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Malignant Gastrointestinal Stromal Tumour – A Case Report

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ABSTRACT

Gastrointestinal stromal tumours (GIST) constitute a broad spectrum of nonepithelial neoplasms arising from connective tissue elements located along the entire length of the gastrointestinal wall. They are rare neoplasms which account for 0.1–1% of gastrointestinal malignancies. The majority are located in the stomach and small intestine, while those arising from the oesophagus, colon and rectum are uncommon. Usually asymptomatic, though depending on the site of origin, they may cause abdominal pain, bleeding or mechanical obstruction. We report a 77 year old gentleman, who presented with abdominal pain and distension. USS and CT revealed a heterogenous mass of uncertain origin. He underwent laparotomy and resection of a partially solid to cystic mass adherent to jejunum and sigmoid colon. Histopathology confirmed it to be gastrointestinal stromal tumour immunohistochemically positive for CD117. Preoperative diagnostic difficulties and management are discussed along with a critical review of literature of this rare, but important entity along with the role of imitanib in the management of unresectable and metastatic GIST.

INTRODUCTION

Gastrointestinal stromal tumours (GIST) are rare neoplasms originating from the connective tissue of the digestive tract and constitute most of the non-epithelial primitive digestive tumours, with a percentage incidence of less than 1% [1]. They are believed to arise from the interstitial cells of Cajal, the pacemaker cells of the alimentary tract [2]. Most GISTs are asymptomatic but may cause abdominal pain or bleeding from ulceration of the overlying mucosa. US endoscopy and fine needle aspiration with subsequent immunohistochemical analysis and study of c-kit gene mutation afford the best diagnostic accuracy. Surgical resection appears to be the best option with little role for radiotherapy and chemotherapy. In spite of its benign nature, long term follow up of patients is recommended.

CASE REPORT

A 77 year old gentleman presented with haematemesis & malaena on an emergency basis. He didn't have any significant past medical history. On examination, he was hemodynamically stable. Abdominal examination was unremarkable. Subsequently, he underwent upper gastrointestinal endoscopy which revealed features suggestive of angiodysplasia in the first part of duodenum, for which he underwent Nd Yag laser ablation. He made an uneventful recovery and was hence discharged.

Subsequently, after a period of 4 months, he presented to the emergency department with few days history of lower abdominal pain and distension. Abdominal

examination revealed a large non tender palpable mass in the lower abdomen which persisted after urinary catheterization. His routine blood tests were normal apart from a Hb of 10.3gm/dl. His chest and abdominal radiographs were normal. An initial abdominal ultrasound revealed a well defined cystic mass with internal echoes extending from pelvis to epigastrium of size 16x17.2x11.5cm (Figure 1). There was also a well defined area in lower right lobe of liver, 3 cm in size suggestive of a solitary metastatic deposit with typical target sign appearance (Figure 2).

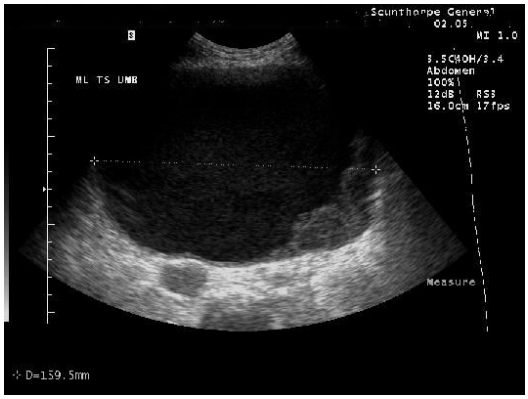

Figure 1: Abdominal ultrasound showing well defined cystic mass with internal echoes.

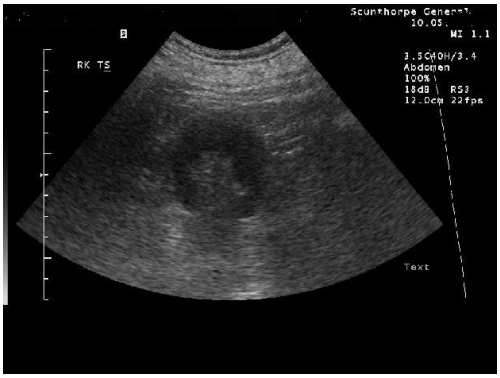

Figure 2: Abdominal ultrasound showing solitary metastatic 'target cell' appearance in the liver.

A CT Scan performed later confirmed the presence of a heterogenous mass with solid and cystic areas and irregularly thickened walls, arising from the pelvis and extending upto the renal hila (Figure 3). The origin of the mass was uncertain.

In view of the ambiguous findings on CT and USS, laparotomy was undertaken. At laparotomy, a large cystic mass with solid component adherent to loops of jejunum in the left upper quadrant, the sigmoid colon and the dome of bladder was found (Figure 4). He underwent resection of the mass along with the adherent loops of jejunum and sigmoid colon and fashioning of end colostomy. He had an uneventful postoperative recovery and was discharged.

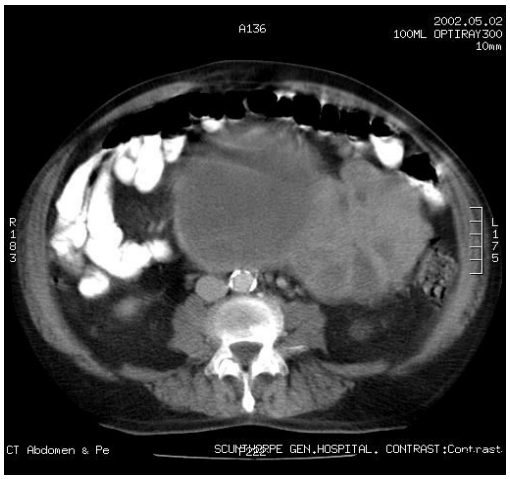

Figure 3: CT showing heterogenous mass with solid & cystic components.

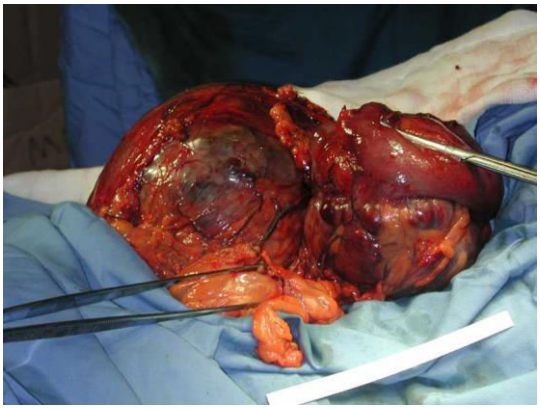

Figure 4: Cystic mass adherent to loops of jejunum and sigmoid colon.

On histological examination, macroscopically, a partially cystic to solid mass with lumen of small bowel directly extending into it and large bowel adherent to it by mesentery was demonstrated. Microscopy revealed sheets of spindle cells of smooth cell origin with foci of mitotic activity, necrosis and pleomorphism with the edge of lesion arising from smooth muscle of muscularis propria of small bowel was demonstrated. Immunohistochemical staining was confirmatory for CD117. In view of the size and evidence of hepatic spread, it was diagnosed to be malignant variety of gastrointestinal stromal tumour (GIST).

The patient subsequently underwent metastatectomy of the hepatic metastasis and later underwent reversal of colostomy. At the end of 12 months followup, he was doing extremely well.

DISCUSSION

GISTs are rare neoplasms which account for 0.1–1% of gastrointestinal malignancies. These tumours have unique histological, imunophenotypic and molecular genetic features that set them apart from typical smooth muscle tumours and schwannomas. Primary mesenchymal tumours of the digestive tract can be divided into the following three major categories according to their different phenotypic features: (1) tumours showing differentiation toward smooth muscle cells, which immunohistochemically express [alpha]-smooth muscle actin and desmin; (2) tumours showing apparent differentiation toward neural elements, as indicated by the expression of S-100 protein; and (3) tumours showing no differentiation toward either cell type even after exhaustive immunohistochemical probing. The tumours included in the third category, the poorly differentiated tumours, are often referred to as GIST [4]. The term itself was first used in 1983 by Mazur and Clark to identify a heterogeneous group of tumours, all of them histologically characterised by hyperplastic fused cells, not necessarily leiomuscular ones, but even neural ones. Gastrointestinal stromal tumours constitute a broad spectrum of nonepithelial neoplasms of the stomach and small bowel. GISTs occur most frequently in the stomach (65%), followed by those of the small intestine (30–35%), and those of the colon and rectum are extremely rare [3].

Gastrointestinal stromal tumours (GISTs) represent rare lesions arising from connective tissue elements located along the entire length of the gastrointestinal wall. GISTs are thought to arise from neural cells of gastrointestinal walls known as the interstitial cells of Cajal or 'pacemaker cells'. They are characterized by a remarkable cellular variability in their differentiation potential. Their common denominator is an immature proliferation of epithelioid or spindle cells often showing partial or incomplete myoid, neural or mixed features of differentiation.

Immunohistochemically most GISTs are positive for CD34 and c-kit protein CD117, a cell surface antigen on the extracellular domain of KIT; the latter is quite specific for GISTs among mesenchymal tumours. CD34 is a myeloid progenitor cell antigen and present in endothelial cells and almost all vascular lesions. Additionally, CD34 has been described in numerous fibroblast-like cells and different mesenchymal tumours [4]. The results of some studies have recently provided evidence showing that the most specific and practicable diagnostic criteria for GIST is the c-kit expression determined immunohistochemically [5-7]. Genetically GISTs commonly show DNA losses in the long arm of chromosome 14, and c-kit gene mutations occur at least in some cases. c-kit is also expressed in the interstitial cells of Cajal, the gastrointestinal pacemaker cells, and relationship of GISTs to these cells has been proposed recently. GISTs differ histologically, immunohistochemically and genetically from typical (esophageal) leiomyomas that are negative for c-kit and CD34 and neither show DNA-losses in 14q nor c-kit mutations.

Mutational analysis of the *KIT* gene (exons 11, 9, 13, and 17) and *PDGFRA* gene (exons 12, 14, and 18) can be helpful in confirming the diagnosis of GISTs if immunohistochemical studies are inconclusive (particularly in CD117/DOG1-negative spindle cell suspect cases) [8]. It also can predict sensitivity to molecular-targeted therapy and prognostic value. Better outcomes with imatinib is observed in tumors harboring *KIT* exon 11 compared to tumors with *PDGFRA* exon 18 mutations (D842V) who are observed to have primary resistance to imatinib both *in vivo* and *in vitro* [9].

In addition to their heterogeneity, another problem in evaluating GISTs is the determination of their malignant potential. Evaluation of malignancy of GISTs is based on mitotic count, tumour size and extra-gastrointestinal spread. It is suggested that tumours with the mitotic rate higher than 5 per 10 HPFs or the size larger than 10 cm have significant risks of recurrence and metastasis, and are histologically considered malignant [3]. Immunophenotype of the tumour cell differentiation has also been proposed by several authors as an important prognostic factor. Rosai suggested that the tumours without differentiation toward smooth muscle and neural elements are regarded as being malignant or potentially malignant [10]. The main features consistently predictive of biological behaviour are size and mitotic rate. Small GISTs (less than 5 cm in diameter) with fewer than five mitotic figures per 50 high-power fields (HPF) may safely be

considered benign, whereas those with size larger than 5 cm or mitotic count greater than 5 to 10 mitoses/50 HPF or more than 10 mitoses/50 HPF should be classified as potentially malignant or malignant.

Congenital GIST has been described. It morphologically resembles adult GIST, except for CD117, which is negative in the congenital tumour, but strongly positive in all adult tumours. This lack of c-kit expression suggests that it is nosologically distinct. Despite the presence of histological features which would cause the tumour to be categorized as malignant in an adult, it is apparent from previous reports of congenital small intestinal stromal tumours that the prognosis is favourable [11].

The age of onset usually ranges between 50 and 70 years, with no sex predilection. Benign GISTs outnumber the malignant ones by a margin of 10:1. Symptoms depend on the site and size of the tumour, and may include abdominal pain, gastrointestinal bleeding from ulceration of the overlying mucosa or signs of obstruction; small tumours may be asymptomatic The major clinical findings are upper abdominal ulcer-like pain, dyspepsia, iron-deficiency anaemia, gastrointestinal bleeding, nausea, vomiting, palpable upper abdominal mass, and weight loss. Some GISTs have developed in the setting of HIV infection, others have occurred in patients with von Recklinghausen's disease and bilateral phaeochromocytoma [12], in association with pulmonary chondroma and extra-adrenal paraganglioma (Carney's triad) and in MEN-1 with duodeno-pancreatic gastrinoma, parathyroid hyperplasia, pituitary adenoma, adrenal adenoma, and lipomas [13]. Other unusual presentations include a large gastric stromal tumour causing gastroduodenal intussusception presenting with intermittent abdominal pain and gastric outlet obstruction [14], an incidentally found GIST within a Meckel's diverticulum in a patient presenting with acute appendicitis [15] and haemoperitoneum caused by rupture of GIST [16].

Pre-operative diagnosis is difficult. The accuracy of endoultrasound is high in diagnosing gastrointestinal stromal tumours, which show a significant potential of malignancy [17]. CT is also helpful in clinching the pre-operative diagnosis. US endoscopy and fine needle aspiration with subsequent immunohistochemical analysis and study of c-kit gene mutation afford the best diagnostic accuracy [18].

Only surgical treatment seems to be definitive. Neither radio- nor chemotherapy is successful. Radical extirpative surgery with clear resection margins is deemed to be curative.

However, all GISTs are considered to have some degree of malignant potential. They are unresponsive to standard chemotherapy and to radiotherapy, and the mainstay of treatment in the past has been surgery. However, recurrence rates are high, and there has been no effective systemic treatment for unresectable GIST or metastatic disease. More recently, imatinib has been approved for the treatment of patients with advanced GIST, in which KIT, a tyrosine kinase receptor, is abnormally expressed. The control of cellular processes, such as cell growth, division and death, involves signal transduction, which commonly involves the transfer of phosphate from adenosine triphosphate (ATP) to tyrosine residues on substrate proteins, by tyrosine kinase enzymes. Activation of oncogenes coding for kinase proteins can lead to the production of kinases that are continually active in the absence of a normal stimulus, leading to increased cell proliferation and/or decreased apoptosis. Imatinib mesylate (imatinib) is an orally administered 2-phenylaminopyrimidine derivative that is a competitive inhibitor of the tyrosine kinases associated with the KIT protein (stem cell factor receptor), the Abelson (ABL) protein and platelet-derived growth factor receptors. Gain-of-function mutations of the KIT proto-oncogene occur in up to 90% of GISTs, allowing constitutive activation of tyrosine kinase (i.e. auto-phosphorylation of tyrosine residues independent of ligand-receptor binding), leading to aberrant cell division and tumour growth. Imatinib selectively inhibits the tyrosine kinase activity associated with KIT, which forms the rationale for its effects in GIST [19].

Imatinib is used in neo adjuvant setting for cytoreductive effect before surgery in advanced tumours and also in adjuvant setting after surgery to reduce the incidence of recurrence and possibility of developing metastatic disease [20]. Imatinib is recommended as adjuvant treatment for at least 1 year after resection of intermediate to high risk GIST as this is associated with significantly improved recurrence free survival [21]. Sunitinib is the second line tyrosine kinase inhibitor which is available for patients who develop resistance to imatinib due to its inhibitory function on multi-kinase receptors [22].

In malignant GISTs, the natural history is characterized by local and peritoneal recurrences, and by metastases, predominantly to liver and lungs, which may occur as long as 30 years after primary resection. The 5-year survival rate for patients with GISTs is about 50%, but this figure decreases to about 35% at 10 years. Malignant GISTs arising in the small intestine have a significantly poorer prognosis than those arising in the stomach. The 10-year survival rates are 17 and 74%, respectively. For patients in whom complete resection is not possible, or in patients with metastatic or recurrent disease, the median duration of survival is 9-12 months, and 10-19 months, respectively [18].

Even in the absence of unfavorable prognostic indicators, because of the uncertain behaviour of benign GIST, a lifelong follow up of all patients managed with potentially curative surgical resection is recommended.

CONCLUSION

Gastrointestinal stromal tumours are rare neoplasms originating from the connective tissue of the digestive tract and constitute most of the non-epithelial primitive digestive tumours, with a percentage incidence of less than 1%. Most GISTs are asymptomatic but may cause abdominal pain or bleeding depending on site of origin. Endo ultrasound and CT scan are helpful in making a preoperative diagnosis. Surgery offers definitive treatment as radiotherapy and chemotherapy seems unhelpful. The definitive diagnosis of gastrointestinal stromal tumour, as currently defined, is usually made only postoperatively by analysis of the histopathological and immunohistochemical findings. Imatinib has offered new hope in combating unresectable or metastatic disease and reducing the incidence of recurrence. Though it is considered to be benign, due to its unreliable benignity, long term follow up is recommended.

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