University Journal of Surgery and Surgical Specialties

ISSN 2455-2860 Volume 3 Issue 3 2017

GASTROINTESTINAL STROMAL TUMOUR IN STOMACH - SPINDLE CELL VARIANT

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Abstract :
Gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. Gastrointestinal stromal tumours (GIST) are rare tumours, with an estimated incidence of 1.5 per100,000 per year. Understanding and treatment of these tumours have improved dramatically over the last several years.Epithelioid and mixed variants are more common in GIST of stomach. Whereas, Spindle cell variant is seen more commonly in the small bowel. A 43 yr old gentleman, presented with GIST of the stomach which turned out to be of spindle cell variant. A Distal partial gastrectomy with a proximal 5cm margin and reconstruction with an Anterior Gastro-jejunostomy and Jejuno-jejunostomy was done. The patient was then started on adjuvant therapy with Imatinib mesylate.This case is presented due to the rarity of the tumour and the less common occurrence of spindle cell variant in a GIST of the stomach.

Keyword :GIST, stomach, spindle cell variant, Imatinib mesylate.

INTRODUCTION -

Gastrointestinal stromal tumors (GIST) are rare malignancies. They represent only 0.2% of all GI tumors. Although rare, gastrointestinal stromal tumours (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract. The term GIST was first employed in 1983 by Mazur and Clark to describe nonepithelial tumors of the GI tract that lacked the ultrastructural features of smooth muscle cells as well as the immunohistochemical characteristics of Schwann cells. GIST exhibit heterogeneous histologic features, and are most often composed of long fascicles of bland ***spindle cells***. *GIST occasionally exhibit* ***epithelioid*** *characteristics. Based upon their histologic and immunohistochemical features, GIST are thought to arise from the* ***Interstitial cells of Cajal*** *(ICC), which are components of the intestinal autonomic nervous system that serve as pacemakers regulating intestinal peristalsis.*

*Over 90% of GISTs occur in adults over 40 years old, in a median age of 63 years. However, GIST cases have been reported in all ages, including children. The incidence between the sexes is the same, with a slight predominance of males. The most common location of GIST is stomach (50-60%) and small intestine (30%-40%). Five to ten percent of GISTs arise from the colon and rectum, and 5% are located in the oesophagus. Other less common locations are those outside of the GI tract, like mesentery, retroperitoneum and omentum. GIST have recently been the subject of considerable clinical and experimental interest, because of the identification of their activating signal (oncogenic mutation of the c-kit receptor) and the development of a therapeutic agent that suppresses tumour growth by inhibiting this signal (**Imatinib mesylate**). The* current management of these malignancies represents a proof of the principle that specific inhibition oftumour-associated receptor tyrosine kinase activity can produce effective cancer treatment. The advent of effective chemotherapy for GIST has altered, but not diminished, the role of surgery for this disease.

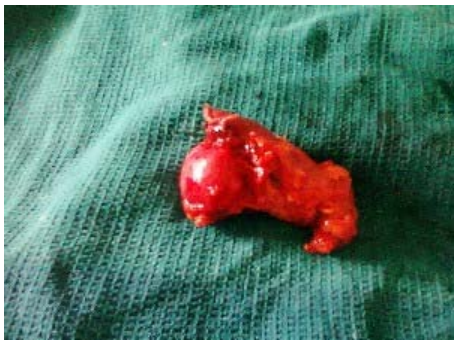
CASE REPORT -

A 43 year old man presented with dull aching upper abdominal pain for 3 months duration. He had nohistory of vomiting, haemetemesis or malaena.On examination of the abdomen, an ill defined, firm to hard mass was felt in the epigastrium, movingwith respiration. There was no hepatosplenomegaly or ascites.OGD scopy showed a smooth extraluminal bulge occupying the pylorus with intact mucosasuggesting an exophytic growth.Contrast enhanced CT scan of the abdomen showed - eccentric wall thickening of the antrum ofstomach with polypoidal protrusion into the lumen and an infeomedial exophytic component (40*43*48 mm). Lobulated luminal surface seen with significant narrowing. The exophytic component in contact with the antero-superior margin of the pancreatic head. NO infiltration evident. No evidence of metastases.

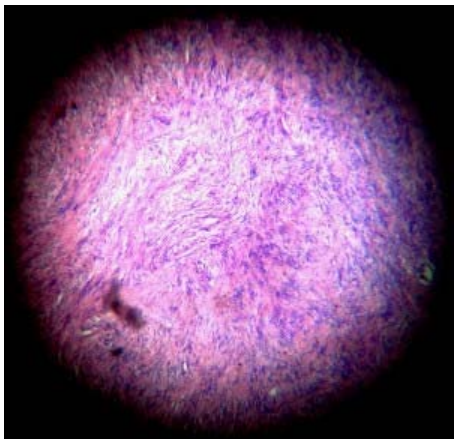
A working diagnosis of GIST was made and we proceeded with a Laparotomy. The findings were as follows -

1) Extraluminal, Intramural growth in the posterior wall of the antrum and pylorus of the stomach.
2) Peritoneum and liver - normal.

The tumour was resected and a Distal partial gastrectomy (with a proximal 5cm margin) was done. Reconstruction with an Anterior gastro-jejunostomy and Jejuno-jejunostomy was done. Post-operative period was uneventful.



Resected specimen - Posterior aspect of distal part of stomach showing tumour
Specimen - After fixing by the pathologist Cut specimen of the stomach with tumour showing intact mucosa and lobulated appearance of tumour



HPE slide showing spindle cell appearance

HPE report -Cellular spindle cell tumour involving submucosa and muscle coat. Overlying mucosa was intact and Non-Neoplastic. No tumour extension seen. Low mitotic rate of <2/50 HPF (High Power Field).

Impression - Gastrointestinal stromal tumour - Spindle cell variant.

Patient was reviewed a week later and was started on adjuvant therapy with Imatinib mesylate.

DISCUSSION -

Gastrointestinal stromal tumors (GIST) are a subset of mesenchymal tumors and represent the most common mesenchymal neoplasms of Gastrointestinal tract. In 1998, Hirota and colleagues demonstrated gain-of-function mutations of the KIT proto-oncogene in the vast majority of GIST. KIT is a receptor tyrosine kinase that is activated when bound to a ligand known as steel factor or stem cell factor. KIT is important in the development and maintenance of components of haematopoiesis, gametogenesis, and intestinal pacemaker cells. Oncogenic mutations of KIT have been identified in neoplasms corresponding to these functions, including mast cell tumors, myelofibrosis, chronic myelogenous leukemia, germ cell tumors, and GIST. GIST are now identified by the near universal expression of the CD117 antigen (~95%), part of the KIT receptor, in the appropriate histopathologic context. CD117 expression is characteristic of most GIST, but not of other gastrointestinal smooth muscle tumours. The application of CD117 staining as a diagnostic criterion for GIST has altered our understanding of the prevalence of this disease. GISTs contain activating c-kit mutations, which play a central role in its pathogenesis. Furthermore, GISTs express CD34 (cluster designation 34) and the KIT on their surface. It was their origin that lead to the introduction of a chemotherapeutic regimen, Imatinib mesylate, a tyrosine kinase inhibitor for c-kit. GISTs are, finally, defined as pleomorphic mesenchymal tumors of the GI tract that express the KIT protein (CD 117- Protooncogene that encodes the transmembrane tyrosine kinase receptor CD 117) and often also CD34 (human progenitor cell antigen) on immunohistochemistry.

Clinical Presentation

The clinical presentation of GIST is varied. Only 70% of the patients are symptomatic, while 20% are asymptomatic and 10% are detected at autopsy. The clinical signs and symptoms are related to the presence of a mass or bleeding. Bleeding comprises the most common symptom leading to acute abdominal pain, haematemesis, melena or anaemia. Another common finding is the abdominal mass. However, most of the patients present with vague symptoms, such as nausea, vomiting, abdominal discomfort, weight loss or early satiety. Rupture of GISTs into the peritoneal cavity is rare and it causes life threatening intraperitoneal hemorrhage. Lymph nodes metastases are not common in GISTs. On the other hand, distant metastases most commonly occurs in GIST tumors of peritoneum, omentum, mesenteric areas and liver. Rectal GISTs frequently metastasize to the lung.

Pathology

GISTs show a variety of differentiation spectrum, ranging from fully differentiated tumors with mixed, neural or ganglionic plexus phenotype to those with incomplete or mixed differentiation.

GISTs are positive for KIT. Generally, GIST vary greatly in size from a few millimetres to>30 cm, the median size though is between 5 cm and 8 cm. Macroscopically, GIST usually has an exophytic growth are smooth gray and white tumours which are-well circumscribed, usually with a pseudo-capsule. Less frequently, a small area of haemorrhage,cystic degeneration and necrosis may be visible. GISTs have many different histological features. ***Epithelioid and mixed tumours are morecommon in the stomach while spindle cell type tumours are more common in the small-lintestine.***Gastric GISTs have a solid or nested form, often with a hyalinized stroma that shows myxoid change. GISTs in the small intestine, though, are more often spindled than epithelioid and may show a paragangliomatous pattern.

Investigations

The endoscopic appearance of a primary GIST is that of a submucosal lesion, with or without ulceration, present in the upper or lower GI tract. These lesions are visually indistinguishable from other GI tumors of smooth muscle origin. Because of their submucosal location, fine needle aspiration (FNA) or core biopsy with endoscopic ultrasound guidance is commonly required to obtain tissue for diagnosis. CT scans are critical to determine the anatomic extent of a GIST and to assist with operative planning. Radiographic signs corresponding to aggressive malignant GIST include calcification, ulceration, necrosis, cystic areas, fistula formation, metastases, ascites, and signs of infiltration of local tissues. The preoperative percutaneous biopsy should not be used because it is associated with a significant risk of tumor rupture or dissemination. The significance of endoscopic ultra-sound guided fine needle aspiration has been pointed out in several studies and the reported accuracy is 80% - 85% .

Surgical resection of the local disease is the gold standard therapy. Its goal is complete resection of the disease with avoidance of tumour rupture. Tumour size determines the survival. Regional lymph node resection has no value since GIST rarely gives rise to lymph node metastases. However, the tumor size or its location may determine the exact extent of resection. En block resection of the local disease is recommended when GISTs adheres to contiguous organ.

Gastrointestinal Stromal Tumor Risk Assessment

Tumor Size (cm)	Mitotic Index (50 HPF)	Risk of Recurrence
<2	<5	Very low
2-5	<5	Low
<5	10-16	Intermediate
5-10	<5	
>5	>5	High
>10	Any	
Any	>10	

Management of advanced GIST (metastatic and recurrent)

Standard treatment for primary gastrointestinal stromal tumor (GIST) is complete surgical resection, with the aim to obtain negative microscopic margins over the organ of origin. Imatinib mesylate is a very active agent for tumor control in advanced and metastatic GIST. The use of Imatinib mesylate in recurrent or metastatic, (operable or inoperable) in a prospective trial has shown response in 50% patients. The 2-year survival after Imatinib therapy is approximately 70%. 50% of the patients showed no progression of the disease.

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