



A REVIEW OF MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS IN CENTRAL INDIA

Oncology

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ABSTRACT

Background: Despite being a rare tumor, Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. A series of patients presenting with GIST at our college was studied and correlated with previously published data.

Settings And Design: The study was conducted in Surgical Oncology Department, SAIMS, Indore. This was an observational study.

Materials and Methods: We reviewed the clinical presentation, imaging features, operative findings and histopathological & immunohistochemistry findings in 12 patients with GIST from 2015 to 2017. Patients were followed for 6 months to two years.

Results: Total 12 patients were studied. Mean age 49.75 years (range 35- 70 years).

Most common location was in stomach (50%), 25% in ileum, 16% in jejunum and rectum was least common seen in 9% case. All except one had a R0 resection. IHC showed cKIT and DOG1 positivity in all cases. Two patients had metastatic lesion. There was single 28-day mortality. All patients received post-operative Imatinib.

Conclusion: GISTs being rare tumor should be reported for appropriate consensus. Improved histopathological and immunohistochemistry techniques have helped to confirm the diagnosis.

Surgery and medical therapy with imatinib and other TKIs is the cornerstone of treatment.

KEYWORDS

GIST, Mesenchymal, cKit, immunohistochemistry.

MATERIAL AND METHODS:

The study was conducted in the department of surgical oncology, Sri Aurobindo Medical College and Post Graduate Institute, Indore, INDIA. Time duration of the study was from September, 2015 to September, 2017.

Written informed consent for publication was taken from each patient. Total 12 patients were included in the study.

10 patients came directly to our OPD and rests two were referred to us from department of gastroenterology.

All patients underwent detailed physical examination after complete history.

All had their computed tomography abdomen done with oral and intravenous contrast.

Patients with tumor in stomach underwent esophagogastroduodenoscopy (EGD).

All these were also biopsied during EGD.

However, GIST was histologically proven only in four cases pre-operatively. In rest two, repeated biopsies were inconsistent.

In rest of the cases of small bowel and rectum, the tumors were biopsied by USG guided semi-automatic tru cut needle FG18 along with coaxial needle FG17. Four biopsies were positive for GIST but repeated biopsies could not prove the histology.

Two patients who presented with intestinal perforation and peritonitis were explored following imaging without pre-op histological evidence.

All patients were explored with laparotomy. Great care was taken not to disrupt the pseudocapsule of the tumor and avoiding of tumor spillage.

All tumors were resected with not more than 5 cm healthy uninvolved margins. Nodal sampling was done in case of enlarged mesenteric lymphadenopathy.

Two patients in whom the pre-operative histological diagnoses were uncertain, frozen section biopsy was done.

All the tumors were subjected to detailed histopathological examinations and immunohistochemistry studies were completed.

c-KIT gene mutation analysis was based on PCR followed by automated DNA sequencing using BigDye™ Terminator Chemistry on ABI Genetic Analyzer 3500 DX platform to generate c-KIT exon 9, 11, 13 and 17 nucleotide sequences. Sequence analysis data was used to determine the presence or absence of tumor borne c-KIT gene mutations.

PDGFRA gene mutation analysis was based on PCR followed by the above automated DNA sequencing to generate PDGFRA exon 12, 14 and 18 nucleotide sequences. Sequence analysis data was used to determine the presence or absence of tumor borne PDGFRA gene mutation.

All patients were started on post-operative medical therapy with imatinib mesylate 400 mg orally daily. All patients were followed up regularly 3-6 monthly with physical examination and imaging.

DISCUSSION:

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumor of the gastrointestinal (GI) tract. The term GIST was coined by Mazur and Clark in 1983 to describe non-epithelial gastrointestinal neoplasms lacking the IHC findings of Schwann cells and not having the microscopic characteristics of smooth-muscle cells. [1] Only 0.1- 1% of all GI tract malignancy can be attributed to GISTs. The most common gastrointestinal location is the stomach (50% to 60%), followed by the small intestine (20% to 25%), rectum (5%), and esophagus (2%). Although, GISTs can occur at any age, these tumors are common in patients aged more than 40 years in one of the largest

retrospective series of gastric GISTs. [2] This was substantiated by two Indian studies. [3,4]

These tumors can develop outside the intestinal tract. Omentum, mesentery, uterus, and the retroperitoneum are usual location. These are known as extragastrointestinal stromal tumors (eGIST). These usually have an aggressive behavior. [5,6,7,8]

In general, GISTs are slightly more incident in males than females. GISTs can occur at any age, with a median occurrence at 60 to 65 years. [9] The SEER study estimated an overall 5-year survival rate of 45%.

These tumors arise from the Interstitial Cell of Cajal (ICC). ICC is the pacemaker of gastrointestinal motility and is found interposed between autonomic nerve ending and the smooth muscle layer of the gastrointestinal wall. [10] They play an integral role in the propagation of intrinsic slow-wave gut peristalsis.

This cell expresses CD34 and Cd117. Morphologically, GISTs can originate spindle cells ($\geq 2/3^{\text{rd}}$ cases), epithelioid cells, or both. [11] Epithelioid-cell GISTs are more common in the stomach and include those that are PDGFRA mutated.

Immunohistochemically, the hallmark of most GISTs is their positivity for cKIT (CD117) and DOG-1. However, immunohistochemical status does not reflect the mutational status with regard to KIT and PDGFRA.

TABLE 1. Immunohistochemical Schema for the Differential Diagnosis of Spindle Cell Tumor of the GI Tract

	KIT(CD117)	CD34	SMA	DESMIN	S-100
GIST	+	+(60%to70%)	+(30%to40%)	Very rare	5%+
SMOOTH MUSCLE TUMOR		+(10%to15%)	+	+	Rare
SCHWANOMA		(usually Antoni B)			+
FIBROMATOSIS	Disputed*	Rare	+	Rare cells	

Abbreviation: SMA, smooth muscle actin.
*Most, but not all authors report that fibromatoses are negative for KIT. [12]

DIAGNOSIS:

The outward growth of most GISTs within the gastrointestinal wall results in relatively delayed presentation, either as large palpable abdominal masses or as causes of GI bleeding, hemoperitoneum, perforations. This leads to upto 25% of GISTs being diagnosed in a clinical emergency, often leading to surgical explorations resulting in anticipation with unforeseen finding of the disease. Another 25% of GISTs are discovered incidentally during diagnostic assessments (whether an endoscopic procedure, ultrasound, or computed tomography [CT] scan) done for other reasons. The remaining are diagnosed because of symptoms of compression from an abdominal mass, or chronic anemia. [2]

GIST has wide spectrum of clinical presentation. It is largely dependent on tumor size and location. Symptoms are usually found in tumors larger than 6 cm in diameter. [13] About 70% of patients with GISTs are symptomatic; the remaining 20% to 30% are diagnosed incidentally or at autopsy. [5,13]

The most common symptom of GIST is abdominal pain and/or GI bleeding. GIST can also cause symptoms secondary to mass effect, including early satiety, bloating, and abdominal pain. Other less common symptoms include pelvic pain, pleuritic chest pain, small bowel obstruction, dysuria, altered bowel movement, nausea, and weight loss.

About 5% of all GISTs are associated with tumor syndromes: familial GISTs, neurofibromatosis type 1 (Nf1), Carney’s triad (CT), and the Carney-Stratakis triad (CSS). [6, 14, 15, 16]

GISTs are rare cancers. Therefore, population-based screening is not of great importance.

TABLE 2. Proposed Approach for Defining Risk of aggressive Behavior in GISTs [11]

	Size	Mitotic Count
Very low risk	<2cm	<5/50HPF
Low risk	2–5cm	<5/50HPF
Intermediate risk	<5cm	6–10/50HPF
	5–10cm	<5/50HPF
High risk	>5cm	>5/50HPF
	>10cm	Any mitotic rate
	Anysize	>10/50HPF

TABLE 3. AFIP- Miettinen risk stratification system [2]

RISK STRATIFICATION OF PRIMARY GIST BY MITOTIC INDEX, SIZE, AND SITE					
Tumor parameters		Risk of progressive disease (%)			
Mitotic index	Size	Gastric	Duodenum	Jejunum/ileum	Rectum
≤ 5 per 50 hpf	≤2cm	None(0%)	None(0%)	None(0%)	None(0%)
	>2 ≤5cm	Verylow(1.9%)	Low(4.3%)	Low(8.3%)	Low(8.5%)
	>5 ≤10cm	Low(3.6%)	Moderate(24%)	(Insu .dat a)	(Insu .dat a)
	>10cm	Moderate(10%)	High(52%)	High(34%)	High(57%)
> 5 per 50 hpf	≤2cm	None†	High†	(Insu .dat a)	High(54%)
	>2cm ≤5cm	Moderate(16%)	High(73%)	High(50%)	High(52%)
	>5cm ≤10cm	High(55%)	High(85%)	(Insu .dat a)	(Insu .dat a)
	>10cm	High(86%)	High(90%)	High(86%)	High(71%)

Defined as metastasis or tumor-related death.

†Denotes small number of cases.
Adapted from Miettinen and Lasota, 2006 from Elsevier

The natural history of advanced GISTs is marked by their potential extension to the peritoneum and/or the liver. Thus, a CT scan is the staging procedure of choice to rule out metastatic disease. Typically, GISTs do not metastasize to lymph nodes.

MANAGEMENT BY STAGE

Localized GISTs with no evidence of distant metastases are treated with surgery, followed by adjuvant medical therapy if the risk of relapse is significant. Both observation and resection for GISTs 1 to 2 cm can be considered. When the disease is localized, surgery is the treatment mainstay.

Indeed, all GISTs ≥ 2 cm in size should be resected when possible, because none of them can be considered benign. Regardless of their size, any small GIST that is symptomatic (e.g., bleeding from erosions through the mucosa) or increases in size on serial follow-up should be resected.

When surgery is unfeasible or could be made less mutilating or easier through downsizing, medical therapy is used if the genotype is sensitive to imatinib, possibly followed by surgery and the completion of a medical adjuvant treatment if the risk of relapse is significant. When the disease is metastatic, medical therapy with TKIs is standard treatment and should be maintained indefinitely.

Surgery should not be accompanied with lymphadenectomy. Adjuvant medical therapy with imatinib was demonstrated to substantially improve relapse-free intervals. Currently, adjuvant therapy is recommended for 3 years. Standard second-line therapy is sunitinib, which is a TKI inhibiting KIT and PDGFRA but also displaying antiangiogenic activity by the inhibition of vascular endothelial growth factor receptor (VEGFR).

RESULTS:

Total 12 patients were studied.
Mean age 49.75 years (range 35- 70 years).
Four were females and rest 8 were males.

Most common location was in stomach (50 %), 25% in ileum, 16 % in jejunum and rectum was least common seen in 9% case.

All except one had a R0 resection i.e., both macroscopic and microscopic negative margins.

The specimen of 5 patients each showed high and intermediate pathological grading. Rest two had low pathological grade.

Two patients had metastatic lesion elsewhere. Both were elderly males. Both of these patients had large bulky tumors and cells of origin were epithelioid to spindle cells.

The largest tumor resected was from the stomach which weighed 3100gm with 35 cm diameter.

Average weight of tumor in males was 640 gms, whereas it was 256 gms in females.

All patients who had high grade tumors were bulky in size. All patients had pre-operative radiological and histopathological studies except for one patient who presented with perforation peritonitis.

In 75% of the cases, mucosal ulceration was found. In the rest cases, neither mucosal ulceration was present nor serosa involved.

Overall serosa was involved in only 5 cases (42%). On microscopy, 10 out of 12(83%) of the specimen were composed of spindle cell and rest had epithelioid to spindle cell.

58% (7 cases) had ≤ 5 mitosis/ 50 high power field(hpf), 16%(2 cases) had 10 mitosis/ 50 hpf, and 25%(3 cases) had 15 mitosis/50 hpf.

All patients, except one, who harbored tumor in stomach had intermediate to high pathological grading.

Tumor in jejunum and rectum had only intermediate to high pathological grade.

Ileal tumors had both high and low pathological grade. Immunohistochemistry studies were done in all cases. c-Kit(CD117) and DOG1 were positive in all cases. CD34 was positive in 8 cases (67%).

SMA (smooth muscle actin) was positive in 4 cases (33%). S100 was negative in all cases.

There was one 28-day mortality of hospital which presented with perforation in the tumor with peritonitis and septicemic shock.

Average duration of stay was 8 days (range 5- 15 days). Two patients had surgical site infection(SSI). No anastomotic leak was seen.

Patients were followed for six months to two years. No patients with R0 resection had relapse during this follow up. The patient with R2 resection in a metastatic scenario had regrowth despite adjuvant treatment. However, the general condition is good.

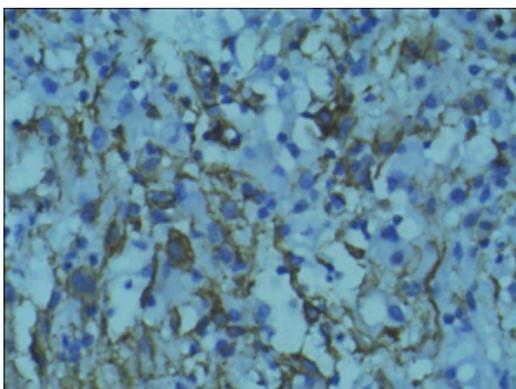


FIGURE 1: IHC showing SMA

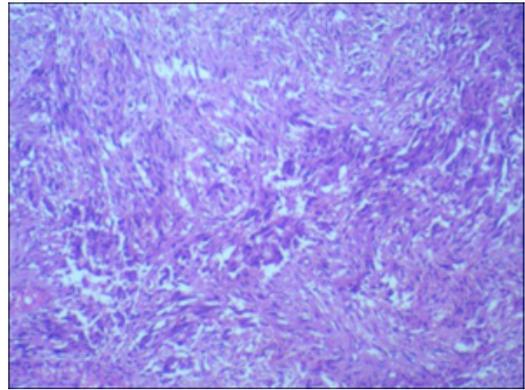


FIGURE 2: MORPHOLOGY: Section shows tumor composed of intertwining bundles of plump spindle cells with scanty intervening stroma. Tumor cells have fusiform nuclei, dispersed finely clumped chromatin, inconspicuous nucleoli and ill-defined pale eosinophilic cytoplasm. Only mild pleomorphism is seen.(100x magnification) H & E staining.

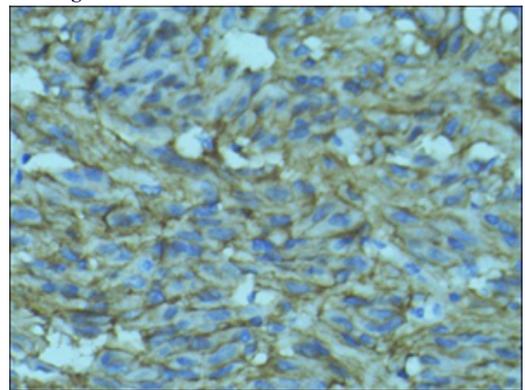


Figure 3: IHC showing diffuse moderate to strong positivity for DOG1 in tumor cells. (400x magnification)

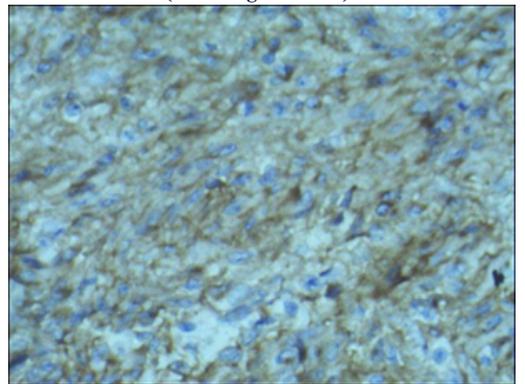


FIGURE 4: IHC showing diffuse moderate to strong positivity for CD 117 in tumor cells. (400x magnification)

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