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Original Article

Clinical And Pathologic Characteristics Of Gastrointestinal Stromal Tumors In 11 Egyptian Patients: Implications For Surgical Management At Cairo University Hospitals.

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Abstract

Background: Gastrointestinal sromal tumors (GISTs) are rare, but have clinical relevance, as malignancy is expected in up to 30% of them. Clinically the majority is gastric and has diverse symptoms. They have no specific radiological features and there is difficulty in predicting their biological behavior

This study was designed to review the clinical characteristics of surgically treated gastrointestinal stromal tumors at our institution and evaluate their immuno histochemical and pathologic features and correlate finding with surgical management and prognosis.

Methods and Results: Patients and disease characteristics were studied in a group of 11 cases (9 gastric, one jejunal and one ileal). In addition, the pathologic features, surgical management, and treatment outcome were evaluated. A preoperative diagnosis was suspected in eight using endoscopy and endo sonography while CT defined local extra gastric spread in one patient .The median diameter of the tumors was 6.6 cm and no liver metastases were detected in any case. Planned cold surgery was possible in 8 of the 11 cases and excision was successful in all. Three cases were operated upon emergency basis. Histological and immunohisto-pathological evaluation confirmed the preoperative diagnosis in all cases .In half of the c-kit positive tumors the lesions were high grade malignant

Conclusion: GISTs are underdiagnosed in Egypt due to their vague presentations, but should be incorporated in the list of causes of GI bleeding .Surgical removal is feasible in most cases and the prognosis is strictly related to tumor size and number of mitoses.

Key words: *Gastrointestinal stromal tumors, GISTs*

Introduction

Until recently, the relatively infrequent gastrointestinal stromal tumors (GISTs) were not recognized as a distinct entity among soft tissue sarcomas, as they were thought to be of smooth muscle or perineural origin. They were classified as leiomyomas, leiomyosarcomas or schwannomas. Recent electron micrososcopy and immuno-histochemical studies indicated that only a minority of GISTs fulfill the typical features expected for smooth muscle neoplasms. The majority has features closer to neural appearance, while the remainder was even more undifferentiated. For this, Mazu and Clark in 1983[1] coined out the term gastrointestinal stormal tumors to include a subgroup of mesenchymal tumors characterized by over expression of the tyrosine kinase receptor KIT (CD117) [2]. They are rare and known to be aggressive and difficult to cure[3].

The cell of origin of GISTs is not certainly known. Kindblom et al. in 1998 [4], proposed their origin from the interstitial pacemaker cells of Cajal, which are responsible for gastrointestinal motility, and suggested the name gastrointestinal pacemaker cell tumors.

Although GISTs are rare (0.1- 3 % of all GI cancers and approximately 5% of all soft tissue sarcomas), they have clinical relevance, as malignancy is expected in at least 10-30% of them [5]. Moreover,

these tumors span a wide clinical spectrum from benign to highly malignant or even metastasizing lesions, having the potential risk of local and distant recurrence [6].

Clinically, most GISTs occur in the 6th decade of life and are exceptionally rare before the age of 40 years, though they were occasionally recorded in children [7]. The majority arise in the stomach (60%) the rest affects the small intestine (30%), and very infrequently they affect the duodenum, colon, rectum or the mesentery, while esophageal lesions are extremely rare [8]. Though some GISTs are asymptomatic [9], more than 50% of patients present by chronic or acute bleeding (due to mucosal erosions), sometimes necessitating emergency treatment. Twenty per cent of patients present with abdominal discomfort or even pain. In the small intestine, bowel obstruction is also frequent, rarely with perforation [10].

GISTs have no specific radiological features that may help in their diagnosis. Barium studies, endoscopy or endosonography may provide useful data helping their localization, while CT may suggest their malignant nature [11]. Percutaneous needle biopsy carries the potential risk of dissemination and is indicated only for clearly unresectable disease [12].

Most GISTs are well circumscribed and pseudo-encapsulated and vary greatly in size, ranging from 1cm to more than 20 cm. They arise in the GI wall, generally with extra luminal development, and not infrequently cause ulceration of the overlying mucosa. Microscopically they are composed of either spindle-shaped cells (70%) or epithelioid cells, while mixed cell population has rarely been encountered. By Immunohistochemistry, and contrary to leiomyomas, GISTs are positive for growth factor transmembrane receptor (KIT), which is the product of the proto-oncogene c-kit on chromosome 4 [13, 14], a fact that helps in their diagnosis.

One of the conflicting features of GISTs is the difficulty in predicting their biological behavior. A proposed scaling system, composed of five minor criteria and two major criteria was put down by Pascal to distinguish members having high malignant potential. Those tumors usually harbor either four of the five minor criteria, or one major criterion, otherwise they are described as having low malignant potential or even diagnosed benign. The major criteria include lymph node involvement and the presence of metastases while minor criteria include tumor size>5 cm, mitotic index>5 mitoses/ 50 HPF, presence of necrosis and infiltration of adjacent structures like the mucosa or serosa [15]. This scaling system significantly correlates with overall survival and makes it possible to detect all GISTs at risk of recurrence, which would benefit from more aggressive treatment. With this scale, the 5-year survival of patients having low malignant potential tumors is 95% and for high malignant potential tumors, less than 20%. A laparoscopic approach is feasible for smaller tumors less than 5cm [16]. In dealing with GISTs - where a definitive diagnosis is only made after surgery - the surgeon should have the readiness to perform complete en bloc removal incorporating the surrounding tissues if Pascal criteria are unfavorable. The role of synchronous resection of liver metastases, or block lymph node dissection for metastatic disease, is still debatable [17]. Recurrent or malignant GISTs are resistant to conventional radiotherapy and chemotherapy with an extremely poor prognosis and 12 months median survival [18]). Recently the molecular-targeted tyrosine kinase inhibitor with anticancer activity against GISTs (imatinib) has given new hope [19].

The purpose of this work is to study the clinical criteria and outcome of treatment of GISTs in Egyptian patients. Concomitantly, the importance of factors like tumor size and number of mitotic figures in determining malignancy, are to be assessed.

Patients and Methods

Detailed clinical, laboratory and radiological studies were done to 11 patients having abdominal masses clinically diagnosed as GISTs. All were presenting for surgical treatment. The study was done at Kasr Al-Aini Hospital from May 2003 through January 2004. Three of those patients were admitted on emergency basis because of serious blood loss with hypovolemic shock, while one of them presented with abdominal sepsis.

Investigations included upper and/or lower GI barium study, endoscopy, endosonography and endoscopic biopsy. The latter was only done if the tumor was protruding through the mucosa. Extraluminal spread and regional lymph node status were assessed by CT. Percutaneous drainage of abdominal sepsis was a preliminary step in one case that on follow up proved to have a residual mass necessitating exploration. All tumors were amenable to surgical resection (three of them as emergency cases). Preoperative tumor diagnosis was possible in the remaining 8, allowing for a planned cold surgery.

Preoperative assessment of the tumor size by ultrasonography and /or CT was of much consideration in trying to predict the tumor behavior. In addition, the size of the removed tumor was determined by direct measurement of the gross specimen and sent to the pathologist to confirm diagnosis and define its subtype and cellular pattern. Immunohistochemical reactions with vimentin, smooth muscle actin and desmin, in addition to c-kit were used to identify the need for tyrosine kinase inhibitor administration postoperatively.

Tumors were graded using Pascale classification as high or low-grade malignancy. The median follow-up was 19 months (from 8 to 30). .In a single case the follow up period was 48 months. Postoperative imatinib mesylate adjuvant therapy was given only to a single patient.

Results

Clinical data: Patients were 6 men and 5 women with age ranging from 18 to 52 years. Six patients had evidence of GI blood loss; one of them-gastric-necessitated emergency laparotomy. Two other patients presented in the emergency unit having acute jejunal obstruction in one and peritonitis due to ileal perforation in the other. Abdominal pain, anorexia, nausea, recent anemia, and epigastric fullness were common symptoms in most patients. A preoperative diagnosis was suspected in eight out of the 11 cases, using gastroduodenscopy and endoscopic ultrasound. . CT defined local extra gastric spread in one patient (Fig 1&2). The median diameter of the found lesion was 6.6 cm (range 2.8-16). No liver metastases were detected in any case. [Table I].

Management: Among the 8 elective cases complete laparoscopic excision with safety margins (aiming at cure) was the procedure used in 5 (45.5%). Conversion to open surgery was not indicated. Open surgery was mandatory in the remaining 3 cases (36.6%) one of them necessitated splenectomy. All those patients had masses less than 5 cm in diameter. Residual omental and pelvic nodules were left in one patient (Fig 4), who received adjuvant treatment post operatively to improve outcome. There was no early postoperative mortality [Table II].

Pathology: All diagnoses made preoperatively were confirmed by immunohisto-pathological evaluation of resected specimens. Postoperative histological assessment revealed that five of the tumors were leiomyomata (using actin and desmin as markers for differentiation), the remaining 6 showed positive c-kit receptors, four gastric and two small intestinal (Table III). Half of the c-kit positive tumors had a high-grade malignancy, two in the stomach and one in the ileum.

Follow-up: Median follow-up period was 19 months (8-30 months). There was an early mortality (8 months postoperatively) due to local recurrence in the omentum. Case No 11 died after 4 years from the first surgery due to massive local recurrence causing bilateral ureteric obstruction. No cases of liver secondaries were observed in this series

Discussion

Conforming with data in most reports [20], more than half of the studied patients (55%) presented with GI bleeding. This bleeding may be so massive to cause serious hypovolemic shock requiring blood replacement and immediate surgery. It is; therefore, wise to consider GIST in the differential diagnosis for GI bleeding.

Despite advances in technology, preoperative diagnosis (especially for small bowel GISTs) is often difficult due to wide spectrum of symptoms that may be present. Endoscopic ultrasound was the investigation of choice in this series as GISTs had distinctive echo pattern of a well-demarcated hypoechoic (mostly submucosal) mass in close proximity to the muscularis propria. A subserosal mass was suspected in one patient by this technique. CT can easily identify the tumor and provides useful data regarding tumor size, local spread and/or distant metastases [21]. Preoperative biopsy (via gastroscopy) was helpful in 8 cases with stomach lesions. This procedure is sometimes impossible when the tumor is subserous or when the mucosa is intact; a finding met with in a single patient and yielded inconclusive result. In small intestinal tumors no preoperative biopsy is feasible. Some authors advocate percutaneous guided biopsy, but it does not generate adequate tissue grading and is associated with a danger of transperitoneal or needle route dissemination of active cells [12],it was not attempted in this series. In one of our patients it revealed pus that proved after laparotomy to be from localized peritonitis following ileal perforation. Histologically, identification of leiomyoma and leiomyosarcoma among other GISTs is easy, while distinction between benign and malignant tumors is difficult and the classification using the standard criteria

commonly used for other tumors is often unreliable. Mitotic count (beside the more important tumor size) is considered one of the strongest pathologic predictors of malignant behavior.

The data obtained here may push to vote with Ludwig and Traverso [22] in considering tumor size more important than cellular characters at the time of resection in predicting aggressive behavior. A distinct correlation was found between tumor size and recurrence, metastasis or death. The larger the tumor (5 cm or more) the more is its ability to give secondaries and more is the necessity to have life-long follow-up including a periodic CT scan due to the risk of recurrence or metastases. Opponents of this view gave no convincing data. They considered that tumors with mitotic counts of >10 mitoses/50 HPF have a significant risk for recurrence and metastases and are considered histologically malignant. However, some tumors with mitotic activity of <1/10 HPFs may metastasize indicating some uncertainty of this parameter particularly if the tumor is Large. Regarding the malignant potential of GISTs, it was found that large tumors, especially those >5 cm have a higher possibility of malignancy. Thus all GISTs < 5cm should be considered as low-grade malignancy with a small risk of local recurrence or metastasis. We used 10 mitoses/50 HPFs as the minimum determinant for high-grade lesions (in addition to tumor size 5-10cm). Only 2 of our GISTs were classified as high-grade lesions; one patient died after 48 months due to repeated local recurrence at the primary site (ileum) in spite of a free first resection margin and the other due to distant metastases

Although significant advances on new chemotherapeutic regimes have been made, yet radical surgical removal still remains the only curative treatment of GIST. If the resection is incomplete due to local causes, the 5-year survival rate drops [3] .Therefore, all tumors should be approached with the intention of performing complete en bloc resection aiming at negative resection margins [3]. In contradistinction to adenocarcinomas, spread to local lymph nodes is rare, negating the need for regional lymph node dissection [23]. In addition, it was found that no statistical relationship exists between the extent of surgical excision and survival, but a strong correlation is present between incomplete tumor excision and tumor recurrence [24]. Moreover, extended resection provides no survival benefit over wide local excision. Therefore, whenever feasible limited resection is adequate particularly for gastric tumors less than 5 cm where wedge excision with safety margin is sufficient. Partial or subtotal gastrectomy is kept for larger masses. In one case of this series hemigastrectomy with splenectomy was mandatory for a relatively large mass having residual pelvic nodules and required postoperative tyrosine kinase inhibitor (Imatinib) treatment.

Particularly for gastric stromal tumors, many studies showed that laparoscopic resection is safe and appropriate. Operating time, and estimated blood loss were equivalent to the open approach, with the advantage of a relatively shorter hospital stay. Moreover, laparoscopic surgery should be preferred for those tumors, as their biologic behavior lends them to curative resection without requiring large margins or extensive lymphadenectomies [25]. Five of the studied patients were successfully treated by laparoscopy; without any need to conversion. Two of them had posterior wall gastric masses necessitated transgastric endoluminal resection. Laparoscopic enucleation was sufficient for a pedicled tumor arising from the lesser curvature.

Conventional chemotherapy is generally inactive in GISTs and was not tried in this work. Adjuvant target therapy by the oral use of the highly selective imatinib mesylate (a tyrosine kinase receptors inhibitor) was used in 2 patients. Its action is based on the c-KIT expression (CD 117) of GISTs. This drug as an adjuvant or palliative therapy is now considered mandatory for unrespectable or metastatic diseases and may be preferred over aggressive, repeated tumor removal [20]. A huge percentage of patients successfully controlled by the drug, relapse or even die on stopping treatment, as happened in the two mortalities of the present series. This pushes a recommendation of continuing on the drug at least until the disease progresses [26]. Contrary to this opinion, some workers consider that though the introduction of this new medication has dramatically shifted the treatment paradigm for metastatic or unresectable disease, demonstrating high response rates and allowing patients to live longer, yet up to 20% of patients do not respond to the drug. Added to this, nearly half can develop resistance over time, reminding us that the drug is not curative in this setting [27]. The role of imatinib in potentially resectable stromal tumors or as neo-adjuvant regimes is still under evaluation. [28].

Reported survival data after surgery for GIST vary widely. Moreover, overall GIST prognosis is of

little value, as low risk and high risk GIST do not have the same natural history after surgical resections. For low malignant potential GIST, the 5-year survival rate (approximately 95%) is similar to the normal population, while for high malignant potential GIST the 5- year survival rate ranged from 0% to 30% (24). Within the limits of the available follow-period in the present study, all patients with tumors <10cm and mitotic fig <10/ 50 HPF were alive at the time of publication without recurrence.

Conclusion

GIST's are probably underdiagnosed in Egypt. Clinical features and treatment outcome, in Egyptian patients, correlate with those mentioned in international literature. GIST may be put in the differential diagnosis of GI bleeding. Surgery, which may be extensive, provides the only hope for possible cure. Re-operation may be needed for locally recurrent disease. Neither radiotherapy nor conventional chemotherapy can offer any help for long-term survival. The prognosis of GISTs is strictly related to tumor size in the first place and also to number of mitoses.

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Table (1): Patients Data

SN	Sex	Ag-yrs	Presentation on Admission
1	M	48	Epigastric fullness & Dyspepsia
2	F	51	Massive hematemsisAnemia
3	F	46	Mass Lt. Hypochondrium - Occult blood in stools
4	M	44	Epigastric pain & fullness
5	M	50	Mild hematemsis
6	M	45	Mild hematamsis *(recurrent)*
7	F	49	Mild hematemsis
8	M	52	Upper abdominal pain - Nausea and vomiting
9	M	43	Intraabdominal abscess (intestinal perforation)
10	F	47	Epigastric fullness nausea - mild hematemsis
11	F	18	Small intestinal obstruction

Table (2): Surgical Procedures

SN	Tumor Site	Surgical Procedure
1	Stomach - Body	Laparoscopic wedge gastrectomy
2	Stomach - Greater curvature	Open wedge gastrectomy (Emergency)
3	Stomach - Mid-body	Open wedge Gastrectomy
4	Stomach - Lesser curvature	Laparoscopic excision of subsersosal liomyoma
5(*)	Stomach - Antrum	Open hemigasterectomy & splenectomy
6	Stomach - Fundus	Open wedge gastrectomy
7	Body of the stomach	Laparoscopic wedge gastrectomy
8	Stomach - Greater curvature	Laparoscopic wedge gastrectomy
9(*)	Terminal Ileum	Open small intestinal resection - Perforated GIST (Emergency)
10	Stomach - Body	Laparoscopic wedge Gastrectomy
11	Mid-jejunum	Open small intestinal resection (Emergency)

(*): Excision was incomplete due local advancement

Table (3): Postoperative pathological data

SN	Size (in cm)	Histology	Mitotic Fig#.	c-kite protein
1	3.5	Leiomyoma	< 5	Negative
2	6.5	Spindle cells	< 5	Positive**
3	9	Mixed cells	> 10	Positive
4	2.8	Leiomyoma	> 5	Negative
5	12.5	Spindle cells	<10	Positive
6	8	Mixed cells	< 5	Positive
7	4.5	Leiomyoma		>5
8	3	Leiomyoma		>5
9	10.5	Epithelioid		<10
10	4	Leiomyoma		>5
11	5	Spindle cells		>5

*Leiomyoma = positive actin & desmin and negative c- kit = liomyoma. ** Positive c-kit= GIST.

Fig (1): Gastric GIST: Site: Greater curvature involving spleen

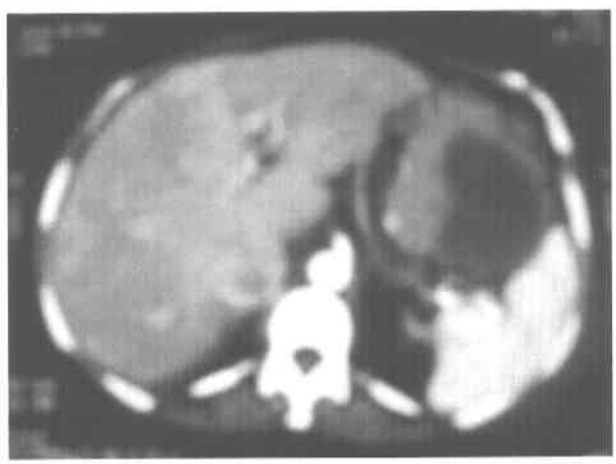


Fig (2): Gastric GIST: Site: anterior wall

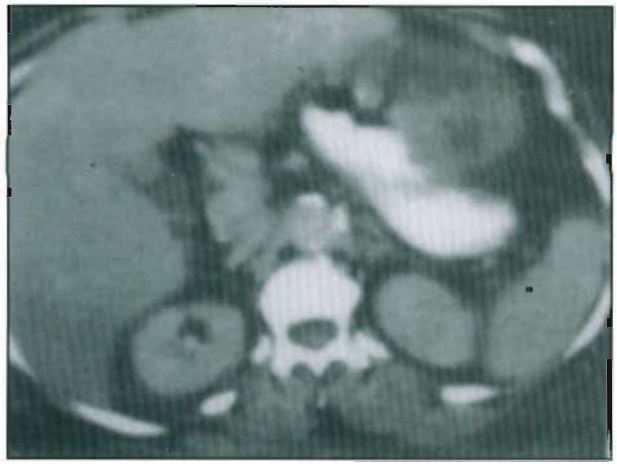


Fig (3) Small benign GIST of stomach, bisected

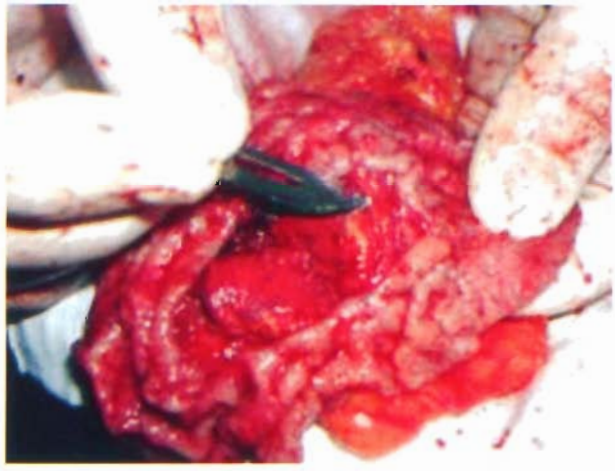


Fig (4): Gastric GIST: Partial gasterectomy& splenectomy and omentectomy

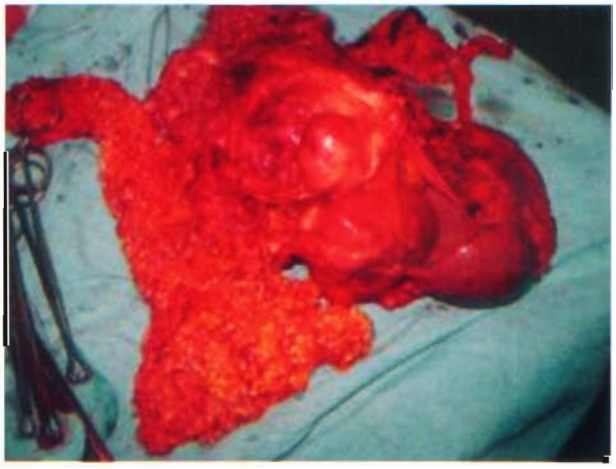
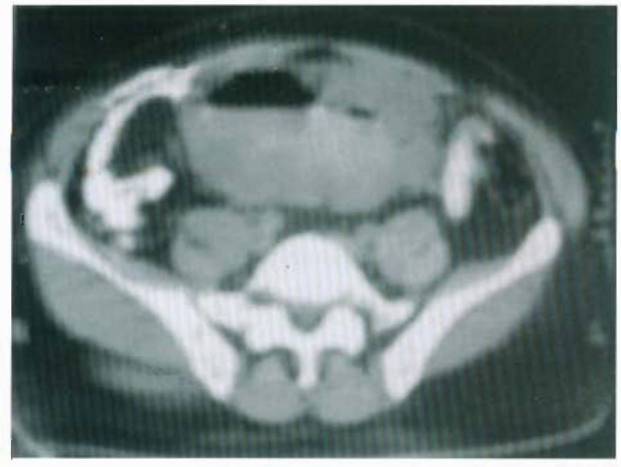


Fig (5): CT; Perforated ileal GIST with intra-abdominal abscess.



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