

## Research Article

# Our experience with gastrointestinal stromal tumors over a period of three years from a tertiary care centre

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### ABSTRACT

**Background:** Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract (GIT). Stomach being the commonest site in the GIT, it can occur in the extra-intestinal areas like mesentery, retroperitoneum, omentum and prostate. Exceptionally rare in urinary bladder. Commonly present as solid tumors but cystic degeneration can occur in large tumors especially in extra intestinal regions and may be mistaken for ovarian tumors. We have studied GISTs for a period of 3 years and presenting certain rare entities we encountered. Aim of the study was to study the age and sex prevalence and relative distribution of GISTs in gastrointestinal and extra gastrointestinal (EGIST) areas in various sites, and morphological features in relation to certain rare variants.

**Methods:** 18 surgical resected specimens of gastrointestinal and extra gastrointestinal masses received at the department of pathology, Andhra Medical College, Visakhapatnam, were studied for a period of 3 years from July 2013 to June 2016.

**Results:** GISTs were found to be common in male patients with male to female ratio of 2:1. GISTs of Small bowel showed female predilection. 40% of EGISTs were of larger size and malignant.

**Conclusions:** Age, sex and morphological features were consistent with literature. Small intestine showed slightly increased prevalence when compared to stomach and large intestine. Tumor size and mitotic count were predictors of outcome. EGISTs showed higher incidence in women and pelvic GISTs have to be carefully evaluated to differentiate them from ovarian tumors.

**Keywords:** GIST, EGIST, Cystic change, Mitoses

### INTRODUCTION

Gastrointestinal stromal tumors are rare tumours of the GIT accounting for 0.1% but constitute most common of the mesenchymal tumors and 5.7% among the Gastro intestinal sarcomas.<sup>1</sup> They arise anywhere in the gastro intestinal tract from the intestinal cells of Cajal with germline mutation of c-kit which is CD117 positive. Stomach is the commonest site.<sup>2</sup> GISTs arise most often from the stomach (60%-70%), followed by small intestine (20%-25%), but rarely from the rectum (5%), esophagus, colon or appendix.<sup>3</sup> They may also occur in the extra intestinal location like mesentery, omentum and

exceptionally rare sites like gallbladder, urinary bladder and prostate.<sup>4</sup> They can occur at any age but uncommon before 20 years. Show male preponderance and about 90% of cases occur in more than 40 years age in both sexes.<sup>5</sup>

#### *Aims and objectives*

To study the age and sex prevalence and relative distribution of GISTs in gastrointestinal and extra gastrointestinal (EGIST) areas in various sites, and morphological features in relation to certain rare variants

**METHODS**

Surgical resected specimens of gastrointestinal and extra gastrointestinal masses received at the department of Pathology, Andhra Medical College, Visakhapatnam for a period of 3 years from July 2013 to June 2016 were studied along with relevant clinical details. A total of 18 cases were studied. Specimens received were thoroughly sampled, processed and sections prepared were studied. Immunohistochemistry was done in cases where there was a diagnostic dilemma.

According to Fletcher et al tumors were classified into very low, low, intermediate and high risk, categories according to tumor size and mitotic count.<sup>5</sup> Tumors <2 cm and mitotic count <5/50 high power field (HPF) were categorized as very low risk; tumor size 2–5 cm and mitotic count <5/50 HPF as low risk; tumor size <5 cm and mitotic count 6-10/50 HPF or tumor size 5-10 cm and mitotic count <5/50 HPF as intermediate risk; tumor size >5 cm and mitotic count >5/50 HPF or tumor size >10 cm and any mitotic rate or tumor any size and mitotic rate >10/50 HPF as high risk.<sup>5</sup> Tumors of the very low risk and low risk were considered as benign and intermediate respectively and high risk as malignant.

**RESULTS**

Total of 18 cases of gastrointestinal stromal tumors were studied, of these 18 cases, 12 were males and 6 were females with a male to female ratio of 2:1. Age of the patients ranged from 33-65 years with maximum number of cases noticed between 50-60 years (Table 1). Commonest clinical complaint was pain abdomen followed by acute intestinal obstruction and mass abdomen in 3 cases and bleeding P/R in 2 cases. Of these 18 cases GIST from stomach and colon were 4 each (22% each) and 5 from small intestine (28%). Extra intestinal GISTS were 5 in number (28%) of which 2 cases were

recorded in mesentery presenting as cystic masses and the remaining 3 cases, one case presented in urinary bladder, one in the pelvis mimicking an ovarian tumor and the third one in retroperitoneum. All the gastric GISTS of colon and stomach were noticed in men and among the small bowel GISTS, 3 cases were noticed in females and 2 in males. Among the extra gastrointestinal GISTS (EGIST) 3 cases were diagnosed in women and 2 in men. Size of the tumors ranged from a very small tumor of 2 cms to a large tumor of 18 cms. Small tumors were solid whereas the large tumors were solid to cystic (Table 2). One pelvic mass showing thin walled cystic appearance totally (Figure 1). Necrotic areas with variegated appearance were observed in 6 cases (Figure 2). Microscopic appearance of the tumors ranged from benign to malignant. Low grade GISTS were less than 5 cms except 2 cases in the pelvic region were 10-18cms size. Out of the 18 cases 10 were very low to low risk group showing circumscribed tumor with spindle cells in sheets and bundles with focal nested pattern showing no mitotic activity or mitotic activity <5/50 HPF (Figure 3,4). 7 were malignant and high risk with >10/50 HPF, 1 was of intermediate risk >5/50 HPF. Among the 7 cases that were diagnosed as high risk GISTS (Figure 5,6) showing increased cellularity, areas of necrosis and mitotic activity (Table 3), 2 cases were noticed in colon, 2 cases in small intestine, 1 in stomach, and two were mesenteric cysts of which one case is totally cystic. One of the EGIST which was originating from the urinary bladder showed extension up to the serosa of large bowel but showed no extension into the bowel wall. Microscopically it was more like a leiomyoma with solid whorling pattern. One case of cystic pelvic tumor was diagnosed as ovarian tumor on ultrasound but peroperative findings showed no connection to the ovary. Microscopic examination showed a benign cystic tumor with nesting pattern resembling a paraganglioma. DDs given were cystic paraganglioma and cystic EGIST. Immunohistochemical profile with positive CD117 staining confirmed the diagnosis (Figure 5).

**Table 1: Age, sex distribution, size and location of GISTS.**

	No of cases	%	Male	Female	Size cms
Stomach	4	22%	4	0	2-9
Small bowel	5	28%	2	3	3-10
Large bowel	4	22%	2	2	2-18
<b>Extra GIST</b>					
Mesenteric cysts	2	28%	2	0	4-18
Retroperitoneal	2		0	2	10-15
Urinary bladder	1		0	1	10

**Table 2: Gross morphology of GISTS.**

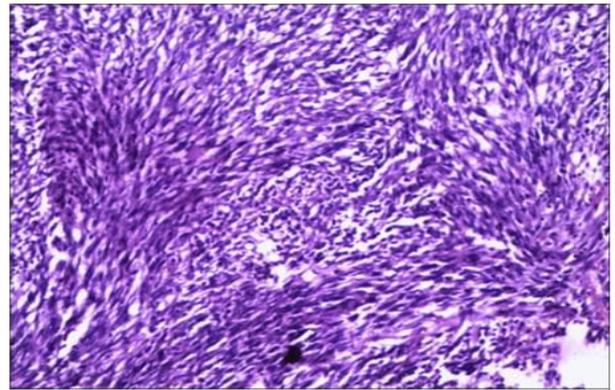
Gross	GIST			EGIST		
	Stomach	Small intestine	Large intestine	Mesenteric cyst	Retroperitoneal	Urinary bladder
Solid	4	4	2	1	1	1
Cystic	0	1	2	1	1	0

**Table 3: Microscopic grading of GISTs.**

Risk	GIST			EGIST		
	Stomach	Small intestine	Large intestine	Mesenteric cyst	Retroperitoneal	Urinary bladder
Very-low	2	2	1	0	2	0
Low risk	1	0	1	0	0	1
Int grade	0	1	0	0	0	0
High risk	1	2	2	2	0	0



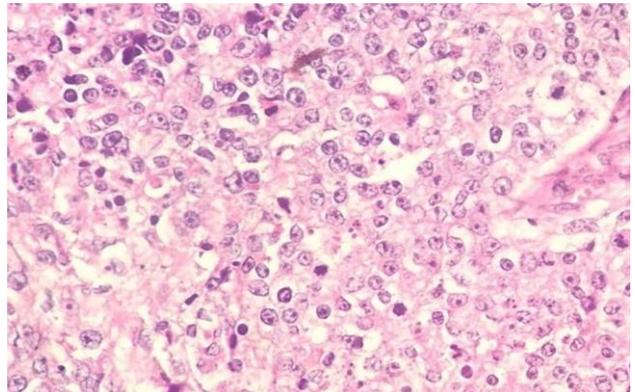
**Figure 1: Gross picture of benign cystic GIST.**



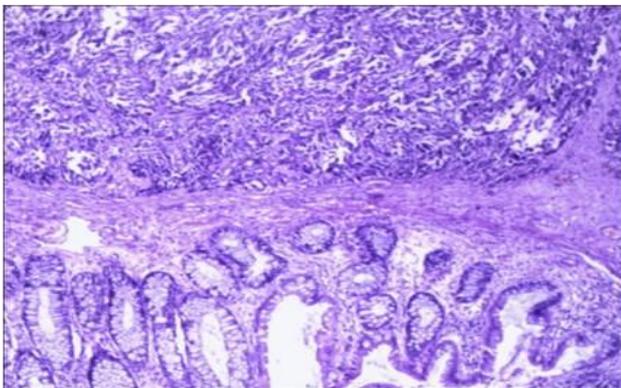
**Figure 4: Bundles and fascicles of benign spindle cells with no mitotic activity, H and E stain (100x).**



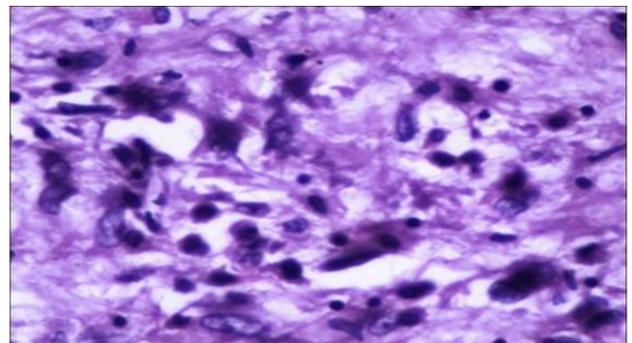
**Figure 2: Gross picture of malignant GIST showing necrosis and haemorrhage.**



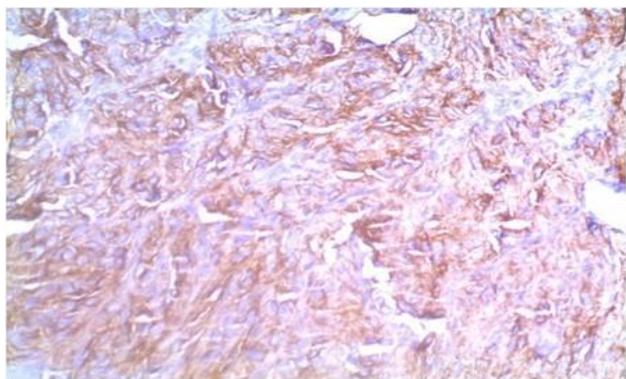
**Figure 5: Malignant GIST with epithelioid cells plump cells with high mitotic activity, H and E stain (100x).**



**Figure 3: Sub mucosal tumor with benign spindle cells, H and E stain (100x).**



**Figure 6: Malignant GIST with nuclear pleomorphism, tumor giant cells and mitotic figures H and E stain (400x).**



**Figure 7: CD117 immunostaining positivity in tumor cells 100x.**

## DISCUSSION

GISTs can arise anywhere in the tubular GIT with male preponderance, common age at occurrence is above 40 years and commonest location is stomach.<sup>6</sup> We recorded a male to female ratio of 2:1 but in the EGISTs the ratio was 1:1.5 with slight female preponderance and all the cases were recorded in age group of  $\geq 30$  years. Stomach was not the common site in our study as it was recorded in the literature, the cause may be the small sample size.

Tumors may range in size and small tumors are usually benign. Numerous studies have attempted to delineate criteria to distinguish benign GIST from malignant GIST and it was found that tumor size and mitotic rate most consistently are the strongest predictors.<sup>7</sup> In our study correlation was found between the size of the tumor and biological behaviour with almost all small tumors showed benign nature except in one case of small intestinal GIST which on microscopy showed malignant features though the tumor was  $< 3$  cms size. Mostly GISTs are solid. Large tumors may be cystic because of necrosis in malignant tumors. Diagnostic difficulty may arise in cystic tumors of pelvic region giving confusion for ovarian tumors.<sup>8</sup> We faced that difficulty with one case which was considered as an ovarian tumor sonologically and preoperatively. But microscopic examination and immune histo-chemical study confirmed the diagnosis of EGIST. According to Miettinen M et al benign behaviour is common in gastric GISTs where the benign tumors outnumber malignant ones by a ratio of 3-5:1 and 20-25% of gastric GISTs and 40-50% of small intestinal GISTs are malignant.<sup>9</sup> We found that the ratio of benign to malignant gastric GISTs in our study was less with 1.25:1. Gastric GISTs showed 75% of benign cases and 25% of malignant cases (3:1) and small intestinal GISTs 40% of benign cases and 60% of malignant cases (2:3) which is slightly more when compared to Miettinen M et al.

Extragastrintestinal Stromal Tumors (EGISTs) are a rarely reported group of tumors that arise outside the GI tract but histologically resemble their GI counterpart.<sup>9</sup> Goh et al, suggested that most, if not all, cases of EGISTs

are likely to represent mural GISTs with extensive extramural growth with eventual loss of contact with the muscle layer of the gut.<sup>10</sup> Approximately 80% are located in the omentum or mesentery and the remainder develop in the retroperitoneum rarely from gallbladder and urinary bladder.<sup>4</sup> Gross appearance of EGISTs varies from firm, fleshy gray-red masses to cystic ones. They lack the whorled appearance of the conventional smooth muscle tumors. Cystic change is seen in majority, associated with extensive hemorrhage or necrosis.<sup>11</sup> A high index of suspicion of GIST should be kept in mind for a large cystic abdominal mass presenting preoperatively with intraoperative cystic fluid content.<sup>12</sup>

Study of AK Chowhan et al showed most of the cases that were more than 10 cm in size and exhibited cystic changes. Reath et al opined that EGISTs with high cellularity, more than 2 mitotic figures per 50 HPF and any amount of coagulative necrosis are more likely to metastasize.

Our study of EGISTs showed 40% mesenteric cysts, 40% tumors of retroperitoneum and 20% from the urinary bladder. Occurrence of GIST in urinary bladder is very uncommon and was rarely described in the literature. Our case showed tumor abutting the muscle coat of urinary bladder but no infiltration into it and no extension to the large bowel. IHC confirmed the diagnosis. 3 out of 5 cases of EGISTs were reported in women with a mean age of 38 years with clinical and sonological suspicion of ovarian cysts. The main differential histopathological diagnoses which were considered in EGISTs were fibromatosis, smooth muscle tumors, neural tumors and malignant fibrous histiocytomas (MFH).<sup>5</sup> The distinction from fibromatosis can be made mainly based on histopathology findings. In fibromatosis cellularity is low and it is composed of spindle cells within a collagenous stroma. Necrosis and mitotic activity is not seen in fibromatosis. Smooth muscle tumors and neural tumors are differentiated from EGISTs on the basis of both morphology and immunohistochemistry. These cases are to be thoroughly sampled to differentiate them from ovarian tumors. In our cases no other masses were found in the GIT along with these tumors ruling out the possibility of metastasis. Positive immune histochemical staining for CD117 is a defining feature of GISTs and in our cases it helped in establishing the diagnosis.

## CONCLUSION

GISTs are the common mesenchymal tumors of GI tract with male predominance and common occurrence in the age group above 40 years. Benign to malignant gastric GISTs in our study was less with a value of 1.25:1, the reason may be small sample size. Unlike other studies the prevalence of GISTs was slightly more in small intestine. Gastric GISTs were mostly benign. Tumor size and mitosis were found to be good predictors of malignant outcome. EGISTs were observed in uncommon sites like pelvis, retroperitoneum, mesentery and bladder. Pelvic

tumors when cystic are to be carefully evaluated as they can be mistaken for ovarian tumors. EGISTs were found to be more common in women. It is essential to search thoroughly for mural nodules of GIST as most of the EGISTs may be extensions of GISTS. In cases of diagnostic dilemma panel of IHC markers help establish the diagnosis.

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