of the colon was reported in one patient (4%). The size of the tumors ranged from 1.5 to 30cm and the average was 10.9 cm.

The most common presenting symptoms were GIT bleeding (32%) and abdominal pain (32%) (Table 2). Four cases (16%) were discovered incidentally during GIT endoscopy for dyspepsia. The patient may be manifested by more than a single complaint or a physical finding. Surgical resection included partial gastrectomy in 15 patients (60%), segmental jejuno-ileal resection in 6 patients (24%), and segmental colon resection in a single patient. Gastrectomy combined with colectomy was done in one case. GIST of the Mickel's diverticulum was reported in 20 years old male under the impression of Meckel's diverticulitis with perforation. However, after ileal resection anastomosis, a diverticular tumor in the specimen was suspected because of the unusual texture on palpation. One patient underwent wedge resection of the duodenum with Roux-en-Y duodenojejunostomy because the primary closure was impossible.

Among the 25 cases, spindle cell type was found in 23 cases, epithelioid cell type in one and mixed type in one case. In spindle cell GISTs, the cells arranged in short fascicles or whorls. The individual cells revealed ill-defined cell borders with ovoid nuclei, fine nuclear chromatin and inconspicuous nucleoli. The cytoplasm had a pale eosinophilic and fibrillary quality. Some cells showed paranuclear vacuolization. The epithelioid GISTs showed rounded cells arranged in nests or sheets with variably eosinophilic to clear cytoplasm. Hemorrhage and/or necrosis were present in some cases. Mucosal ulceration or serosal invasion sometimes could be seen in some malignant GISTs. CD117 was done to all cases and showed positivity in 24/25 (96%) of cases and most tumor demonstrated cytoplasmic staining, less commonly membranous staining pattern was observed in epithelioid cells. The negative CD117 case showed positivity for CD34 and focal positivity for smooth muscle actin and was negative for S-100 and desmin. Regarding behavior according to tumor location: 31.25% of gastric cases were malignant, while 37.5% of small intestinal GISTs were malignant. The number of cases with uncertain potential was higher in gastric group (37.5%) than in small intestinal group (25%) while the reverse was true for benign cases.

There were no postoperative mortalities. Postoperative complications were reported in five patients (20%).

Three patients had wound infection, one patient had superficial wound dehiscence, and another patient had postoperative ileus. All postoperative complications were managed conservatively. After a mean follow up of 32 months (range 6-60), one patient had been explored to relieve postoperative adhesive intestinal obstruction and another one complicated by incisional hernia. Recurrent GISTs were found in the liver of 2 patients and as peritoneal deposits in another 2 patients (Fig. 3).

Table 2. Clinical and pathological characteristics of patients with GISTs.

Age	
Range	17-75years
Mean	53.9
Sex	
Male	15/25 (60%)
female	10/25 (40%)
Site	
Stomach	16/25 (64%)
Small intestine	8/25 (32%)
Colon	1/25 (4%)
Presenting symptoms	
Abdominal pain	8 (32%)
GIT bleeding	8 (32%)
Dyspepsia	4 (16%)
Abdominal mass	4 (16%)
Bowel obstruction	3 (12%)
Nausea and vomiting	3 (12%)
Bowel perforation and peritonitis	1 (4%)
Hiccough	1(4%)
Size	
Range	1.5-30cm
Mean	10.9cm
Histopathology	
Spindle cell	23/25 (92%)
Epithelioid cells	1/25 (4%)
Mixed	1/25 (4%)
Behavior	
Probably benign	9/25 (36%)
Probably malignant	8/25 (32%)
Uncertain malignant potential	8/25 (32%)
Immunohistochemistry	
CD117 positive	24/25 (96%)
CD34 and smooth muscle actin positive	1/25 (4%)

DISCUSSION

GISTs are the most common mesenchymal tumors of the GIT⁽¹⁰⁾ with an estimated incidence of 1.5/100 000/year.⁽¹¹⁾ No association between geographic location, ethnicity, race, or occupation has been established. A few clinical settings are associated with the development of GISTs, such as neurofibromatosis type 1 (Von Recklinghausen disease) and Carney triad.⁽¹⁰⁾ GISTs typically occur in individuals above 50 years of age and rarely develops before the age of 40 years^(6,13-15) and arise only exceptionally in children.^(5,14) In the present study, the mean age at presentation was 53.9 years (range 17-75 years), and 4 cases (16%) were diagnosed before the age of 40 years. Regarding gender distribution, there is slight male predominance.^(2,15,16) Males constituted 60% of GISTs in this study.

GISTs vary greatly in size, morphology and malignant potential, creating a continuum of neoplasms with uncertain malignant potential ranging from virtually benign tumors to overtly malignant aggressive cancers.

The proportion of overtly malignant or high-risk GISTs is considered to be 20-45% of all GISTs.^(5,12) In the present study overtly malignant GISTs represented 32% of cases.

The large and hypervascular GISTs may contain cystic and necrotic tumor components. The more indolent GISTs are typically small, localized, and well-defined sometimes incidentally found tumors. Other GISTs may present with overt metastases already at the time of the diagnosis^{5,6}. The size of GISTs varies from 1 to 40 cm⁷. In this study, the size of the tumors ranged from 1.5 to 30 cm (average 10.9 cm).

The detection of GIST may be an incidental finding during evaluation of nonspecific symptoms. Presenting signs and symptoms depend on the size and anatomic location of the tumor. Symptoms tend to arise only when tumors reach a large size or are in critical anatomic location. In the present study, tumor originated most frequently from the stomach (64%), the small intestine was the second most frequent site (32%). These findings are similar to other reports.^(7,10,17-19) The most common clinical manifestations for symptomatic GISTs is gastrointestinal bleeding from mucosal ulceration and abdominal pain.^(7,18,19) In agreement with these studies, the most common presenting symptoms in the present study were GIT bleeding and abdominal pain. Other signs and symptoms included dyspepsia, nausea and vomiting, abdominal mass, hiccough, and manifestations of intestinal obstruction or peritonitis. Gastrointestinal obstruction is rare, due to the tumor's outward pattern of growth. Often, intestinal obstruction is due to intussusception predisposed by the tumor and not by the tumor itself.

Surgery is the mainstay of therapy for nonmetastatic GISTs. Complete surgical resection with clear margins is the only curative approach for localized GIST.^(10,20,21)

The tumor is often fragile, especially if it is large or there is extensive intratumoral hemorrhage or necrosis. Therefore, meticulous surgical technique is necessary to avoid intraoperative tumor rupture, which is associated with a poor prognosis.^(10,22,23) GISTs tend to protrude from the tissue of origin and displace adjacent organs, and therefore a wedge or segmental resection of the underlying organ is often possible. Consequently, negative surgical margins are usually attained. For limited tumors, resection can be achieved with minimal morbidity in most gastric and intestinal GISTs. Larger tumors may require multi-organ resections. In addition, the presence of an adherence to an adjacent structure, regardless of tumor size, should be approached with the en bloc resections. In the present study, gastrectomy combined with colectomy was done in one case.

The type of resection performed is classified as R0 if there is no residual disease or microscopic involvement of surgical resection; R1 when there is microscopic residual disease; and R2 when there is macroscopic residual disease. R0 surgery is clearly recommended and should be aimed for.^(10,22) On the contrary, it is not necessary to excise the whole organ of origin as well as locoregional lymph nodes, since the probability of lymph node metastases is very low.⁽²⁴⁾ Laparoscopic surgery has been shown to be effective for removal of these tumors without needing large incisions²⁵. If the laparoscopic surgery is planned, the technique needs to follow the principles of oncologic surgery. A laparoscopic surgery is clearly discouraged in patients who have large tumors or whenever multiorgan resections are required.^(11,24)

The rare combination of Meckel's diverticulum complicated by GIST has been reported in the literature as case reports.⁽²⁶⁻²⁸⁾ In this study, a 20-year-old male patient had this rare combination and presented as bowel perforation and treated by ileal resection. The standard treatment for symptomatic Meckel's diverticula is surgical resection; however, the management of asymptomatic Meckel's diverticula is controversial.⁽²⁹⁾

Some authors have suggested that asymptomatic Meckel's diverticula should not be removed unless the patient is at an increased risk of developing complications. The risk factors included male gender, young age, diverticulum larger than 2 cm, and presence of heterotopic tissue.⁽³⁰⁾ Others accept prophylactic diverticulectomy for asymptomatic patients.^(27,31,32) In contrast to the significant morbidity of up to 33% with complicated Meckel's diverticula, the postoperative morbidity associated with prophylactic diverticulectomy is between 0% and 6%.²⁹ Moreover, Meckel's diverticulum may be a site of tumors as GIST which may be clinically occult.

In rectal and duodenal GISTs en bloc resection is usually required.⁽²⁴⁾ In duodenal GISTs, major resection via a pancreaticoduodenectomy or a pancreas-sparing duodenectomy is indicated when the tumors are located

at medial wall of the second portion of the duodenum involving the ampulla of Vater.³³ Wedge resection with primary closure is performed for small lesions if the remaining lumen is adequate and the ampulla of Vater can be preserved.^(34,35) Resection of larger tumors involving the antimesenteric border of second and third part of the duodenum where the resulting defect is too large to close primarily, a Roux-en-Y duodenojejunostomy was created.^(36,37) In the present study, one patient underwent wedge resection of the duodenum with Roux-en-Y duodenojejunostomy.

In conclusion there is modest increase in GISTs diagnosed over the last several years due to improved diagnostic criteria and better awareness. GISTs occur most frequently in the stomach followed by the small intestine, and may be found in rare sites as Meckel's diverticulum and duodenum. The most common presentations are gastrointestinal bleeding and abdominal pain. Surgical treatment is usually by partial or segmental resection; however, larger tumors may require en bloc resection of adjacent organs.

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