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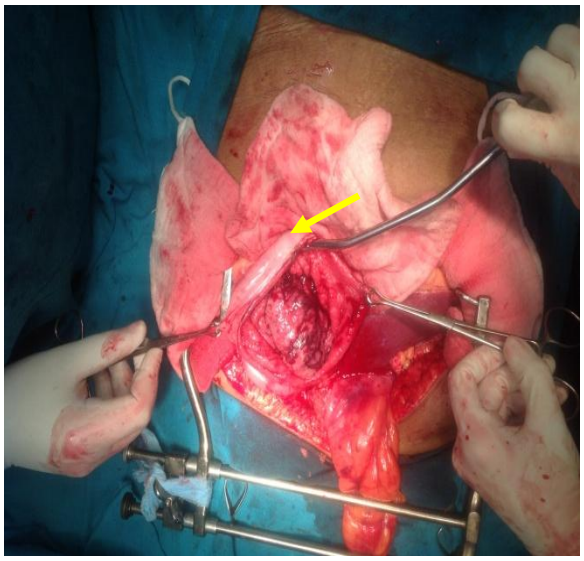
GIST: A Case Report with Historical Review and Recent Approach to Management

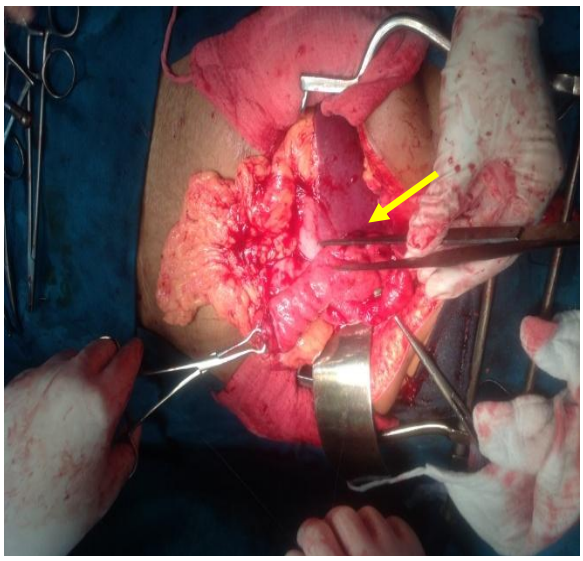
Dr Arunima Verma[1], Dr Sunil Kumar[2],
[1] *Associate Specialist Surgery, Tata Main Hospital, Jamshedpur*
[2] *Senior Specialist and HOD Surgery, Tata Main Hospital, Jamshedpur*

Case Report:

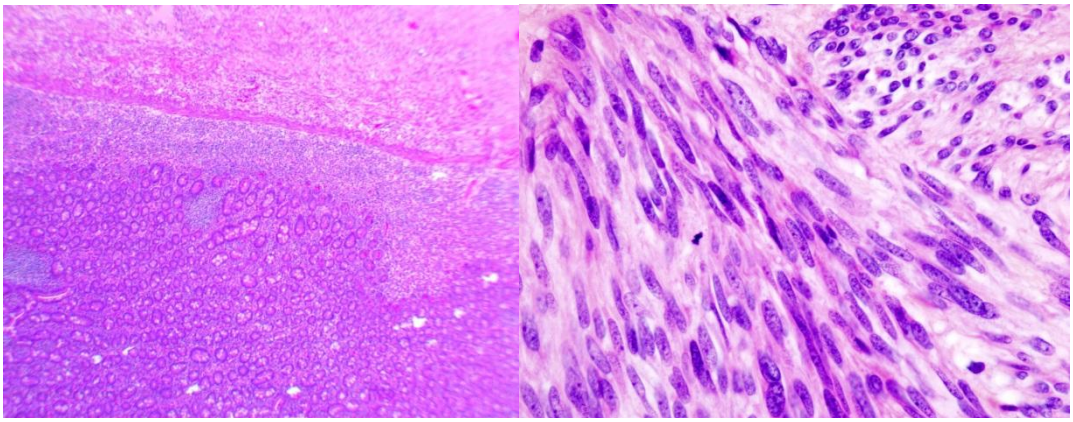
A 57 year female presented with complaints of pain abdomen with haematemesis off and on for one month and with loss of appetite and weakness for one week. She had no other comorbid illness. On examination she was average built, normal vitals and normal abdominal examination with minimal pallor. An ultrasound of abdomen was done which was reported normal. She then underwent upper gastrointestinal endoscopy in which a large cauliflower like growth was seen to arise from the fundus of stomach. Multiple endoscopic biopsies were taken and sent for histopathological examination which was reported as GIST with low malignant potential. A CT scan was done which showed growth in fundus of stomach and other intra- abdominal organs were reported to be normal. Patient underwent exploratory laparotomy with wide local excision of the gastric area having the tumour. On laparotomy, a fleshy mass was palpated in proximal stomach and rest of the intra-abdominal organs were found to be normal. Wide local excision of the gastric growth which was 6.5x6.5x4.5 cm (T3 according to TNM classification)was done taking approximately 2 cm margin of the normal stomach with view to have a R0 resection , and then the stomach repaired in two layers with a Ryle's tube in situ. The Ryle's tube was removed on the 8th Post-operative day and patient started taking orally and was discharged. The Histopathology reported malignant GIST with mitotic activity 2-3/ HPF and resected margins free of tumour. Immunohistochemistry showed CD117 positive tumour. Hence, the tumour was a high risk tumour with UICC stage IB (T3 and 2-3mitosis/ HPF of gastric GIST). Patient was started on Imatinib mesylate 400mg/day orally. Patient underwent UGIE and CT scan abdomen at 6 month interval twice, and both were found to be normal on both occasions. The patient is still on imatinib and is being monitored with CT scan abdomen and pelvis at 6 month interval.



Gastrostomy with GIST in fundus of stomach (Yellow arrow at growth)



Gastrostomy with resected margins for repair (Yellow arrow at Ryle's tube in situ)



Microscopic view showing proliferation of stromal cells and blood	HPF showing abnormal mitosis in stromal cells

I. Introduction

Gastrointestinal Stromal tumours (GIST) are the most common primary mesenchymal neoplasms of the Gastrointestinal tract[1]. GISTs may arise anywhere in the entire length of the tubular gastrointestinal tract from the esophagus to the anorectum, but the most common site is the stomach (40-50%) followed by the small intestine and associated mesentry (20-40%), esophagus (<5%) or colon and rectum(5-15%) [10].Omental, mesenteric and retroperitoneal tumours comprise less than 5% and are known as EGIST (Extragastrointestinal stromal tumours). In 1930s to 1950s, stromal tumours of the gastrointestinal tract were believed toarise from the smooth muscle origin and were classified as leiomyoma, leiomyosarcoma or leiomyoblastoma [2-4]. With the application of immunohistochemistry in 1980s, a subset of stromal tumours were found to stain positively for neural crest markers and were thought to arise from the gastrointestinal pacemaker cells, the interstitial cells of Cajal(ICC) [2-4, 5]. The term GIST was first introduced in 1983 by Mazur and Clark[6] to describe the non-epithelial tumours of the gastrointestinal tract that were thought to arise from the ICC.

GISTS are rare tumours, with an estimated incidence of 1.5/100,000/ year (unadjusted data) [7]. This incidence only covers the clinically relevant GISTs and the actual incidence is much higher because of the presence of minute lesions referred as stromal tumourlets [8] found in general population. Kindblom et al reported the annual incidence of gIST in Sweden to be 20 cases per million based on a retrospective study [9].

GIST occurs predominantly in the age between 40-60 years with median age being around 60 years. Gastric GISTs have been identified in patients ranging from 8 to 95 years of age. Occurance in children is rare, but paediatric GISTs represents a distinct subset. There is a slight male preponderance in adult patients with GIST but paediatric GIST is marked by female predominance [11,12]. The paediatric GISTs also are marked by the absence of KIT/ platelet derived growth factor alfa (PGDFRA) mutations, gastric multicentric location and possible lymph node metastases [13].

There are several syndromes which are associated with GISTs and they are:-

1. Type-I neurofibromatosis – linked to wild-type GISTs and are predominantly located at small bowel and are possibly multicentric[14].
2. Carney triad Syndrome – have gastric GISTs alonwith paraganglioma, pulmonary chondromas and may occur at any age [15].
3. Carney- Stratakis Syndrome – in this there is germ- line mutations of succinate dehydrogenase subunit B (SDHB), SDH subunit C(SDHC) and SDH subunit D (SDHD), which results in a dyad of GIST and paraganglioma [16,17].

In brief, four major disease categoties are seen to exist -

1. KIT mutated GISTs which arise at various anatomical sitesrepresent the bulk of the disease.
2. PDGFRA mutants which have a favourable outcome.
3. Paediatric Type (Carney type) GISTs developing in children or adults irrespective of the presence or absence of Carney triad seem to represent a distinct clinicopathological and molecular triad, and
4. NF-I associated GISTs which lack kinase mutations and tend to have a favourable course.

Pathology, classification and risk stratification:

All GISTs are thought to have malignant potential. Development of metastases is dependent on the degree of aggressiveness [18]. Histologically most GISTs are composed of spindle shaped cells (70%), others being dominated by epitheloid cells (10-20%) or a mixture of spindle and epitheloid morphologies (10-20%) [19]. Depending on the behavior, GISTs range from benign to malignant and are classified according to size and mitotic count as – very low risk, low risk, intermediate risk and high risk. Besides this classification, several alternative schemes have been proposed for the assessment of the malignant potentialin GIST. From the time GIST was identified as a separate entity, controversies regarding its malignant potential have existed. In the pre-KIT era, Franquemont et al used tumour size (<5cm vs ≥ 5cms), mitotic count (<5 vs ≥5/10 HPFs) and PCNA proliferative index (<10% vs ≥ 10%) to classify GIST into low and high risk subgroups, respectively [4,20]. In this system, all GISTs and true smooth muscle neoplasms were included, hence with emergence of KIT positivity, this system grading was not comparable to the later studies. The next system to be used was National Institute of Health (NIH) consensus criteria, so- called Fletcher's criteria which divided GIST into four risk groups based on size of tumour, 5cms being adopted as cut off value to define low vs non-low risk tumours. The drawback with this system was that the anatomic site of tumour and tumour- rupture was not taken into consideration [21,22,23].Taking anatomic site of tumour into consideration, Miettinen et al stratified GISTs into four risk groups – very low, low, moderate and high risk, as in NIH system with an addition of " benign tumours" that carried no risk of malignancy. This classification was based on a large series comprising more than 2000 GISTs from different anatomic sites. This is also known as the Armed Forces Institute of Pathology (AFIP) criteria [1,24,25]. On comparing the NIH and AFIP systems, NIH tends to overgrade the gastric tumours and down grades a subset of non-gastric tumours. The prognostic significance of anatomic site has been confirmed in other studies as well [23].

Gold et al proposed a normogram for estimation of the risk of tumour progression. In this system, the three criteria of anatomic site (gastric vs small intestine vs colon/ rectum vs extragastrointestinal), size (in a continuous non-linear fashion) and mitotic index (<5 vs ≥5 per 50 HPFs) were taken and points were assigned. The total of the points determined the 2- and 5- year recurrence free survival probability, however, this remains to be further analysed [26]. Revised NIH criteria proposed by Joensuu used NIH system as base and included the tumour rupture as a high risk factor irrespective of the tumour size and mitotic count [27].

Recently proposed UICC TNM system for classifying GIST is based on an urgent need for a standardized approach for histopathological evaluation and reporting of GIST with better risk stratification. However, it s usefulness still needs to be tested by various clinical studies. TNM has used four T-categories based solely on the basis of tumour size, and then combined with mitotic rate and tumour site to define Clinical UICC stage. Nodal metastasis is rare in GIST, hence pNx is not recommended and any patient who has not had regional lymph node examination is considered to be pN0. The presence of either a nodal or a distant metastasis makes the stage UICC IV.[30]

Despite the availability of so many risk stratification systems, the relevance of infiltration of subserosal fat or omentum/ mesentry, penetration of visceral peritoneum by tumour cells/ tumour rupture and the multiplicity of apparently primary tumours within the omentum/ mesentry still needs to be addressed. EGIST, is a predominantly extramural tumour localized to omentum / mesentry and the difference between EGIST and GIST needs to be defined. EGIST has been shown to have a poor outcome generally in few published series [28,29], but its risk stratification has not been addressed separately. Omental EGISTs have a better prognosis than those in mesenteric location. In a multivariate analysis by Ruiz- Tovar et al, the masculine gender , constitutional syndrome, abdominal mass at diagnosis, small bowel and retroperitoneal location and actin-negative tumours were reported as bad prognostic factors[37]. Also, high cellularity, mitotic activity(>2 mitoses/50 HPF) and presence of necrosis were significantly associated with an adverse outcome[29].

Management: The management of GIST needs a multidisciplinary treatment planning involving the pathologists, radiologists, surgeons and medical oncologists. Most of the patients with GIST are asymptomatic, but patients with advanced disease may present with symptoms of a mass lesion, abdominal pain or bleeding. 10-30% are detected incidently during laparotomy, endoscopy or other imaging studies and 15%-50% may present with overt metastatic disease [31]. All cases of GIST should have an evaluation of the anatomic extent of the lesion before operation. Most of the relapses affect the peritoneum and the liver and this is taken into account in staging the disease. Contrast enhanced computed tomography of the abdomen and pelvis is the invesgtigation of choice for staging and follow-up. Radiographic signs like calcification, ulceration, necrosis, cystic areas, fistula metastases, ascites and signs of infiltration correspond to aggressive malignant GIST. Other imaging modalities like MRI and contrast-enhanced ultrasound may be alternatives, especially , MRI is better in preoperative staging in cases of rectal GIST. In asymptomatic patients, staging work-up should include chest CT scan or X-ray. PET scan or FDG-PET-CT/ MRI maybe useful for early detection of tumour response to molecular targeted therapy which may help in planning the operative approach in patients with malignant metastatic disease [11,18]

Localized Disease:

Surgical resection is the standard treatment of choice for localized GIST with the aim of complete surgical excision, without lymph node dissection for clinically negative lymph nodes, as unlike intestinal adenocarcinoma, GIST rarely metastasize to lymph nodes[18]. A R0 resection is the goal, which means excision margin without tumour cells. A 1-2 cms marginwas advocated for acheivingadequate resectionmargin, though it may result in higher risk of peritoneal relapse[32]. Hence, when R0 surgery implies major functional sequelae, an informed decision can be made to have a R1 margin where excision margin contains tumour cells, specially in low risk lesions[11]. If R1 excision is carried out at the first attempt, the option of a repeat surgery to achieve R0 resection maybe considered, provided the original site of lesion can be found and major functional sequelae are not foreseen.

Considering the role of laparoscopy in GIST, it is a feasible option when used following the principles of oncologic surgery. Previously laparoscopic approach was advocated for Gastric GIST lesions upto 2cms but in the recent studies it has been found that laparoscopic and laparoendoscopic resection of Gastric GISTs of size upto 8.5cms results in low perioperative morbidity and effective long term control of disease. The applicability of laparoscopic approach should be based on a variety of factors including patient characteristics, tumour size, invasion and location as well as surgeon's experience and laparoscopic expertise[33].

For locoregionally advanced tumours requiring mutilating surgeries like total gastrectomyand other major procedures associated with significant morbidity, neoadjuvant treatment with imatinib mesylate is recommended with aims for cytoreduction. Patients are treated with imatinib 600mg/day for a period of 6-12 months prior to definitive surgery. There are limited data to guide the physician on when to stop imatinib before surgery; however, stopping imatinib 2-3 daysbefore surgery is considered safe and can again be started once the patient recovers from surgery. Imatinib given prior to surgery has the advantage of decreased risk of bleeding and tumour rupture. The response of imatinib is monitoredwith standard CT/ MRI pre- and 2month post-imatinib treatment, and is important as 10-15% of patients may be primarily refractory to imatinib and in them aggressive surgery would be needed. FDG- PET also is useful in rapid assessment of tumour response to imatinib and also there might be development of imatinib resistance in patients which would be diagnosed [34,35]

There is a substantial risk of relapse in patients of GIST which is defined by the risk classification systems. After operation, recurrence typically develops at the local site of resection, peritoneum and liver. Despite histopathological complete resection, tumour recurs in 40-90% [32,36]. Hence, adjuvant therapy with imatinib should be given in high risk groups, and a shared decision making is considered for the intermediate risk group, and not given in low risk group.Adjuvant therapy should be considered in patients in whom there has been spillage of tumour cells into the peritoneal cavity due to tumour rupture at the time of surgery. For this group the optimal duration of imatinib therapy is not known, but for high risk group, a three year standard treatment with imatinib is advocated.

Metastatic Disease:

Only 50% of GISTs are resectable at presentation and surgery to treat advanced or metastatic GIST is not recommended unless there is an immediate clinical need, such as to remove an obstructing tumour. For these patients, imatinib is the standard treatment in a dose of 400mg/day orally. In people whose disease progresses at this dose of imatinib, increasing the dose to 600 or 800mg/day is not recommended as per the NICE guidelines but studies have shown that the dose increase may result in partial or stable disease and better progression-free survival (PFS) in a small subgroup of patients.Treatment should be continued indefinitely in this group as interruption of treatment is generally followed by relatively rapid tumour progression [38].

Response of patient to imatinib is closely monitored throughout the treatment, but if the response of tumour is good and persists after five years of treatment, the risk of relapse is decreased and monitoring maybe relaxed from 3 months to 6 months. With good response, complete surgical excision of the residual metastatic disease when done, is related to good prognosis.

In patients who have intolerance to imatinib or the tumour progression continues, the second line treatment with sunitib should be considered. If this fails, the third line targeted therapy is with regorafenib.

Follow-up:

Since the impact of follow-up strategies on the clinical outcome in patients who have undergone GIST resection are not known, the most appropriate tests and the frequency for testing for metastatic or recurrence of disease are ill-defined. The follow-up schedules differ across institutions and are usually based on the risk status of the tumour. For example, a high risk tumour may be routinely followed up with CT or MRI every 3-6 months for 3 years while receiving the adjuvant therapy and again every 3 months for 2 years and 6 months until 5 years after stopping the adjuvant therapy. For additional five years, an annual CT/MRI may be done.

For the low risk tumours, every 6-12 months a CT/ MRI maybe done for 5 years. No routine follow-up is indicated in very low risk GIST as there is no added advantage [11].

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