*Original Article*

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# Gastro Instestional Stromal Tumours: Diversity of Presentitions and Treatment Protocols

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**Abstract**

*Introduction:* Gastrointestinal stromal tumors (GIST) are specific, C- Kit (CD117) - positive, mesenchymal tumors of the gastrointestinal tract which encompassing a majority of tumors, previously considered gastrointestinal smooth muscle tumors. Diagnosis is based on histological and immunohistochemical examination characterized by c-kit (CD117,CD34) staining. *Objective:* To present diversity of presentations of this disease and treatment protocols based on 4 variety of presentations in our case studies. *Materials and Methods:* We present an analysis of clinical presentation and course, surgical management and pathological features of 4 patients with gastrointestinal stromal tumors treated in our institution. *Result:* Our results confirm that in stromal tumors complete surgical resection remains the mainstay of treatment in localized gastrointestinal stromal tumors. *Discussion and conclusion:* Complete removal of the tumor is curative in localized tumours with no recurrence in 2 yrs follow up. In large lesions with metastasis c-kit targeted chemotherapy and surgery gives a better disease free stage.

**Keywords:** Gastrointestinal Tumours; Jejunal GIST; Chronic Intussusception; Imatinib; C-Kit; CD-117.

## Introduction

Gastrointestinal tumours are rare, but more and more cases are recongnized and treated successfully with surgery and tyrosine kinase inhibitors since 2005 [1,2,3,20]. They are believed to originate from interstitial cells of Cajal or related stem cells. These tumours are diagnosed by CECT and histologically confirmed by the Immunohistochemistry for CD117 and CD34. This article analyse clinical presentation and course, surgical management and pathological features of 4 patients with gastrointestinal stromal tumors treated in our institution. Our results confirm that in stromal tumors complete surgical resection remains the mainstay of treatment in localized gastrointestinal stromal tumors. Clinically, their behavior is difficult to predict, and mitotic count and tumor size seem to be the most effective prognostic factors. It is conceivable that treatment and prognosis of metastatic and non-resectable GISTs, as well as the adjuvant treatment of high-risk, radically excised GISTs will be strongly impacted by the c-kit target therapy.

GIST may be part of a genetic syndrome, but this is very rare. A genetic syndrome is a set of symptoms or conditions that occur together and is usually caused by abnormal genes. The following genetic syndromes have been linked to GIST:

1.Neurofibromatosis type 1 (NF1).

2. Carney triad. Carney triad was originally described in 1977 and consists of Gastric GIST, Extra adrenal paraganglioma, and pulmonary chondromas. The majority of patients are females under the age of 30 years. The GISTs tend to be gastric and lack c-kit or PDGFR1A mutations.

## Case Reports

*Case 1*

72 yr old male patient presented with abdominal pain, anemia and mass in the epigastrium. Upper GI

endoscopy revealed a smooth surfaced mass in the fundus extending to the luman of stomach. No ulceration was seen and mucosa appeared smooth.CT studies showed a smooth filling defect of the stomach giving impression of a leiomyoma.

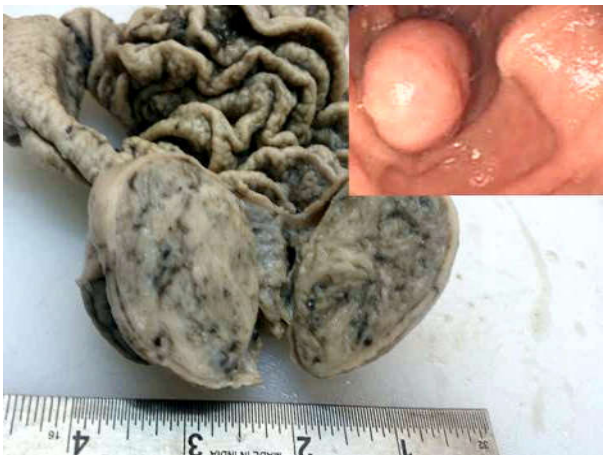

**Fig. 1:** Gastric GIST endoscopic view and specimen(fixed)

Laparotomy revealed a lobulated mass extending from the cardiac end. Partial gastrectomy done and the specimen studied with microscopy and IHC . The excised lesion was composed of areas of spindle and epithelioid cells, and immunohistochemical analysis showed positive staining withCD117, DOG1 and SMA.

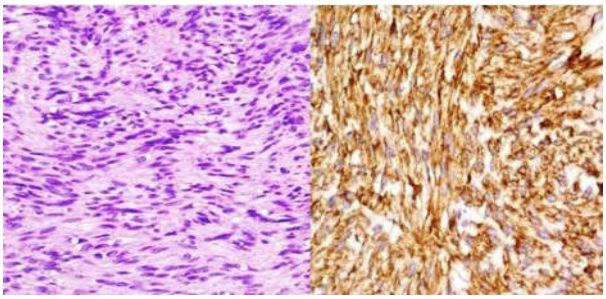

**Fig. 2:** Histopathological picture of GIST and Immuno-histochemistry

*Case 2*

48 yr old male patient presented with abdominal mass, anemia, malena. Clinical examination revealed a mass filling the epigastrium, umbilical and hypochodrial areas. Endoscopy could not see after the mid gastric area due to the mass effect. The duration of the symptoms was 1 yr. The CT showed a mass arising from the jejunum infiltrating the major vessels and extending superficially. CT guided biopsy was taken and it revealed spindlecellneoplasia and IHC showed positive CD117. Considering the inoperability patient was put on Imatinib with supportive care but expired in 3 months time.

*Case 3*

72 yr old female patient presented with features of recurrent bouts of bleeding with diarrohoea and weight loss. The patienthad features of small gut subacuteobstruction. Thecolonoscopy was normal. Upper GI endoscopy showed a bulging mass into the posterior wall of stomach without any mucosal changes.

CT showed a lobulated irregular lesion arising from the 2nd part of the jejunum and the vessels was not infiltrated. She had comorbidities of Coronary disease and Diabetes mellitus.Laparotomy revealed a lobulated reddish growth from the mid jejunum with small adhesion with the omentum. The tumour is resected with jejunum and end to end anastomosis done.

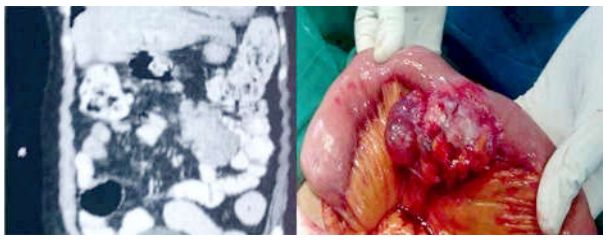

**Fig. 3:** CECT of the GIST of jejunum and specimen

The mass was more than 15 cms in size and mitotic figures were more than 15/HPF. The immuno-histochemistry revelaed positive CD117. Partially posititve for CD 37.

The patient on Imitanib and in the follow up period for 2 yrs.

*Case 4*

An adult chronic intussusception. 40 yrs old male patient presented with abdominal pain, diarrhea and bleeding perrectum of 1 month duration. He was investigated with ultrasound and it revealed an ileocolic intussusception. The CECT showed ileocolic intussusception with mass in the wall.

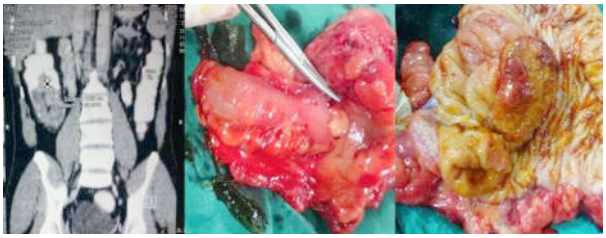

**Fig. 4:** CT, peroperative and specimen of Chronicintussuception due to GIST

Laparotomy revealed a chronic intussusception with ileocolictype and a well defined mass in the wall of caecumnear the leading end. Rt.

Hemicolectomy was done and the Histopathology and immunochemistry revealed GIST without metastasis to the nodes.

*Analysis*

All our patients with GISTs were adults over 40 years old. The incidence peak of diagnosis is 70 years. There is a slight male predominance and all the cases were from high altitude areas of Kerala, (Wayanad and Palakkad).

*Main Observations in our Cases were;*

1. Most of them had good general condition irrespective ofthe tumour. Feature of slow progressing intestinalobstruction was the presentation. All of them showed the features of Anemia. Post operative period was very smooth without complications.
2. Local resections with margin of 8-10 cms were made in all resected cases and the margins were free of tumour.
3. Distant metastasis were not seen in any case even though the tumour was very large and extending outside the jejunum in one case.
4. Depending on the prognostic criteria Imatinib is given.
5. A wide resection is the best option of treatment for GIST.
6. The number of cases diagnosed as GIST are on increase compared to earlier days probably due to Immunohistochemistry studies.

**Discussion**

Gastrointestinal stromal tumours (GISTs), first described by Mazur and Clark in 1983, are rare mesenchymal tumours of the alimentary tract . The vast majority of GISTs occur in a sporadic and isolated form, but can be features of multiple neoplastic syndromes. GISTs comprise 0.2% of gastrointestinal tumours and only 0.04% of small intestinal tumours. Jejunal GISTs are the rarest subtype. Only 10–30% progress to malignancy[1,2,3].

*Pathology*

The tumour originate from the stem cells that differentiate toward the pacemaker cell (Interstitial cell of Cajal) They are believed to result from activating mutations of proto-oncogenes c-KIT or platelet-derived growth factor receptor alpha polypeptide. These mutations increase tyrosine kinase receptor activity, resulting in uncontrolled proliferation of stem cells that differentiate into intestinal cells of Cajal . These cells are called pacemaker cells of the alimentary tract like that of Aurbachs plexus. Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. The recent pathological studies classify the gastrointestinal soft tissue neoplasms like leiomyomas, schwannomas, leiomyoblastomas, or leiomyosarcomas, are GISTs based on histology, immunohistochemistry, and molecular study. GIST vary greatly in size from a few millimeters to more than 30 cm, the median size being between 5 and 8 cm. Macroscopically, GIST usually has an exophytic growth and the common intra-operative appearance is that of a mass attached tothe stomach, projecting into the abdominal cavity and displacing other organs. Mucosal ulceration may be present at the summit of the lesion in 50% of cases. On gross appearance they are smooth gray and white tumors which are well circumscribed, usually with a pseudo-capsule. A small area of hemorrhage or cystic degeneration and necrosis may be visible. Gastric GISTs have a solid or nested form, often with a hyalinized stroma that shows myxoid change. GISTs in the small intestine are more often spindled than epithelioid and may show a paragangliomatous pattern. Another characteristic is the eosinophilic structures, composed of collagen, which are stained brightly with periodic acid-Schiff (PAS) stain. GISTs (> 95%) are positive for CD117. In 60%-70% of the patients, IHC for CD34 (mesenchymal/ hematopoietic precursor cell marker) is also positive. Vimentin and smooth muscle actin is positive in 15% to 60%. GISTs (10%-15%) have no detectable KIT or PDGFRA mutations [wild-type GIST (WT-GIST)]. Absence of mutations does not exclude the diagnosis of GIST. DOG1 is a calcium dependent, receptor activated chloride channel protein expressed in GIST; this expression is independent of mutation type and can be used in the diagnosis of KIT-negative tumors [5,6,20].

Immunohistological and pathological tests are diagnostic when results are combined. Immunohistochemical assay for CD117 antigen, an epitope of the KIT receptor tyrosine kinase, is the mainstay of diagnosis. Approximately 95% are positive for CD117 antigens. However, false-positive results may occur due to weak reactivity to other mesenchymal neoplasms. The morphology of jejunal GISTs is varied: tumours may be composed of spindle cells (70%), epithelioid cells (20%) or mixed spindle and epithelioid cells (10%). Similar histological

features may be seen with leiomyosarcomas and leiomyoblastomas. Definite diagnosis therefore relies on a combination of both immunohistochemical assay and morphological histology[7].

A 2002 study by Fletcher et al characterized the malignant potential of GISTs, and is widely cited. The two best predictors were tumor size and number of mitotic figures per high-power field, both of which demonstrated statistical significance [8].

*Proposed Approach for Defining Risk of Aggressive Behavior in Gastrointestinal Stromal Tumors, Namely Risk Factor, Tumour Size and Mitotic Figures*

| | | |
|---|---|---|
| Very low risk | <2cms | <5/50HPF |
| Low risk | 2-5cms | <5/50HPF |
| Intermediate | <5cms | 6-10/50HPF |
| | 5-10cms | <5/50HPF |
| High risk | >5cms | >5/HPF |
| | >10cms | Any Mitotic Rate |
| | Any Size | >10/50HPF |

*Clinical Manifestations*

Of the GIST gastric lesions are the commonest. Jejunal GISTs are very rare with 0.04% of all the GISTs and they are asymptomatic while small and may be diagnosed incidentally from CT, endoscopy, during surgery or from symptomatic liver metastases. Enlargement causes variable symptomatology; Only 70% of the patients with GIST are symptomatic. While 20% are asymptomatic and the tumors are detected incidentally, 10% of the lesions are detected only at autopsy. Symptoms and signs are not disease specific, they are related more to the site of the tumor. Bleeding (30%-40%) comprises the most common symptom after vague abdominal discomfort (60%-70%).

Bleeding is attributed to the erosion into the GIT lumen. Bleeding occurring into the peritoneal cavity due to a ruptured GIST can lead to acute abdominal pain presenting as a surgical emergency. Bleeding into the GI tract lumen, causing hematemesis, melena or anemia, is usually more chronic on presentation. Most of the patients present with vague symptoms, such as nausea, vomiting, abdominal discomfort, weight loss or early satiety [8,9]. Symptoms are usually site specific. These include dysphagia in the esophagus, biliary obstruction around the ampulla of Vater or even intussusception of the small bowel. Lymph node metastases are uncommon in GIST. Distant metastases most commonly occur in GISTs of the peritoneum, omentum, mesentery and the liver. GISTs have a high tendency to seed and hence intraperitoneal or even scar metastases are known to occur. GI bleeding or non-specific GI symptoms such as bloating or early satiety. Around 40% are associated with ulceration, and 28% presenting with overt GI bleeding. Bleeding may be acute (haematemesis or malaena) or chronic (anaemia). Around 20% grow large enough to present with pain, a palpable mass or obstruction secondary to intussusception [9,10,11].

*Investigations and Diagnosis*

Barium studies identify 80% of GISTs, capsule endoscopy81.1%, CT scans 87% and MRI scans close to 100% . Certain factors make diagnosis challenging. Exophytic growth with minimal or no luminal protrusion, which is common, makes endoscopic diagnosis difficult. Poor bowel filling and necrotic areas make GISTs difficult to visualize on CT and cyst degeneration may be misdiagnosed as abscesses or inflamed intestinal loops[9,12,13]. CECT in most of cases give evidence of the lesions and extend. MRI and SPECT are contributory and not diagnostic as such.

*Treatment of Gist*

Surgery is the primary treatment of choice in localized or potentially resectable GIST.While removing the tumour avoid rupture and spillage of cells. The tumors are fragile and should be handled with care, with an aim to achieve complete gross resection of the tumor with an intact pseudocapsule and a clearance margin of the bowel. Multivisceral and radical surgery should be avoided where ever possible. Segmental or wedge resection with an aim to obtain histologically negative margins is sufficient. Resection should be accomplished with minimal morbidity. Re-resection is not indicated for patients with an R1 resection. Lymphadenectomy is not required as GISTs have a low incidence of nodal metastases[14].

This is further treated with tyrosine inhibitors as adjuvant or post operative therapy.Imatinib mesylate is a tyrosine kinase inhibitor with activity against ABL, BCR-ABL, KIT, PDGFRA, PDGFRB and CSF1R. Its structure mimics adenosine triphosphate (ATP) and it binds competitively to the ATP binding site of the target kinases. This prevents substrate

phosphorylation and signaling, thereby inhibiting proliferation and survival. Patients with advanced GIST started on imatinib have shown a 35%-49% 9 year survival. The presence and the type of KIT or PDGFRA mutation status are predictive of response to imatinib. Exon 11 mutations occur in the KIT juxtamembrane domain and are the most common mutations in GISTs. Tumors with exon 11 mutations have better response rates to imatinib, with a longer progression free survival (PFS) and overall survival (OS). Exon 9 mutations occur in the KIT extracellular domain; these mutations are specific for intestinal GIST. Exon 9 mutations are associated with a decreased response to imatinib and a poorer PFS. There have been multiple trials testing the most appropriate dosing of imatinib. 400 mg/d has been found to have equivalent response rates and OS compared to higher doses, which are associated with more side effects. Indications for a higher dosing (800 mg/d) include patients with an exon 9 KIT mutation or those with tumors which continue to progress on the standard 400 mg/d dosage [14,15].

Complete resection is with a prognosis of 95% 5-year survival. For GISTs exceeding 10 cm, the National Cancer Institute recommends adjuvant imatinib [16]. Imatinib gives a 14% absolute reduction in recurrence rate, achieving 97% recurrence-free survival. Sunitinib is an approved second-line agent which is effective in many non-responders to imatinib therapy. Personalizing the treatment of GISTs and tailoring treatments to tumor genotype using combination therapies in order to prevent emergence of resistance is essential to optimize patient outcomes [17-20].

## Conclusion

GISTs are the most common mesenchymal tumors of the GI system. Improved knowledge of the oncogenic drivers and resistance mechanism operant in GIST has acted as a foundation for the general understanding of the role of targeted therapies in human cancers. Surgery is the primary treatment of choice in localized or potentially resectable GIST. Surgery and imatinib form the first-line therapy and their effectiveness for the majority of patients has been revolutionary.

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