



## Gastrointestinal Stromal Tumour of stomach –A case report and the Role of Imatinib

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### Case Report

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### Abstract

**Introduction:** Gastrointestinal Stromal tumour (GIST) is relatively an uncommon tumour, accounting for <1% of all gastrointestinal tract (GIT) tumours. Surgical resection for resectable cases remains the mainstay treatment. However, imatinib and most recently sunitinib has emerged as a vital care for locally advanced, recurrent or metastatic cases.

**Objective:** We are reporting our case due to its rare occurrence and to address the important role of imatinib in GISTs.

**Methods:** Report of a rare case.

**Results:** A 62 years-old man was referred to surgical department with haematemesis for 2 days. On examination patient was grossly anaemic with tachycardia and hypotension. Haemoglobin was 6.2gm%. Upper GI endoscopy showed a growth in the fundus of stomach with an ulcer in its center. Biopsy of the growth reported as GIST. CT scan abdomen reported as having a mass of 3x4 cm. in the fundus of the stomach without any other abnormalities. After resuscitation patient was subjected to proximal gastrectomy followed by gastro-oesophageal anastomoses.

Histopathological examination of the specimen reported as GIST of the stomach. Post operative period was uneventful and at the end of 4<sup>th</sup> year follow-up patient is disease free.

**Conclusion:** Haematemesis is a cardinal presentation of GIST of the stomach. Surgery alone is adequate for resectable GIST.

**Keywords:** Gastrointestinal Stromal tumour of GIT, Imatinib therapy

### Introduction

Gastrointestinal Stromal Tumour (GIST) accounts for < 1% of all GIT tumours.<sup>1</sup> Its occurrence in GIT is rare however; it is the most common mesenchymal neoplasm of the GIT. Incidence is reported as around 10-20 per million people, per year.<sup>1</sup> GISTs can arise from any part of the GIT but stomach is the most common site of involvement (50- 60%) followed by small intestine (30%-40%), colon and rectum (5% to 10%), oesophagus (5%) and rarely omentum, mesentery, gallbladder, pancreas, liver and urinary bladder also can involved.<sup>1</sup> In stomach GIST, commonly involved site is the body followed by cardia or fundus and antrum; multiple regions involvement are rarely seen.<sup>2</sup> Over 90% of GISTs occur in adults over 40 years old (median age of 63 years) with slight male gender predominance. However, there are no associations with geographic location, ethnicity, race or occupation in the occurrence of GISTs.<sup>1</sup>

### Case Review

A 62 years-old man was referred to surgical department with haematemesis for 2 days. He also had complaints of fullness of stomach with abdominal discomforts for last 2 months. He was a known hypertensive on antihypertensive medications. He was a chronic smoker. Family history was non contributory. On physical examination patient was grossly anaemic. Pulse rate was 102/min, low volume and blood pressure was 98/62 mm of Hg. Laboratory examination showed as haemoglobin- 6.2gm%, INR 1.1 and urea - 4.2mmol/l (3.2 – 8.2). Rest all routine examinations including chest X-ray were normal. Urgent upper GI endoscopy showed a growth in the fundus of stomach with an ulcer at the center but no active bleeding, no other pathology detected in the stomach (Fig-1). Endoscopic biopsy of the growth reported as GIST. CT scan abdomen reported as having a mass of 3x4 cm. in the fundus of the stomach without any other abnormalities.



After adequate resuscitation with parental fluid and 4 points of blood transfusion, confirming the diagnosis as haematemesis due to stomach GIST patient was subjected to proximal gastrectomy followed by gastro-oesophageal anastomoses with the help of a circular stapler. Histopathological examination of the specimen reported as GIST of the stomach. Post operative period was uneventful and at the end of 4<sup>th</sup> year follow-up patient is disease free.



Fig-1: Endoscopic view of the fundal GIST with the ulcer in its centre.

## Discussion

Exact cause of GIST is not clear. However, it is seen that there is an abnormality in the gene called *c-kit* of almost all cases of GIST.<sup>3</sup> Commonly it is believed that GIST initiates in the interstitial cells of Cajal (ICC) that is present in the wall of the GIT, or a primitive cell in the GIT which then can develop in to an ICC.<sup>3</sup> GIST cells strongly express two types of kinases- i) tyrosine kinase growth factor receptor c-KIT, which leads to the formation of a protein KIT called as cell-surface marker CD117 and ii) platelet derived growth factor receptor (PDGFR) similar to ICC.<sup>3,4</sup> This receptor (c-KIT) is activated by a growth factor termed as stem cell factor (SCF), which stimulates signal transduction pathways such as cell growth, differentiation and cell death. In most of the GISTs the KIT is abnormal and is always active, leading to unregulated cell proliferation and formation of malignant growth.<sup>1,5</sup> PDGFR also acts the similar way as c-KIT and cause unregulated cell proliferation. Almost 95% GISTs express KIT and 7% express (PDGFRA) usually in mutated forms.<sup>4</sup> These proteins (KIT & PDGFRA) act as enzymes called tyrosine kinase, which are important in the diagnosis and treatment of GIST.<sup>3</sup> These unique kinase mutations serve as targets for medical therapy which is

evidently the tyrosine kinase inhibitor, Imatinib.<sup>6,7</sup> The responsiveness of GISTs to treatment with imatinib varies substantially depending on the exonic location of the KIT or PDGFRA mutation.<sup>4</sup>

In the early stage, GIST can be asymptomatic. The clinical features of GISTs depend mainly on the size and location of the tumour. It includes abdominal mass, abdominal pain or discomfort, haematemesis, melaena, anaemia due to mucosal ulceration (Stomach GIST) and intestinal obstruction. Approximately half of the newly diagnosed are likely to present as metastatic or unresectable on the first presentation.<sup>3,4</sup> Diagnosis is best done by an immunohistochemical test for the presence of the CD 117 and on the basis of histological characteristics of the tumour biopsy which can be better obtained through endoscopy or endoscopic ultrasound-guided needle aspiration (EUS-FNA).<sup>3,8</sup>

In terms of treatment, complete surgical resection is the treatment of choice for people with GIST amenable to surgery. GISTs have been known to be typically resistant to standard sarcoma adjuvant chemotherapy and radiotherapy.<sup>6</sup> The development of imatinib has revolutionized the management for GISTs and is truly a medical marvel in the era of molecularly targeted therapy. Imatinib is a single-transduction inhibitor designed to selectively inhibit certain classes of tyrosine kinase that includes the c-KIT receptor expressed in most of the GISTs.<sup>3</sup> Imatinib binds to activated c-KIT receptor and blocks the cell signalling pathway to prevent uncontrolled cell proliferation. Recent development in pathology suggests that a small minority of GISTs that test negative for the c-KIT receptor may also respond to imatinib. However, it is currently still debatable.<sup>3</sup> Imatinib was first licensed for the treatment of chronic myeloid leukaemia. Imatinib received European marketing authorisation in May 2002 for the treatment of adult patients with KIT (CD117)-positive unresectable and /or metastatic malignant GISTs based on a single, uncontrolled phase II study in 147 patients (91% were c-KIT positive) with unresectable and /or metastatic GISTs.<sup>3,9</sup> The adjuvant role of imatinib has been clearly established through a study done by the American College of Surgeons Oncology Group (ACOSOG) whereby adjuvant imatinib therapy can help to significantly increase recurrence free survival at 1 year in patients with GIST following cytoreductive surgery.<sup>7,10</sup>

Based on data from a German Multicenter Trial, imatinib 400 mg/day lead to disease stabilisation in 81.6% of patients with unresectable or metastatic malignant GIST while 34% of patients attained a tumour remission (partial or complete response).<sup>11</sup>



However, the ideal duration of imatinib therapy is still unclear. Some guidelines have been established regarding the use of imatinib by National Institute for Clinical Excellence (NICE), UK (reviewed in October-2007) as follows:<sup>3</sup>

- 1) Oral Imatinib at a dose of 400mg/day to be taken with a glass of water at meal times.
- 2) Ideal candidate for first line therapy are with KIT (CD117) positive unresectable and/or metastatic GISTs
- 3) Initial therapy should be continued up to 12 weeks and then must evaluate the response.
- 4) Only if there is response to imatinib within 12 weeks of therapy, should continue till there is further evidence of disease progression or drug toxicity.
- 5) In neoadjuvant settings imatinib 400mg/daily should be given until unresectable tumours shrink to a resectable size.

The European Organization of Research and Treatment of Cancer (EORTC) 62024 and Scandinavian Sarcoma Group (SSG) Trial XVIII are two large ongoing studies in Europe to further evaluate to optimal duration of adjuvant imatinib as well as refining patient selection criteria.<sup>7</sup>

Till recent past, imatinib therapy was continued until there is disease progression or emergence of prohibitive toxicities in all pivotal trials.<sup>7</sup> Currently, the recommended adjuvant therapy is a daily dose of 400mg/day for 1 year, because up to 6-12 months time period is needed to achieve the maximum effects of imatinib therapy. However, the benefits of longer duration remain to be proven.<sup>9</sup> The dose can be increased up to 800mg/day for those patients that progress on with the early prescribed dose.<sup>6</sup> Van Glabbeke et al.<sup>12</sup> in a meta-analysis noted statistically significant progression-free survival benefit in the high-dose arm, approximately 23 months versus 19 months but no overall survival advantage. Serious adverse events were more common in the high-dose arm. Common side effects of imatinib like nausea, diarrhoea, eyelid oedema, peripheral oedema, muscle cramps and fatigue are mostly well tolerated.<sup>6,11</sup>

Imatinib is also used as neoadjuvant therapy for downsizing GIST to facilitate less extensive surgery especially for an initially unresectable tumour.<sup>9,10</sup> One of the main challenges in imatinib therapy in GIST was to evaluate the treatment response.<sup>12</sup> So far, Choi response criteria<sup>13</sup> are informative in assessing the imatinib response in terms of reduction of tumour size and density using CT scan or MRI scan. NICE stated that PET scan assessment of tumour metabolism at 1 week of imatinib therapy could provide early information on patient response to imatinib therapy.<sup>3</sup>

Prognosis of patients with GISTs mainly depends on the resectability of the tumours. Based on the current accepted risk stratification for GIST, the primary disease site together with tumour size and mitotic count provide a model for the risk of future recurrence following resection of localized disease.<sup>14</sup> Gastric GISTs have been proved to carry a better prognosis compared to other sites.<sup>3</sup> Metastatic or

unresectable GIST prognosis is very poor and hardly any patients survive beyond 5 years.<sup>3</sup> Any patient shows response to imatinib therapy carries a better prognosis in all aspects.<sup>3</sup> However, clinical efficacy of imatinib is limited by two concerns: rare development of drug intolerance by some patients and the fact that the majority of patients (up to 40%) will eventually develop treatment-refractory disease that is resistant to this form of selective Tyrosine Kinase Inhibitors.<sup>15</sup> Even, response to dose escalation is short-lived. Sunitinib has been approved worldwide as second-line therapy following failure of imatinib but the benefits are more often limited than first line therapy with the emergence of treatment resistant disease in less than a year.<sup>15</sup> Hence, the issue of management options in imatinib and sunitinib resistant GISTs has drawn tremendous interest with wide range of newer and more potent small molecule TKI that target KIT and/or PDGFR in development.<sup>7</sup>

## Conclusion

GIST is a rare variant of GIT tumours. Surgical resection still remains the mainstay treatment for GISTs. It is often not curative in advanced cases. In the past decade, Imatinib has emerged as a standard care for patients with locally advanced, recurrent or metastatic GISTs expressing KIT (CD117).

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#### **AUTHORS' CONTRIBUTIONS**

Authors contributed equally to all aspects of the study.

#### **PEER REVIEW**

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#### **CONFLICTS OF INTEREST**

The authors declare that they have no competing interests