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CASE REPORT

Gastrointestinal stromal tumours; report of three cases

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ABSTRACT

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract, arising from the interstitial cells of Cajal. They have variable malignant potential, ranging from small lesions with a benign behaviour to fatal sarcomas. In this paper, the authors report three cases of GISTs involving respectively the stomach, the duodenum and the jejunum. Our series included two women and one man aged between 42 and 74 years. The presenting symptoms included abdominal pain (n=2), gastrointestinal bleeding (n=1), abdominal mass (n=1), weight loss (n=1) and anemia (n=1). The three patients underwent surgical treatment. Histological examination of the surgical specimen coupled with immunohistochemical study confirmed the diagnosis of GIST in all cases. Detailed immunohistochemical studies are useful in successfully identifying any case of GIST, which is crucial to clinical treatment. New insights into the origin and progression of GISTs are setting the stage for further therapeutic innovations, with the goal not just to control disease growth, but to eliminate all tumour cells at the time of initial therapy.

Key words: gastrointestinal stromal tumour, immunohistochemistry, stomach, small intestine, pathology

INTRODUCTION

Gastrointestinal stromal tumours (GIST) are relatively rare, accounting for 1-2% of all gastrointestinal malignancies and are the most common mesenchymal tumours of the gastrointestinal tract in adults. [1,2] GIST can occur anywhere along the gastrointestinal tract; however, the majority arise in the stomach (50–60%) and in the small intestine (30–35%).[1]

In this paper, the authors report three new cases of GIST, that were treated and diagnosed at our institution.

CASE REPORT

We report three cases of GIST that were operated at the General Surgery Department of Mongi Slim hospital of Tunis between March 2013 and July 2014. The cases were retrieved from the files of the registry of surgery of the same hospital. Medical records were scrutinized for epidemiologic characteristics, initial manifestations of the disease, methods of diagnosis, laboratory findings, surgical treatment and follow-up. Diagnosis of GIST was based upon clinical, imaging and histopathological findings. All patients underwent imaging evaluation during the preoperative period. All specimens were surgically obtained. Tissues were fixed in 10% phosphate buffered formaldehyde, embedded in paraffin and sections were prepared for routine light microscopy after staining with hematoxylin and eosin. Immunohistochemical analysis was performed using the avidin-biotin complex technique with antibodies against CD117, CD34, DOG1, S-100 protein, smooth muscle actin. Patient confidentiality was maintained.

There were two female and one male patients aged between 42 and 74 years (mean = 57 years). Diagnostic imaging techniques included abdominal ultrasonography (n=3), CT scan (n=3) (Figure 1a and Figure 3) and endoscopic ultrasound in one case (case 2). Based on CT scan findings, preoperative diagnosis of GIST was accurately made in only one case (case 1) (Fig. 1a). The tumours involved respectively the stomach, the duodenum and the jejunum.

The patients underwent respectively : partial gastrectomy with distal duodenopancreatectomy (case 1), duodenal tumorectomy (case 2) and jejunectomy with colectomy (case 3). The patients of our series did not receive Imatinib.

Macroscopically, the tumours ranged in size between 3 and 16,5 cm (mean = 10,16 cm) (Fig. 1b). On cut section, the tumours were whitish (n = 2) or grey in colour (n=1). Foci of necrosis were noted in two cases (case 1 and 3) (Fig. 1b) and haemorrhage was detected in only one case (case 1). Histological examination of the surgical specimen coupled with immunohistochemical study established the diagnosis of spindle cell GISTs in all cases. Skeinoid fibres were identified in two cases (case 2 and 3) (Fig. 2).

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Postoperative course was uneventful in two cases (case 2 and 3). However, one patient (case 1) presented on postoperative day 14, peritoneal effusion with splenic vein thrombosis.

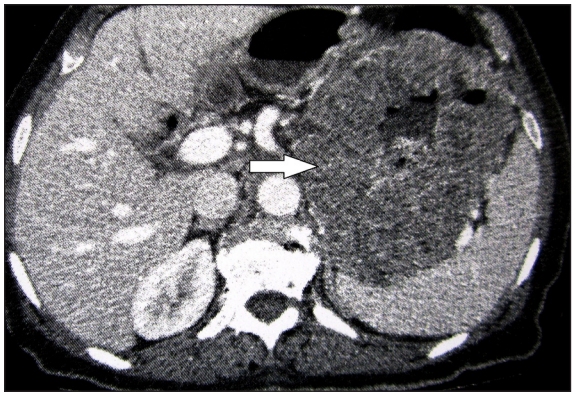

Figure1, Imaging findings and macroscopic characteristics of gastric GIST (Case 1).
Figure1a. CT scan demonstrating a hypodense mass in the gastric wall with central necrosis (arrow).

Recurrence and metastases were not detected during the follow-up period which ranged between 6 and 12 months.

Clinical data and histological findings of the three patients of our series are summarized in tables 1 & 2.

DISCUSSION

Gastrointestinal stromal tumours are believed to originate from interstitial cell of Cajal, the gut pacemaker of the autonomic nervous gut system, or their related stem cells.[3,4] GISTs usually occur in adults, with a median age of 55 -60 years and incidence of 10 to 20 new cases per million/year.[5] Most GISTs are sporadic and have no established risk factors. However, some GISTs arise in the setting of specific tumour syndromes. Although most patients have symptoms or a palpable tumour at presentation, 25% of GISTs are discovered incidentally during imaging or surgery for other disorders and a few (about 5%) are found at autopsy.[6,7] The most frequent symptoms are bleeding into the bowel or abdominal cavity, anemia, and abdominal pain, but others can include dyspepsia, nausea or vomiting, constipation or diarrhea, frequent urination and fatigue.[7,8] Hemorrhage, tumour rupture and bowel perforation or obstruction might need emergency surgery. Endoscopic contrast-enhanced ultrasound is especially valuable for assessment of large gastric, duodenal, rectal, or rectovaginal GISTs. A small gastric GIST could have a large extragastric extension not visible at endoscopy. Because metastases are infrequent outside the abdomen, imaging of the abdomen and the pelvis with contrast-enhanced CT or MRI will usually suffice.[9] Gastric GISTs can occur in any part of the stomach. They vary from minimal mural nodules to large complex masses with variably intraluminal and external components.[10] Some GISTs are attached to the gastric wall with a narrow pedicle forming an apparently external mass.[11] Occurring anywhere in the duodenum or small intestine, GISTs vary from minimal mural nodules to large complex masses usually with predominant external extension, which may be pedunculated. Some form dumbbell shaped masses, typically with minor intraluminal and major extraluminal components. Large tumours are often cystic and haemorrhagic. Advanced tumours involve multiple loops of bowel and develop diffuse or multifocal peritoneal spread, often obscuring the primary site of origin. Microscopically, most GISTs demonstrate 3 main histologic subtypes: spindle cell, epithelioid, and mixed type. Most of gastric GISTs are spindle cell tumours, while epithelioid histology is seen in 20-25% of cases, with a number of cases showing mixed histology.[10] Distinctive histological patterns among spindle cell GISTs include sclerosing type, seen especially in small tumours that often contain calcifications. The palisaded-vacuolated subtype is one of the most common, whereas some examples show diffuse hypercellular pattern and others show sarcomatoid features with significant nuclear atypia and mitotic activity.[10,11] Duodenal and small-intestinal GISTs are usually spindle cell tumours with diffuse sheets or vague storiform arrangements of tumour cells. Tumours with low biological potential often contain extracellular collagen globules ("skeinoid fibres"). Nuclear palisading may occur, but perinuclear vacuolization is rare. Nuclear pleomorphism is rare and mitotic rate is often low. Over 90% of GISTs, including virtually all KIT-mutant tumours, have KIT protein expression that can be detected by immunohistochemistry.[12] Most of the small number of GISTs that do not stain with KIT antibodies have no detectable KIT mutations and instead harbour mutation in

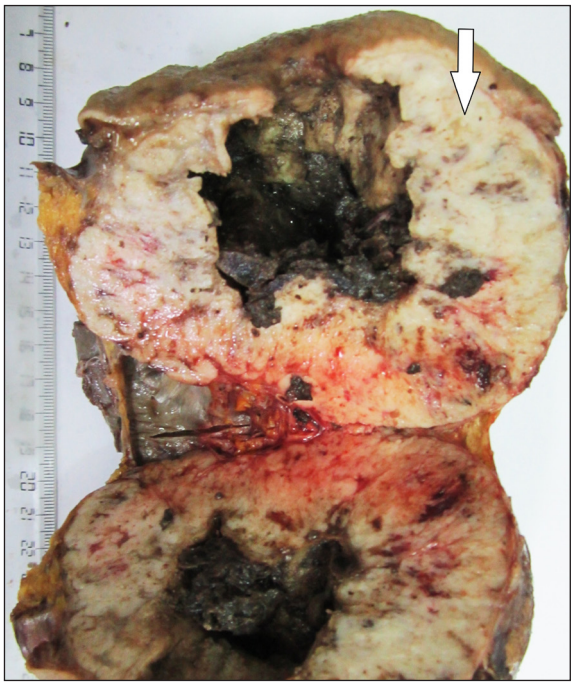

Figure 2a, On cut section, there was a submucosal mass in the gastric wall measuring 11 x 9 cm with central necrosis and haemorrhage (arrow).

Table 1, Clinical data in three patients with GIST

	Case 1	Case 2	Case 3
Age / sex	74/F	42/F	55/M
Medical history	Hypertension cholecystectomy	Operated for ovarian cyst and mammary adenofibroma	Ulcerative colitis
Location	Stomach	Duodenum	Jejunum
Clinical Presentation	Abdominal pain, weight loss, anaemia	Gastro-intestinal bleeding	Intestinal transit disorder, Abdominal mass and pain
Imaging studies and endoscopic exams	Abdominal ultrasonography and CT scan	Abdominal ultrasonography and CT scan Endoscopic ultrasound Esogastroduodenoscopy	Abdominal ultrasonography and CT scan colonoscopy
Treatment	Partial gastrectomy with distal splenopancreatectomy	Tumorectomy	Jejunectomy and colectomy
Postoperative course	Peritoneal effusion Thrombosis of the splenic vein on post-operative day 14	uncomplicated	uncomplicated
Follow-up	Still being followed-up. No recurrence (follow-up period = 12 months)	Still being followed-up. No recurrence (follow-up period = 6 months)	Still being followed-up. (follow-up period = 6 months)

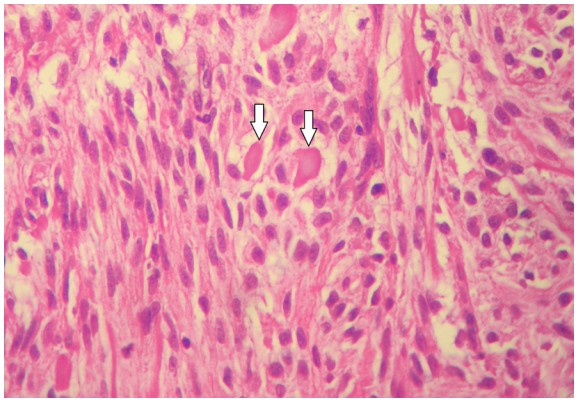

Figure 2, Histological characteristics of duodenal GIST (Case 2). Spindle cell tumour proliferation with diffuse sheets arrangements. Note the distinctive extracellular collagen globules or skeinoid fibres (arrows) (hematoxylin & eosin, original magnification x 400).

PDFRA.[12] These tumours tend to be epithelioid and have stromal sclerosis. The remaining KIT-negative GISTs do not have mutations in either KIT or PDFRA and belong to the group of wild-type GISTs.[12] DOG1 is a newer highly specific GIST marker that is a chloride channel protein highly expressed in GISTs.[12] DOG1 antibody has strong cytoplasmic and membranous staining in over 95% of GISTs. CD34 is commonly present in GISTs but is less specific than KIT or DOG1. Smooth muscle actin and muscle-specific actin can be variably expressed in GISTs, but desmin expression is rare.[12] Surgery is the only curative treatment for localized GISTs.

Surgical treatment should be planned after cancer staging by imaging studies in collaboration with an expert radiologist in order to verify the resectability of the tumour.[13] The goal is to obtain a total resection of the tumour with the entire pseudocapsule with negative microscopic margins. The peritoneal cavity should be examined with care to identify potential metastases or peritoneal dissemination of the tumour.[14] In spite of an R0 resection, there is a wide variation in the behaviour of the GIST depending on the different characteristics of the tumour, with recurrence rates that vary between 0 and 90%.[15,16] Recurrences are located most frequently in the peritoneum, tumour bed or in the liver, or as a metastatic liver disease. Lymph node involvement is exceptional and lymphadenectomy is not indicated except in cases of macroscopic involvement of regional lymph nodes.[15,16] Imatinib was the first molecular-targeted therapy to be approved for the treatment of GIST. Several other new tyrosine kinase inhibitors like regorafenib, nilotinib, and dasatinib are under research for treatment of GIST. The most useful and best studied prognostic factors of GISTs are tumour size and mitotic activity (typically expressed as number of mitotic figures per 50 high power fields (HPF), with a total area of 5 mm2). Tumour

Table 2, Tumour characteristics of the three cases of our series

	Primary tumour site	Tumour size (cm)	Histology	Mitotic index / 50 HPF	Immunohistochemical profile	*Risk stadification
Case 1	Stomach	11	Spindle cell GIST	9	CD117+;CD34+; DOG1+; S100 Protein-; SMA -	High risk
Case 2	Duodenum	3	Spindle cell GIST Skeinoid fibres	2	CD117+; CD34-; DOG1+; S100 Protein focally +; SMA -	Low risk
Case 2	Jejunum	16,5	Spindle cell GIST Skeinoid fibres	10	CD117+; CD34+; DOG1-; S100 Protein-; SMA -	High risk

HPF : High power field.
*Risk stadification according to Miettinen and Lasota

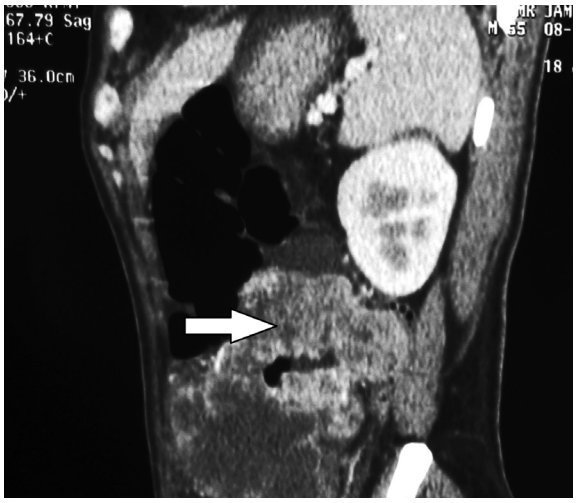

Figure 3, Imaging findings of jejunal GIST (Case 3).
CT scan revealed diffuse thickening of the jejunal wall with an enhancing heterogeneous parietal mass (arrow).

rupture has been described as a determining factor in the appearance of locoregional recurrences.[17,18] The location of GISTs in the gastrointestinal tract may influence the degree of malignancy. As noted by some authors, most malignant stromal tumours are localized in intestine.[19] During the past decade, basic and translational research advances have provided a detailed understanding of the molecular pathogenesis of gastrointestinal stromal tumours. We now understand that most GISTs have KIT or PDGFRA mutations and respond to specific small-molecule tyrosine kinase KIT inhibitors with promising clinical results.[19] Primary and secondary drug resistance has resulted in the birth of second-generation tyrosine-kinase inhibitors, which have shown activity in imatinib-resistant and sunitinib-resistant GISTs. Additionally, current research is now focused on investigating other molecular mechanisms that lead to tumour progression with the hope of providing alternative therapeutic modalities to reduce recurrence and to prolong survival in patients diagnosed with GIST.[19]

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