

A CLINICOPATHOLOGIC AND IMMUNOHISTOCHEMICAL PROFILE OF GASTROINTESTINAL STROMAL TUMOURS (GIST)

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ABSTRACT

BACKGROUND

Gastrointestinal Stromal Tumours (GISTs) represent only 0.1-3% of all Gastrointestinal (GI) malignancies and account for 80% of gastrointestinal mesenchymal neoplasms. They range from incidentally detected asymptomatic GISTs to large malignant tumours. Three key prognostic factors have been mitotic rate, tumour size and site. Immunohistochemical testing for KIT (CD 117) and sometimes for DOG1 is essential in confirming the diagnosis.

The aim of the study is to bring forward the varied clinical presentation and our single centre experience for management and therapeutic outcome of GIST.

MATERIALS AND METHODS

15 patients with primary GIST diagnosed over a 3-year period from 2013 to 2016 were studied clinically and histopathologically; the treatment procedures and outcome were analysed.

RESULTS

The mean age of patients was 51.5yrs. with a male-female ratio of 2:1, abdomen pain (80%) was the most common symptom, stomach the most common site (60%), 95% of cases were CD 117 positive. Surgery was considered in 90% of patients and two cases were given neo-adjuvant therapy with imatinib.

CONCLUSION

GIST are the most common mesenchymal tumours of the gastrointestinal tract with an increasing incidence. They have a varied clinical presentation depending on the tumour location, size and growth pattern. The gold standard for treatment is surgical resection. Imatinib, a tyrosine kinase inhibitor, is the primary therapy for unresectable, recurrent or metastatic disease.

KEYWORDS

GIST, Contrast-Enhanced CT, CD-117, Imatinib Mesylate, IHC (Immunohistochemistry).

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BACKGROUND

Gastrointestinal Stromal Tumours (GISTs) are considered as the most common mesenchymal neoplasms of the gastrointestinal tract. Stromal tumours arising from the GI tract were initially classified as smooth muscle neoplasms including leiomyomas, leiomyoblastomas and leiomyosarcomas following description by Stout and colleagues in 1940.^{1,2} The term gastrointestinal stromal tumours was first described as a separate entity by Mazur and Clark in 1983.³ In 1998, Hirota and colleagues

discovered a specific mutation in the intracellular domain of the c-KIT proto-oncogene in GISTs as well as a near-universal expression of KIT protein in GISTs by immunohistochemistry and confirmed the origin of these tumours from Interstitial Cells of Cajal.⁴

The clinical behaviour of GIST is variable ranging from entirely benign to highly aggressive. Several factors can aid in the stratification of the risk of malignant behaviour for GIST including anatomical location, tumour size, mitotic activity and genotype. Approximately, 80% of GISTs harbour oncogenic mutations in KIT and 8-10% harbour oncogenic mutations in PDGFRA, which encode tyrosine kinase receptors. These advances led to the development of molecular targeted therapy for adjuvant and neo-adjuvant protocols using tyrosine kinase inhibitors like imatinib mesylate. These agents act by competing for the ATP binding site on the target kinase, inhibiting tyrosine kinase and reducing cellular proliferation.

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The advent of effective chemotherapy for GIST has altered, but not diminished the role of surgery, which remains the standard therapy for all resectable non-metastatic tumours.⁵ The reported resectability rate for localised primary GIST is 70-80%.⁶

MATERIALS AND METHODS

The present study was conducted over a period of three years (2013-2016) at Government Medical College, Thrissur. A total of 15 patients who were diagnosed with GIST at different sites with varied clinical, radiodiagnostic and histopathological findings were studied prospectively and retrospectively and followed up for a minimum of one year. Clinical and pathological data of each patient was recorded, laboratory and radiological workup done and the immunohistochemical profile was performed using CD117 and DOG1. The type of resection performed was classified as R0, if there was no residual disease or microscopic involvement of surgical resection; R1 when there was residual disease; and R2 when there was macroscopic residual disease. Histopathological assessment of the tumours was done and they were categorised as low, intermediate and high risk. Neo-adjuvant therapy with imatinib was initiated in necessary cases.

RESULTS

Fifteen cases of GIST were studied over a period of three years (2013 to 2016). Of these, 10 were males and 5 females. The age of the patients ranged from 41 to 70 years. The mean age was found to be 51.5 years (Table 1).

Patients presented with abdominal mass, bleeding episodes, abdominal pain and intestinal obstruction. A rare presentation of bilateral deep vein thrombosis due to compression of common iliac veins by a giant jejunal GIST was also seen (Table 2).

The locations of the tumours in the gastrointestinal tract were as follows- stomach 60%, jejunum 20%, duodenojejunal flexure 6%, ascending colon 6% and rectum 6%.

Ultrasound abdomen and contrast-enhanced CT was taken in all cases (Figure 1). In two cases, Tru-cut biopsy from secondaries in liver were taken and these two patients were given neoadjuvant therapy with imatinib.

Upper GI endoscopy was done in 9 cases and the findings were-

- Bulge into lumen - 5 cases.
- No bulge/ulcer in mucosa - 4 cases.

Colonoscopy was done in 2 cases, which showed the lesion and the exact site was assessed.

Tumours were divided into three risk categories based on histology - low, intermediate and high. The total number of tumours in each category were- 8 in the high-risk group (53%), 4 in the intermediate (27%) and 3 in the low-risk group (20%).

Immunohistochemically, 14 cases showed positivity for CD117 and one case where CD117 was negative IHC showed DOG1 positivity (Figure 2).

Two cases were treated with neoadjuvant imatinib for disseminated lesion.

Age Group (Yrs.)	Number of Cases
41-50	2
51-60	8
61-70	5

Table 1. Age Distribution of Patients

Presentation	Number
Abdomen pain	12
Abdomen mass	11
Obstruction	4
Bleeding	6
Deep vein thrombosis	1

Table 2. Clinical Presentation of Cases

Procedure	Number
Wide excision stomach	6
Subtotal gastrectomy	2
Total gastrectomy	1
Jejunaresection	3
Right hemicolectomy	1
Anterior resection	1
Duodenojejunalflexure resection	1

Table 3. Operative Procedures Followed

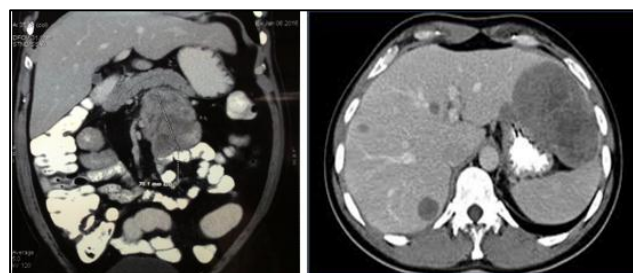


Figure (a) Figure (b)
Figure 1. CT Showing GIST in (a) Small Bowel (b) Stomach

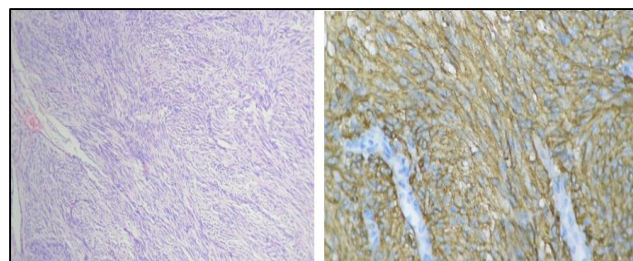


Figure (a) Figure (b)
Figure 2. H and E Section Showing GIST of Spindle Cell Variety (a); IHC Showing Positivity with CD117 (b)

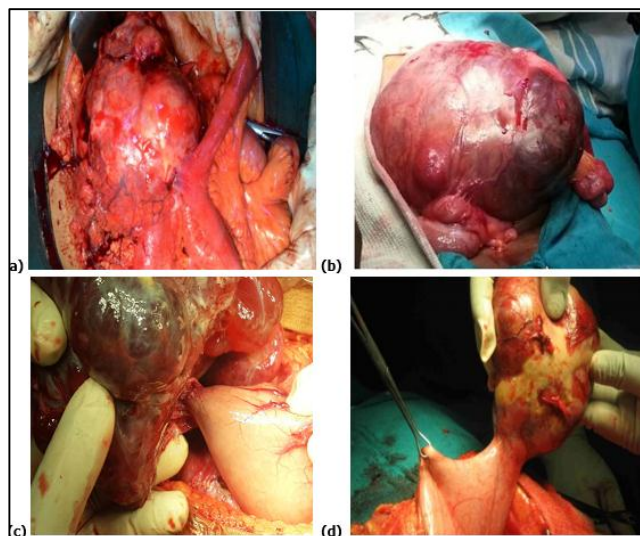


Figure 3. GIST Small Bowel (a, b); Stomach (c, d)

DISCUSSION

Gastrointestinal stromal tumours are typically diagnosed in people between 60 and 70 years old. Although, case reports of paediatric GIST do exist, occurrence before age 30 is extremely rare. Most studies report no gender differences.^{7,8} Age distribution in our study shows the most common occurrence in the fourth and fifth decades of life. This series shows a male predilection with a male:female ratio of 2:1.

The majority (63%) of GIST are found based on the patient's symptoms, although about a third can be found incidentally during abdominal imaging, endoscopy or surgery. GIST most commonly occur in the stomach (50-60%), less frequently in the small bowel (20-40%) and rarely (10%) in the rectum.⁹

The clinical presentation of GIST is highly variable and depends on tumour location, size and growth pattern. Small GIST, generally less than 2 cm, rarely cause symptoms and are most frequently discovered incidentally by endoscopy or radiological imaging.¹⁰ Lau et al reported that 22% of GIST are found incidentally.¹¹ On endoscopy, a submucosal bulge is identified with overlying normal mucosa if no ulcers have occurred. Most common symptoms recorded in the present study was abdomen pain (78%) followed by abdomen mass and bleeding episodes. Most common site was stomach (60%). We had a rare site of presentation in the duodenojejunal flexure. Initial imaging investigation was ultrasound. Contrast-enhanced CT was done in all cases to assess the site of tumour and involvement of the adjacent structures.

GISTs vary greatly in size ranging from <1cm to more than 30 cm. In this study, the tumour size ranged from 5cm to as massive as 11cm (Figure 3).

Upper GI endoscopy was done in 9 cases out of which 6 cases showed lumen bulge. Colonoscopy was done in 2 cases to assess the distance from anal verge.

Liver Tru-cut biopsy was taken in two cases where hepatic metastasis was present and these two patients were given neoadjuvant therapy with imatinib.

The current treatment of patients with GIST requires a multidisciplinary team including a medical and surgical oncologist. Surgery is the mainstay therapy for GIST with a primary goal of complete resection with negative tumour cell margins and preservation of an intact capsule to avoid tumour rupture or haemorrhage.

Wide excision of stomach was the most common procedure done in the present study (Table 3).

GISTs should be handled with care to avoid tumour rupture. Since the tumour does not show an infiltrative pattern of spread, a margin of 1cm is considered sufficient.⁶ It is important to send an intact specimen as macroscopic size of the lesion and presence of necrosis are major prognostic factors determining the risk categories of the lesions.

The diagnosis of GIST is confirmed histologically and by immunohistochemical staining techniques. Histologically, these tumours fall into one of three cell types- spindle cell (70%), epithelioid (20%) or mixed (10%). Assessment of the malignant potential of a primary GIST lesion is important. Tumour size (with threshold levels of 2 cm, 5 cm and 10 cm) and mitotic index are common features used to assess prognosis. 53% patients in our study were categorised in the high-risk category based on histological parameters, which include mitotic index and cellular atypia.

Tumour site is also considered an important independent prognostic indicator. Studies have shown that patients with small bowel GIST have a higher rate of recurrence than those with gastric tumours. There are also differences in the rate of disease progression based on location in the stomach.¹² The most significant is the higher frequency of malignant behaviour for GIST located in the gastric fundus and at the gastroesophageal junction-cardia region compared with the antrum.

Hirota et al first proposed a gain-of-function mutation in the c-KIT proto-oncogene, which is found in most GIST.⁴ The epitope of the c-KIT protein (its antigenic determinant), is the CD117 antigen. CD117 is expressed in virtually all (approximately 95%) GIST, both spindle and epithelioid types and is absent in other tumours such as leiomyomas and schwannomas.¹⁴ cases in the present study showed positivity for CD117 and one case where CD117 was negative IHC showed DOG1 positivity.

Standard cytotoxic chemotherapy is not effective in treating GIST.¹³ With the introduction of Tyrosine Kinase Inhibitors (TKI), there has been a dramatic increase in survival. Currently, the standard of care is imatinib at 400 mg daily for advanced GIST with an increase in dose to 800 mg daily for patients with disease progression or those with an exon 9 KIT mutation.¹⁴

Sunitinib malate (Sutent, Pfizer Inc., New York, NY, USA) is a second-line TKI used for patients with imatinib intolerance or resistance. In our study, all patients except 2 were given imatinib. Follow up was based on abdomen examination and ultrasound once in every six months.

In this 3 year follow up period, there were 2 mortalities. Recurrence of the disease was seen in 3 cases that were initially in the high-risk category. For these patients, our

oncology department had started sunitinib as a second line drug.

CONCLUSION

GISTs have received much attention for many reasons. The rapid expansion of molecular and clinicopathological knowledge of GIST has given this disease a promising future.

Our series is based on 15 patients focusing on our initial experiences with GIST. The age distribution coincides with the international literature, but there is a predilection for males. The study could infer that lesions >5cm definitely have a higher chance of recurrence, irrespective of the risk categorisation.

Local resection with 1-2cm margin with the aim of organ preservation should be the principle of surgical treatment. IHC should be done routinely while assessing specimens of GIST, not only because it is the hallmark of diagnosis, but also an important predictive factor. Though the study period was short, our study recommends the use of imatinib in the adjuvant setting in high-risk, recurrent and metastatic settings.

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