GIST: A CLINICOPATHOLOGICAL ANALYSIS OF 10 CASES

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Abstract- GISTs account for approximately 80% of gastrointestinal mesenchymal tumours. The literature about GIST remains confusing because tumour classification and terminology are continually refined. Furthermore, the exact definition of GIST varies among authors.

Mostly occur in the stomach and small intestine with rare occurrence in the rectum (5%), colon (1%), oesophagus and appendix. The diagnosis of GIST is currently based on morphologic features and immunohistochemical demonstration of KIT (CD 117). Early resection is treatment of choice. STI-571 (Imatinib), a KIT tyrosine kinase inhibitor has recently shown promise in the treatment of metastatic GISTs. The three key prognostic factors have been mitotic rate, tumour size and site. The five year survival rate declines and prognosis becomes poor with increase in the size and mitotic activity.

This article deals with the study of GIST at different sites with varied clinical, radiodiagnostic and histopathological findings, and treatment approach. We have analysed 10 different cases of GIST and have drawn possible conclusions.

Index Terms- GIST- mesenchymal tumours- clinical presentation- radiodiagnostic and histopathological findings- treatment

I. INTRODUCTION

Gastrointestinal stromal tumours (GISTs) initially presumed to be of "true" smooth muscle origin, encompass a heterogenous, and as yet incompletely understood, group of mesenchymal tumours with respect to their origin, cellular differentiation, and prognosis (1). GISTs include most tumours previously designated as leiomyoma, cellular leiomyoma, leiomyoblastoma and leiomyosarcoma (2).

GISTs are believed to originate from a mesenchymal stem cell that differentiates towards an Interstitial Cell of Cajal(ICC) phenotype .

GISTs are characterized with diverse clinical presentations, including acute and chronic gastrointestinal bleeding, abdominal pain, presence of an abdominal mass, anorexia and intestinal obstruction (3).

The diagnosis of GIST is currently based on morphologic features and immunohistochemical demonstration of KIT (CD 117). However, some tumours (approximately 4%) have clinicopathologic features of GIST but do not express KIT (4).
Complete surgical resection is the most important means of cure for GISTs (5). The advent of STI-571 (Imatinib) has markedly altered the clinical approach to GIST. It has proven to be effective in metastatic GIST and is also under investigation as a neoadjuvant and adjuvant therapy (6).

This study is a comparative analysis of 10 patients with GIST, managed over a period of last 8 years in our department. The presenting signs and symptoms, radiologic features, histopathological findings and treatment were evaluated.

II. MATERIAL AND METHODS

Ten patients having GIST were treated over a period of last 8 years in the Department of Surgery at Krishna Institute of Medical Sciences University, Karad. Age of the patients ranged from 35 to 72 years. Out of these ten patients, seven were men and three women. The authors analysed the clinical presentation, method of diagnosis, locations of the tumours, surgical treatment, histopathological findings, and postoperative outcomes.

III. RESULTS

Diagnosis was made with a combination of clinical findings, ultrasonography(USG), CT scan of abdomen, intraoperative findings, postoperative histopathological study and immunohistochemistry. Pain in abdomen was a common complaint accompanied with other complaints of either lump in abdomen or generalized weakness. Clinical presentation varied according to the site of GIST. For example, difficulty in defecation and per rectal bleeding for rectal GIST, where as lump in epigastrium for gastric GIST. One Patient presented with peritonitis due to perforation of rectosigmoid mass.

USG abdomen and pelvis in 5 patient's revealed rounded, heteroechoic, well defined, vascular, pedunculated mass with calcification in the body of stomach in case of gastric GIST. The one with GIST in the jejunum revealed heteroechoic mass from the small bowel in the hypogastrium likely to be malignant. Another one with GIST in the jejunum revealed similar findings with a mass of 8x5x4 cm arising from the small bowel with increased vascularity. The one with GIST in the rectum revealed bowel wall thickening involving sigmoid colon and rectum, suggestive of malignancy. And the one with proximal ileal GIST revealed a mass arising from proximal ileum about 10x8x5 cm located on the pelvic brim with heteroechogenecity.

CT scan of abdomen in 4 patient's revealed exophytic, cavitatory, mild to moderately enhancing growth communicating with the stomach posteriorly and involving left lobe of liver with jejunal loops, likely to be lymphoma of jejunum with secondary involvement of the stomach and left lobe of liver, in case of gastric GIST.

There was no lymphadenopathy or free fluid in the peritoneal cavity.Another CT scan in a patient with hepatic extra GIST revealed features suggestive of abscess of left lobe of liver rupturing through the inferior surface with a large extrahepatic component. CT scan was done in both the cases of retroperitoneal GIST. One of it revealed a solid tumour measuring 4x3.5x3 cm in the retroperitoneum between the abdominal aorta and inferior vena cava. It was compressing the pancreas but no definite invasion was seen. The another one revealed a 6.5x4.5x3 cm mass behind the right lobe of liver in the retroperitoneum, apart from the right adrenal gland.

UGI scopy and barium study was done in both the patients with gastric GIST and the findings correlated with those of either USG or CT scan of abdomen. Sigmoidoscopy with biopsy was carried out in case of rectal GIST.

Table 1: Comparison of clinical and radiodiagnostic findings of GIST at different sites:

Site	Clinical features	Radiodiagnostic findings
Sigmoid colon	-pain in abdomen -acute distension of abdomen -per abdomen= guarding, rigidity, liver dullness obliterated.	Emergency exploratory laparotomy was done with clinical diagnosis of hollow viscus perforation; erect chest Xray showing pneumoperitoneum.
Rectum	-bleeding per rectum -tenesmus -hard mass on PR examination	USG- bowel wall thickening involving sigmoid and rectum, 8cm long and 3.9cm thick, likely malignant.
Retroperitoneum, between the aorta and IVC	-pain in abdomen, intermittent, dull aching -per abdomen= mild tenderness in epigastrium	CT scan- solid tumour measuring 4x3.5x3 cm in the retroperitoneum between the abdominal aorta and IVC, compressing the pancreas
Jejunum	-pain in abdomen -loss of appetite -per abdomen= tenderness in epigastrium, umbilical region	USG- heteroechoic mass arising from the small bowel in hypogastric region, likely malignant.
Fundus, body of stomach	-generalised weakness -loss of appetite -bilateral pedal oedema	USG- rounded, heteroechoic, well defined, pedunculated, vascular mass with calcification, noted in the body of stomach
Jejunum	-umbilical discomfirt with pain in periumbilical region -per abdomen= tenderness at the umbilical region	USG- heteroechoic mass arising from the small bowel in the infraumbilical region, 8x5x4 cm, with increased vascularity.
Lesser curvature of stomach	-pain in abdomen -loss of appetite -generalised weakness -per abdomen= epigastric rounded, fixed, tender mass	CT scan- exophytic, cavitatory, moderately enhancing growth communicating with stomach posteriorly, involving left lobe of liver with thickened jejunal loops.
Retroperitoneum, behind the right lobe of liver	-pain in right upper abdomen, dull aching -per abdomen= tenderness in right hypochondrium	CT scan- a 6.5x4.5x3 cm mass behind the right lobe of liver in the retroperitoneum, apart from the right adrenal gland.
Proximal ileum	-pain in lower abdomen, intermittent, colicky -per abdomen= tenderness in hypogastrium	USG- mass arising from proximal ileum, 10x8x5 cm, located on the pelvic brim with heteroechogenecity.
Liver	-pain in abdomen -lump in abdomen -per abdomen= tender hepatomegaly	CT scan- hepatic abscess of left lobe rupturing through inferior surface with large extrahepatic component.

All 10 patients underwent exploratory laparotomy and lesion was primarily dealt with. Total excision of the tumour was possible in all cases except one which had GIST located in the lesser curvature of stomach with perforation into the lesser sac through

posterior gastric wall. The tumour was extending upto abdominal aorta posteriorly making it nonresectable. Debulking of the tumour was done with closure of perforation and feeding jejunostomy.

Table 2: Operative procedures performed for GIST at different sites:

Site	Exploratory laparotomy proceeds
Sigmoid colon	Wide excision of ruptured sigmoid colon diverticulum with primary end to end anastomosis with transverse loop colostomy.
Rectum	Abdomino-perineal resection with appendicectomy.
Retroperitoneum, between the aorta and IVC	Excision of the tumour
Jejunum	Excision of affected jejunal segment with end to end jejuno-jejunal anastomosis with appendicectomy with mesenteric lymph node biopsy.
Fundus, body of stomach	Left abdominothoracotomy with anterior gastrotomy with submucosal excision of polypoidal mass.
Jejunum	Excision of affected jejunal segment with end to end jejuno-jejunal anastomosis with appendicectomy with mesenteric lymph node biopsy.
Retroperitoneum, behind right lobe of liver	Excision of the tumour
Proximal ileum	Excision of affected ileal segment with end to end ileo-ileal anastomosis with appendicectomy with mesenteric lymph node biopsy.
Liver	Excision of the mass in the left lobe of liver.

Surprisingly, all tumours in 10 patient's were malignant GISTs including gastric GISTs in 2 patient, which are usually known to be benign, and hepatic extra GIST in one patient.

One of the gastric GIST was intramural and the other was extramural in 2 patient. There was increased cellularity, mixed cell type, with mitotic activity ≥ 5/50 high power fields (hpf), and presence of myxoid background. KIT (CD 117) and Smooth Muscle Actin (SMA) was detected in both the cases.

Small bowel GISTs in 3 patient's is grossly measured 5 to 8 cm in their largest dimensions. Two of them i.e. one jejunal and one ileal were intramural, while another jejunal was extramural. The tumours were relatively monotypic with spindle cells in majority; and epitheloid cells and mixed pattern at places. They had intermediate risk mitotic activity. KIT was detected in all 3 cases and SMA in both the cases of jejunal GISTs. Desmin was positive in ileal GIST.

The GISTs in retroperitoneum in 2 patient had a size of around 5 cm and more. Both were hypocellular, composed of spindle cells that were immunoreactive for vimentin and KIT. Sigmoid colon GIST was a mass measuring 15x10x5 cm forming a diverticulum with perforation in its wall. It was a cellular mesenchymal tumour composed of spindle cells with moderately pleomorphic nuclei and prominent nucleoli. Mitotic activity was 5-6/hpf. The cells expressed KIT and SMA strongly and diffusely.

Rectal GIST was an intramural highly cellular mass composed of spindle cell. They coexpressed CD34 and KIT. Hepatic extraGIST was a tumour measuring 8x6x4 cm in size with mixed cellularity of spindle and epitheloid cells. They coexpressed KIT and SMA.

Table 3:Comparison of site of occurrence, histopathology and immunohistochemistry:

Site	Histop[athology	Immunohistochemistry
Stomach	Increased cellularity, mixed cell type, mitotic activity ≥5/50 hpf, with myxoid background	KIT, SMA
Small bowel	Spindle cells in majority, with epitheloid cells and mixed pattern at places; low mitotic activity	KIT, SMA, Desmin
Retroperitoneum	Hypocellular tumours composed of spindle cells	KIT, Vimentin
Sigmoid colon	Composed of spindle cells with pleomorphic nuclei and prominent nucleoli, mitotic activity 5-6/50 hpf	KIT, SMA

Rectum	Highly cellular mass composed of spindle cells	KIT, CD34
Liver	Mixed cellularity of spindle cells and epitheloid cells	KIT, SMA

All the patients had a favourable postoperative period with primary healing of operative wounds except the one with GIST in the lesser curvature of stomach. Owing to her poor general condition and intraoperative findings of gastric perforation with extension of GIST to retroperitoneum, she succumbed on second postoperative day and expired. Rest of the patients were on complete parenteral regimen for the initial postoperative period. Gradually they were converted to solid diet and discharged.

Rehabilitation and appropriate dietary regimen were recommended. At regular check ups at our department and in the last 5years of follow up, 6 of these patients did not present with any signs of either disease recurrence or its dissemination. The one with hepatic extraGIST came with recurrence and multiple peritoneal deposits within 2 years of surgery. He is presently on Imatinib drug therapy and responding.

Thus till date, the patient with sigmoid GIST has a well functioning transverse loop colostomy and has been planned for its closure. Even the one with rectal GIST has a sigmoid end colostomy functioning optimally. Those with jejunal, ileal, gastric and retroperitoneal GISTs are all asymptomatic till date. All patients are receiving Imatinib with good compliance.

IV. CONCLUSION

This study shows a male preponderance in occurrence of GISTs. They have a peak incidence in persons aged 35 to 70 years, but have a broad distribution.

Clinically, these tumours have a wide spectrum at presentation. They range from incidentally detected, asymptomatic GISTs, to large malignant tumours, which frequently cause the patient to seek medical attention. The symptoms are as a result of their size or tendency to ulcerate and bleed. The most common presenting signs and symptoms include abdominal pain, gastrointestinal bleeding manifested by haematemesis or malena, and a palpable mass. Although these tumours rarely cause obstruction, they can perforate.

GISTs can exhibit one of the two growth patterns. In the endoenteric growth pattern, tumours tend to be submucosal or intramural; these are more likely to ulcerate early on, and bleeding typically leads to a relatively early diagnosis. An exophytic pattern is much slower, and the tumour is not found until a palpable mass or bleeding from excavation into the bowel lumen is noted.

The aim of radiodiagnostic examination is to locate GIST lesions, evaluate local invasion and detect distant metastases. The radiographic characteristics of GISTs mirror the gross appearance of these tumours. Unfortunately, these radiographic findings are nonspecific and represent several entities. Also, the distinction between benign and malignant GISTs cannot be made with radiologic examinations unless metastatic disease or tumour invasion of adjacent structures is depicted.

CT scan performed with both oral and intravenous contrast materials is ideal in defining endoluminal and exophytic extent of the tumour. Larger GISTs with necrosis appear as heterogenous masses with enhancing borders of variable thickness, and irregular central areas of fluid, air or oral contrast attenuation that reflect necrosis. The diagnosis can be suggested in the presence of a large, complex intestinal mass with liver lesions but without significant lymphadenopathy.

On sonograms, larger GISTs appear as complex masses with cystic and solid components. It is ideal for guided needle biopsy of known lesions.

Regardless of the location of GIST, barium enhanced images demonstrate predominantly intramural masses with potential exophytic components. The tumour margins usually are smooth, but with ulceration, some surface irregularity is present. As with other intramural masses, the tumour borders form right or obtuse angles with the adjacent visceral wall.

Histologically, these are spindle cells with varying cellularity, either spindled or epitheloid. The cells are arranged in whorled, fascicular, and palisaded patterns. In general, tumours invading the mucosa, tumour size, and mitotic rate are the most useful prognostic indicators. However, there is considerable variation and tumours arising in different sites of GI tract may behave differently despite similar histologies. Immunostains for CD117, CD34, desmins, actins, vimentin should be performed on these tumours. Immunohistochemical studies detect expression of these markers by tumour cells.

Surgical intervention aims at complete resection of the tumour. Even if the tumour is large and has spread into other organs, this may improve long term survival. Imatinib has led to a remarkable improvement in the treatment of GIST and may promise a longer lifespan as compared to those not taking the drug.

V. DISCUSSION

Recent breakthroughs regarding GISTs and their pathogenesis have redefined diagnostic criteria and have led to the development of molecularly targeted drug therapy. New treatment options mandate more accurate information regarding the incidence, prevalence, clinical behaviour and prognostic factors of GIST (7).

GISTs occur in the entire gastrointestinal(GI) tract and are the most common mesenchymal tumours of the GI tract 9-10. They range from small benign tumours to sarcomas at all sites of occurrence (8). A great majority of them occur in the stomach (60% to 70%) and small intestine (25% to 35%), with rare occurrence in the colon and rectum (5%), oesophagus (<2%) and appendix. Some GISTs are primary in the omentum, mesentry or retroperitoneum and are unrelated to the tubular GI tract (9).

GISTs are characterized with diverse clinical presentations, including acute and chronic GI bleeding, abdominal pain, presence of an intra-abdominal mass, anorexia and intestinal obstruction (3).

GISTs can be histologically identified as highly cellular spindle cell or epitheloid mesenchymal tumours and morphology is somewhat site dependent. However, common to all these

tumours is expression of KIT (CD 117 antigen), which is a major diagnostic criterion (9).

Endoscopic ultrasound guided fine needle aspiration biopsy (EUS-FNA) is considered to be a reliable and accurate method for the evaluation of submucosal lesions in the GI tract. When combined with cytologic and immunocytochemical studies, EUS-FNA is accurate and efficient in the diagnosis of GIST (10).

Although the prediction of malignancy in this group is notoriously difficult, tumours that have mitotic activity counts exceeding 5 per 50 high power fields (hpf) or those larger than 5cm have a high frequency of intra-abdominal recurrence and liver metastasis. In contrast, tumours smaller than 2cm and those with mitotic activity counts < 5 per 50 hpf are likely to be benign10. However, a small proportion of tumours apparently lacking mitotic activity do metastasize. Traditionally the 3 key prognostic factors have been mitotic rate, tumour size and site (8).

Accordingly, tumour size < 2cm and mitotic activity < 5/50 hpf are very low risk; tumour size 2-5 cm and mitotic activity < 5/50 hpf are low risk; tumour size < 5cm or 5-10 cm and mitotic activity 6-10/50 hpf or < 5/50 hpf respectively are intermediate risk; and tumour size > 5cm or of any size and mitotic activity > 5/50 hpf or > 10/50 hpf respectively are high risk (11). Benign GISTs outnumber malignant GISTs in the stomach, where as malignant GISTs are common in the intestines (8).

Complete surgical resection is the most important means of cure for GISTs (5). Aggressive surgical resection, achieving complete resection, can lead to prolongation of life and may be a potential cure for patients with GISTs (12).

A KIT tyrosine kinase inhibitor, STI-571 (Imatinib) has recently shown promise in the treatment of metastatic GISTs 9. It has proven to be effective in metastatic GISTs and is also under investigation as a neoadjuvant and adjuvant therapy (6).

5 year survival following surgical resection varies between 35% to 65% (13). For GISTs in oesophagus and stomach it is 70-75%, in small intestine it is 55% and in colon and rectum it is 60% (14).

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