Section: Pathology

Original Research Article

HISTOMORPHOLOGICAL AND MMUNOHISTOCHEMICAL STUDY OF GASTROINTESTINAL STROMAL TUMOR

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ABSTRACT

Background: Aim: Gastrointestinal stromal tumor [GIST] is the most common mesenchymal tumors of gastrointestinal tract. The aim is to explore the clinical, histomorphological, immunohistochemical aspects and to know the tumour biology.

Material and Methods: A retrospective study was conducted for a period of 6 years from January 2018 to June 2023 in department of pathology, ESICMC & PGIMSR, Bangalore.

Results: Total cases were 16 with age range of 38-75 years. Male to female ratio is 1.7:1. Abdominal mass is the commonest clinical presentation in 56.2 % cases, followed by pain abdomen and bloody stools. Stomach [43.7%] is the most common location, next being small intestine, rarely seen in esophagus, appendix, rectum and as extraintestinal mesenteric GIST. The tumor size ranged from 1-18 cms and cut surface showed well circumscribed, firm, grey white, lobulated mass. Microscopically, spindle cell morphology [11 cases] is commonest. Epitheliod and Mixed cell type seen in 2 and 3 cases respectively. On Risk assessment, majority [37.5%] belonged to high risk category. CD117 was positive in 87.5% cases. CD 34, SMA and S-100 were positive in 43.7%, 43.7% and 37.5% cases, respectively. Two cases of CD 117 negative GIST was found to be DOG 1 positive.

Conclusion: GIST needs to be distinguished from other mesenchymal tumors. Clinical, histomorphological along with Immunohistochemistry [IHC] enables definitive diagnosis. DOG1 is useful in diagnosis of C-kit negative GIST. Risk stratification considering the anatomical location, size and mitosis prompts optimum management and targeted therapy.

Keywords: GIST, CD34, Immunohistochemistry, Mesenchymal tumors

INTRODUCTION

Mesenchymal tumors of gastrointestinal encompass a wide variety since they can originate from muscle, neural, vascular, or fibroblastic tissue.[1] Of all the mesenchymal tumors, Gastrointestinal stromal tumor [GIST] is the most common with an annual incidence of 14-20 per million people.[2,3]

GIST can occur anywhere in the gastrointestinal tract; with 55% of it arising from the stomach, 31% in the small bowel, 6% in the colorectal region, and < 1% in the esophagus. Rarely, GIST arise in the appendix.[4]Extragastrointestinal stromal tumors [EGISTs] seen in <5%, occur in the mesentry, omentum,retroperitoneum and pleura, are often mets from an undetected primary or detached mass from the gastrointestinal system.[5]Many smaller GISTS are detected incidentally during an endoscopy or scan.Overall GISTs are slightly more common in males with peak incidence in 6th decade of life.[6] Clinically, Present with vague abdominal complaints, ulcer symptom, acute or chronic bleeding, abdominal mass, obstruction, or perforation.

Tumor size, mitotic index, and location have been used to categorize GISTs to predict the clinical

behavior of these tumor.[7] Also histomorphology along with Immunohistochemistry [IHC] including CD117 and DOG1 gene expression enables a definitive diagnosis and treatment plan.In this setting, the present study was taken up to explore the clinical, histomorphological, immunohistochemical aspects and to know the tumour biology of GIST.

MATERIALS AND METHODS

A retrospective study was conducted on all diagnosed cases of GIST in department of pathology at ESICMC & PGIMSR, Bangalore. Duration of the study is 6 years from January 2018 to June 2023.

Clinical details were collected from the department case files and medical records. Radiological details and nature of surgery were noted.

Gross morphological features like size, site and appearance on cut surface were recorded.Changes in the adjacent mucosa if any noted. Distance of the tumor from the surgical margins was measured. Lymph node and mesentery when received were grossed to look for nodular deposits, appearance on cut surface noted and representative bits were taken up for processing.

Histopathology and IHC slides were retrieved and reviewed microscopically. H&E stained slides were studied for cellularity, histological type. Microscopically presence of perinuclear vacuoles, pleomorphism, mitosis, nuclear palisading, collagenous stroma, necrosis, invasion etc was looked for.

Histological grading was done considering mitotic rate as below.

GX: Grade cannot be assessed

G1: Low grade, mitotic rate <5/5mm2

G2: High grade, mitotic rate >5/5mm2

Counting of mitosis was initiated in an area exhibitinghighest mitotic activity and further continued with consecutive HPFs. 50 hpfs is equivalent to 5mm3.

Finally, risk assessment of disease progression in primary GIST wasperformed using guidelines from Miettinen and Lasota.[8]and categorized as no risk, very low risk, low risk, intermediate risk and high risk group. For biopsies, risk stratification was done considering morphological and clinicoradiological features.

Immunohistochemistry was done on formalin fixed paraffin embedded blocks using peroxidase antiperoxidase method with secondary antibody from Biogenix manufacturer. Markers like CD 117, CD 34, Ki67, SMA, S100, Vimentin etc were applied and evaluated. Additional marker such as DOG1 was used wherever feasible. Patients who were treated with imatinib before surgery were excluded from study.

RESULTS

During the study period, 16 cases of GIST were received in department of Pathology constituting 0.05% of total specimens received. Age range was 38-75 years with the mean age being 57.5 years. Majority were males with male to female ratio of 1.7:1.

Abdominal mass is the commonest clinical presentation in 56.2 % [9/16 cases] and history of associated pain in 7 cases [43.7 %]. Blood in stools was in 6 cases [37.5 %] of which black tarry stools detected in 5 patients, however fresh blood in stools was in a patient with rectal GIST.

Stomach is the most common location with 43.7% [7/16] cases; the next commonest location is jejunum in 3 cases and duodenum in 2 cases. We had 1 case each of esophagus, appendix, rectum and extraintestinal mesenteric GIST.

On gross examination the mass was polypoidal projecting into the lumen of GI tract, some were serosal while others were intramural along the wall. The tumor size ranged from 1-18 cms with the mean size of 6.1 cms. On cut surface, the tumor is well circumscribed, firm, grey white, lobulated however necrosis was seen in 5 cases. Surface mucosal ulceration was seen in 3 (3/5) cases of polypoidal growths [Table 1][Fig 1].

Microscopically, spindle cell morphology is commonest, seen in 11 cases. These spindle cells were arranged in syncytial pattern and in intersecting fascicles. The individual cells had elongated nucleus, inconspicuous nucleoli and paranuclear vacuoles with faintly eosinophilic to indistinct cytoplasm. Epitheliod GISTs showed round cells in sheets and nests with clear to eosinophilic cytoplasm as seen in 2 cases. Mixed cell type showing both spindle and epithelioid morphology were seen in 3 cases. Omental nodules were grossed and tumor deposits were confirmed by microscopy in 4 cases [Table 2][Fig 2].

Low grade histology was seen in 4 cases while high grade was seen in 12 cases characterized atypical mitosis of >5/50 hpf along with, perivascular whorling and necrosis.

On Risk assessment, 37.5% [6/16 cases] belonged to high risk category, 5 cases being low risk, 2 cases each of moderate and very low risk and one case of incidentally detected jejunal GIST belonged to no risk category and the size was 1.5*1 cm exhibiting spindle cell morphology.

Immunohistochemistry showed CD117 positivity in 87.5% [14/16 cases] displaying cell membrane and cytoplasmic positivity.CD 34, SMA and S-100 were done in all cases and were positive in 7 [43.7%], 7 [43.7%], and 6[37.5%] cases, respectively. In addition, vimentin was positive in 10 cases[62.5%] [Fig 3].Two cases of CD 117 negative GIST was found to be DOG 1 positive. All cases were negative for EMA & CK in the present study.

Interestingly, our study had one case of synchronous malignancy in gastrectomy specimen. Histomorphology showed GIST with heterologous elements-osteogenic differentiation and adenocarcinoma in 71-year male. GIST was CD117 positive and CK 7 positivity in adenocarcinoma.

Cystic presentations in GISTs are very rare, have relatively indolent behaviour and favorable prognosis.[9] We had one case of Cystic GIST, presented clinically as mesenteric cyst. Microscopy showed spindle cell morphology with marked cystic change and strong CD 117 positivity on IHC.

Table 1: Table showing age, sex, clinical features, site and gross morphology of GIST

Sl No.	Age	Sex	Clinical features	Site	Size	Locationof tumor grossly	Necrosis	Metastatic nodules
1	75	M	Mass per abdomen	Stomach	18*12 T4	Serosa	+	Multiple omental nodules
2	49	M	Pain	Duodenum	2.5*2 T2	Muscle layer	-	-
3	47	F	Pain GI Bleed	Stomach	3.5*2.7 T2	Muscle layer	-	- -
4	38	F	Mass P/A Bleeding	Stomach	6.4*3 T3	Serosa	-	-
5	62	m	Pain Mass P/A	Stomach	6.3*4.5 T3	Polypoidal	+	-
6	58	M	Pain	Stomach	2.9*2.2 T2	Serosa	-	-
7	42	M	GI bleed Mass P/A	jejunum	4.5*3.5*1.5 T2	Serosa	-	-
8	63	M	Pain	Mesentery	2.1*1 T2	Mesentery	-	-
9	53	M	Incidental	jejunum	1.5*1 T1	Muscle layer	-	-
10	43	F	Mass P/A	jejunum	11*6*4 T3	Serosa	-	- Deposits at sigmoid colon and mesocolon
11	72	F	Pain Mass P/A	Stomach	6.1*5.2 T3	Polypoidal	-	-
12	48	M	Bleeding Mass P/A	Rectum	5.2*2*1 T3	Polypoidal	+	- Liver nodule, paracolic lymph node
13	74	F	GI bleeding Mass P/A	Stomach	8*7*6 T3	Polypoidal	+	-
14	71	m	Dysphagia Hoarseness	Esophagus	6.6*3.5*3.5 T3	Polypoidal	-	-
15	63	m	Pain	Small intestine	8*6.5*6 T4a	serosa	+	Omental nodules
16	62	f	Pain Mass P/A	Appendix	5.5*4 T3	Serosa	-	-

Table 2: Table showing microscopic features, histological grade and risk assessment

ss	Cell type	Cytoplasmic vacuoles	Mitosis /5mm2	MYXoid stroma	Hyalinisation	Nuclear palisading	Skenoid fibres	Perivascular whorling	Mucosal/Fat invasion	Necrosis	Histological grade	Omental nodules /mets	Risk assessment
1	Spindle	-	>5/5 mm^2	+	+	+	-	+	-	+	High	+	High risk
2	Spindle	-	<5/5 mm^2	-	+	-	+	-	-	-	Low	-	Low risk
3	Spindle	+	<5/5 mm^2	-	+	-	-	-	-	-	Low	-	Very low
4	epithelioid	-	<5/5 mm^2	+	+	-	-	-	-	-	Low	-	low
5	epithelioid	-	>5/5 mm^2	-	-	-	-	-	+	-	Low	-	High
6	Spindle	-	<5/5 mm^2	-	+	-	+	-	-	-	Low	-	Very low

7	Spindle	+	<5/5 mm^2	+	-	-	+	-	-	-	Low	-	Low
8	Spindle	-	<5/5 mm^2	-	-	-	-	-	-	-	Low	-	Low
9	Spindle	-	<5/5 mm^2	-	+	-	+	-	+	-	Low	-	None
10	Spindle	-	<5/5 mm^2	-	-	-	-	+	-	-	Low	+	High
11	Spindle	+	<5/5 mm^2	-	+	-	-	-	-	-	Low	-	Low
12	Mixed	-	>5/5 mm^2	-	-	+	+	+	+	+	High	+	High
13	Mixed	-	>5/5 mm^2	-	-	-	+	+	-	+	High	-	high
14	spindle	+	<5/5 mm^2	-	-	-	-	-	-	+	Low	-	moderate
15	Mixed	-	>5/5 mm^2	-	-	+	-	-	-	+	High	+	High
16	Spindle	-	<5/5 mm^2	-	-	-	-	-	-	-	Low	-	moderate

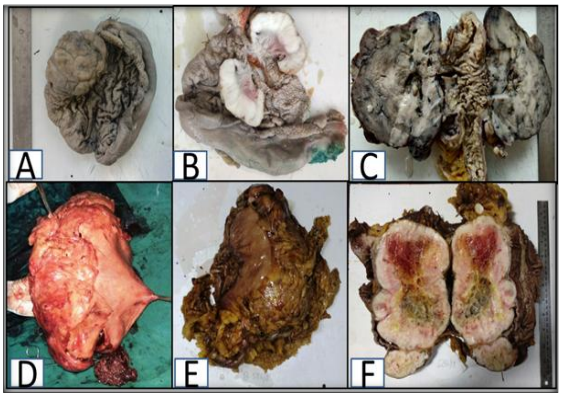

Figure 1: A&B External and cut surface of gastric GIST.Fig C:Cut surface of small intestinal GIST. Fig D, E, F Intraoperative, gross appearance and cut surface of Gastrectomy with omentectomy specimen of GIST

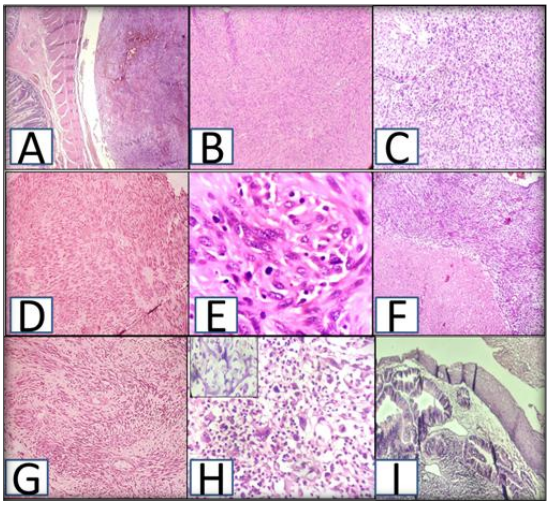

Figure 2: A Microphotograph showing origin of GIST from muscle layer (H&E 10x).Fig B Spindle morphology (H&E 40x) Fig C :Epitheliod morphology (H&E 40x) Fig D: Nuclear palisading (H&E 10x).Fig E:Atypical mitosis (H&E 40x) Fig F: Necrosis (H&E 40x) Fig G: Perivascular whorling(H&E 40x) Fig H: Osteoclast like giant cells with osteoid like material in inset(H&E 40x).Fig I:Adenocarcinoma in synchronouis GIST(H&E 40x)

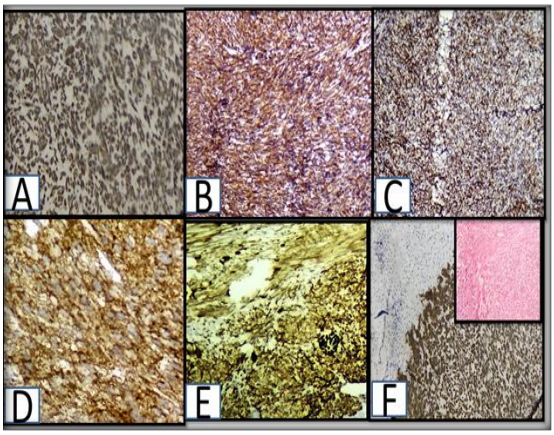

Figure 3 IHC:A: CD 117 showing cytoplasmic and membranous positivityFig B:Cytoplasmic positivity in VimentinFig C: Cytoplasmic positivity in SMA Fig D: Membranous positivity in CD 34 Fig E: Nuclear and cytoplasmic positivity of S100 Fig F:Metastaticdeposit to liver showing strongCD117 positive (Inset showing H&E of same)

DISCUSSION

GIST was first described as a separate entity in 1983.[10]Specific mutation of c-KIT proto-oncogene by immunohistochemistryconfirmed the origin of these tumours from Interstitial Cells of Cajal.[11,12]

Itcan develop anywhere in the digestive tract; Large series have shown the stomach to be the most common site.[13,14] We also observed stomach is the commonest site for GIST similar to studies conducted by Funs et al,[15]Wang M et al,[16] Haridas et al,[17] and Krishnappa et al.[18]

GISTs occurs in any age, often in males with peak incidence in the sixth decade [19]. We also observed male preponderance with median age of occurrence in 60 years and is in concordance with studies conducted by Ravikumar et al,[19]and Nagraju et al.[20]

Clinically abdominal mass followed by pain abdomen was the most common clinical presentation similar to studies conducted by Prachucho et,[21] and Nagraju et al.[20] In a study by

varsha et al [22], pain abdomen was common followed by mass per abdomen.

Gastric GIST frequently manifests as an intraluminal component with or without umbilicated mucosal ulcers. Similarly, in our study, intraluminal component was seen in 60% of gastric GIST and on risk assessment; majority of them belonged to high risk category.

Microscopically, spindle cell morphology [68.7%] was the commonest histology on microscopic examination and this inconcordance with studies by Kim et al,[23] [77.4%], Parab et al,[24] [70%] and Patnayak et al.[25] Anatomical location influences the histological morphology and 60% of gastric GISTs have spindle cell morphology. In our study, we had 57% of gastric GIST exhibiting spindle cellmorphology. Small intestinal and colonic GIST also have spindle cell morphology with vague storiform pattern. Skenoid fibres are characteristically found in this site and are the indicator of favourable prognosis. We observed skenoidfibres in 3 out of 5 small intestinal GIST and all of them belonged to low risk or no risk category. Among the large intestinal gist, the incidence of anorectal GISTis slightly higher than that of colonic GIST. In our study, one case of rectal GIST was observed exhibiting mixed morphology, belonged to high risk category with metastatic deposits in the liver and paracolic lymph node.

About 20−25% of gastric GISTs and 40−50% of small intestinal GISTs are clinically malignant and common sites of metastasis are the abdominal cavity, peritoneum, lung and liver. Rarely bones, soft tissue and skin may be involved.[26,27] We had metastasis in 40% of small bowel GIST and 14.2% of gastric GIST similar to Ravi et al study[19]. Gastric and duodenal GIST presented with omental nodules, rectal GIST with liver metastasis and jejunal GIST with mets to sigmoid colon and mesocolon.

Risk assessment of disease progression varies according to anatomic sites. Small Bowel GIST carries higher risk of progression than Gastric GIST of same size and mitosis. With adjuvant kinase targeted therapies, it is crucial to diagnose and categorize risk group for optimum management of these cases.[28]Majority of cases [37.5%] in our study belonged to high risk category followed by low and moderate risk category, in concordance with studies conducted Ravikumar et al,[19] and Rauf et al.[29]

On immunohistochemistry, 80−85% of GISTs are CD117 positive, 60-70% are positive for CD34, 30-40% for SMA, 5% for S-100, and 1-2 % for Desmin. [29,30] In our study, 87.5% cases were positive for CD117 similar to studies conducted by Kim et al,[23]Steigen et al,[31] and Krishnappa et al.[18] Though activating mutations in either KIT [75%–80%] or platelet-derived growth factor receptor alpha [PDGFRA] [5%–10%] are commonly found in GISTs, approximately 6% of GISTs are KIT-negative,[32] and generally have a favourable prognosis.[33]We encountered two KIT negative GIST exhibiting DOG 1 positivity.

CONCLUSION

GIST needs to be distinguished from other mesenchymal tumors. Clinical, histomorphological along with IHC enables definitive diagnosis. DOG1 is useful in diagnosis of c-KIT negative GIST.Risk stratification considering the anatomical location, size and mitosis prompts optimum management and targeted therapy.

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