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Case Series

Pathology Section

Histomorphological Spectrum and Immunohistochemical Features of Gastrointestinal Stromal Tumour: A Series of Eight Cases

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ABSTRACT

Gastrointestinal Stromal Tumours (GISTs) are rare tumours of the Gastrointestinal Tract (GIT), consisting of <1% of all primary GIT neoplasms. Recent studies show an increased incidence, which may be due to improved diagnostic facilities. In contrast to the literature's judgement and the findings of many Western research, which state that the stomach is the most common place, it was observed that the small intestine was more common. Consequently, the goal of this case series was to characterise the clinicopathological, histomorphological, and immunohistochemical spectrum of GISTs as well as their risk categorisation in accordance with the modified Miettinen and Lasota's algorithm. Eight patients with GISTs diagnosed between January 2017 and December 2020 at tertiary care centre of Gujarat, India are presented in this case series. There was one young woman among the patients, others were middle or old age male or female and had a median age of 58.5 years. The most typical presentation was abdominal pain, albeit in one instance it was an unexpected discovery. One example of Extra GISTs (EGIST), where there were several retro and intraperitoneal masses, and one small intestinal GIST each had lymphoma as the tentative clinical diagnosis. Predominant spindle cell morphology was observed in contrast to other studies. Even if molecular studies are not available in resource-limited countries, the basic Immunohistochemistry (IHC) panel is the most useful in the final diagnosis. Risk stratification criteria are helpful for prognostication and further management with the use of appropriate targeted therapies.

Keywords: Miettinen and lasota, Mitosis, Risk stratification, Spindle cell

INTRODUCTION

The GISTs arise from the interstitial cells of Cajal, the pacemaker cells, comprising <1% of all primary GIT tract neoplasms [1]. The peak age of occurrence is 60-65 years, equally affecting males and females, which may be detected incidentally radiologically or present with abdominal symptoms [2]. More than 60% of them take place in the stomach. EGIST occur in the omentum, mesentery, retroperitoneum, and perineum. Histomorphologically, GISTs are hypocellular to densely cellular lesions [1]. The identification of primary mutations in KIT (tyrosine-protein kinase) (75-80%) or Platelet-derived growth factor receptor alpha (PGFRA) (7-15%) genes by IHC has revolutionised the diagnosis and led to the development of targeted therapy [1]. The diagnosis and treatment of small GISTs are important as surgery is the mainstay of treatment in Asian countries as compared to medical therapy in western countries. Optimal treatment of GISTs requires a team effort, including gastroenterologists, surgical and medical oncologists, pathologists, and radiologists [3]. This case series was done to study the clinicopathological, histomorphological, and IHC spectrum of GISTs along with their risk stratification according to the modified Miettinen and Lasota's algorithm [4]. The American Joint Committee on Cancer (AJCC) Cancer Staging (TNM) 8th edition was used for staging and grading [5]. Following permission from the Institutional Ethics Committee of Clinical Research (No. 289/2021) was approved, eight patients with GISTs diagnosed between January 2017 and December 2020 are presented in this case series.

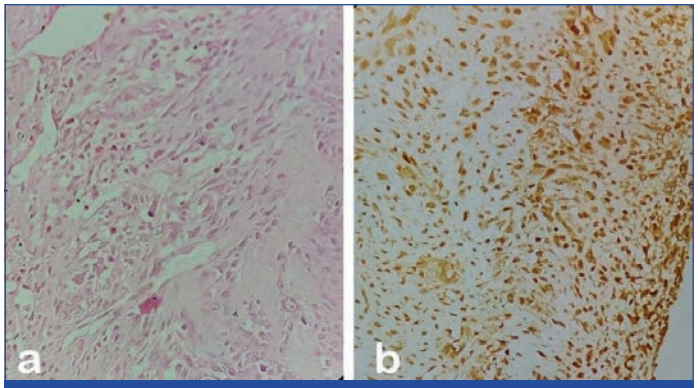
CASE SERIES

Case 1

A 36-year-old man presented to the Department of Surgery with chief complaints of epigastric discomfort for a month and vomiting for five days. A well-defined, spherical, broad-based isoechoic lesion measuring 4.3x3.4 cm with central anechoic cystic regions was seen on Ultrasound Sonography (USG), emerging from the wall of the pylorus producing luminal compression and stomach dilatation. A comparable tumour was detected using Contrast-Enhanced Computer Tomography (CECT), which raised the probability of GIST. Based on clinical findings and radiological investigations, the possibility of GIST or leiomyoma was considered. The histopathology laboratory received a 0.5 cm size upper GI scopy biopsy which microscopically showed mainly moderate chronic inflammation with no submucosal tissue. Eventually, excision of mass with distal stomach, pylorus and omentum was performed. Grossly, a submucosal tumour in region of pylorus measuring 4.0x3.5x3.0 cm was seen. The cut surface of the tumour was well-circumscribed, greyish-white with a few cystic areas. Sections from the tumour showed spindle cells arranged in fascicles and whorls with a round to oval nucleus with minimal pleomorphism and eosinophilic cytoplasm with pointed ends [Table/Fig-1a]. Mitosis was <5 per 20-25 hpf (high power field). Omentum was free from metastasis. A diagnosis of spindle cell tumour, suggestive of GIST, grade G1, very low-risk category was given. Strong, diffuse IHC positivity for CD117 [Table/Fig-1b] and vimentin confirmed the provisional diagnosis. S-100 was weakly positive and desmin was negative, which excluded neural and smooth muscle origin tumours. For six months there was no recurrence after which the patient was lost to follow-up.

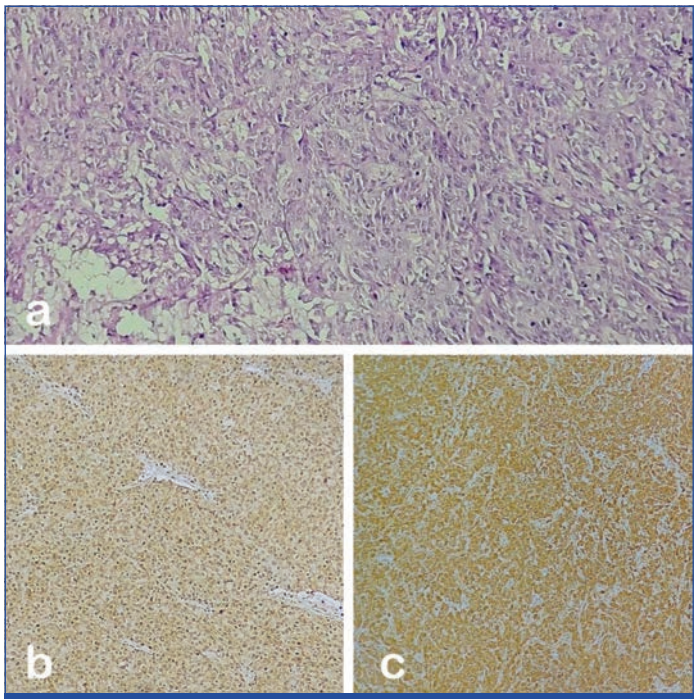
Case 2

A 75-year-old male consulted a general surgeon at the Outpatient Department (OPD) for symptoms of increased frequency of stool with difficulty in defaecation for six months and weakness for one year. For 20 days he felt a mass in the left iliac fossa. On the CECT abdomen, an 8.5×7.3 cm size lesion was reported in the left hypochondrium, heterogeneous with postcontrast enhancement and non enhancing necrotic areas. Depending on clinical and



[Table/Fig-1]: a) Stomach GIST shows spindle cells arranged in short fascicles (H&E stain, 40X); b) Immunohistochemistry for CD117 positive shows strong and diffuse cytoplasmic staining (IHC, 40X).

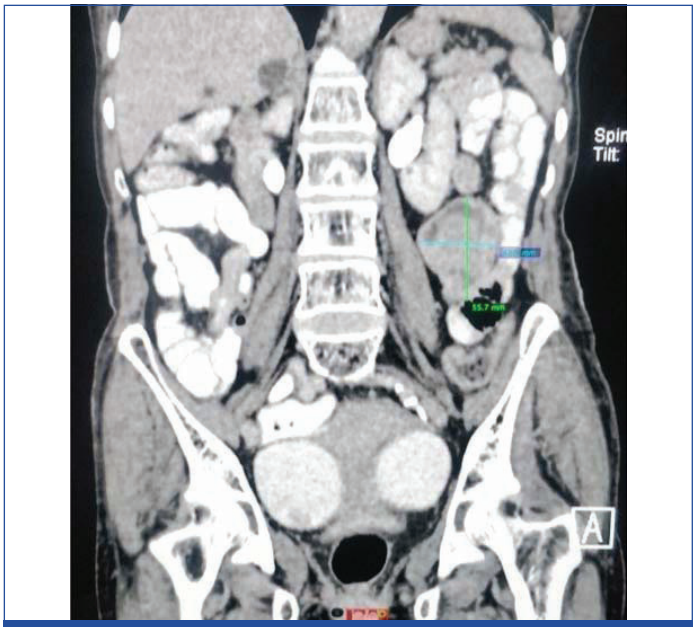
radiological grounds, a probable diagnosis of GIST or carcinoma was given. Well-defined necrotic lesions were also noted in the bilateral inguinal and iliac region, 3.8×3.0 cm on the right-side and 2.8×2.3 cm on the left-side. Multiple fluid density cystic lesions were seen in the liver with water lily sign, the largest measuring 15.3×11.3 cm. The possibility of multiple hydatid cysts was suggested. Biochemical investigations were normal. Peroperatively, multiple soft tissue masses were seen bulging on the outer surface of the jejunum. Multiple, nodular, soft to firm tumours were received, the largest measuring 3.0 cm. On cutting, greyish-white with haemorrhagic areas were seen. Histomorphologically mainly round to oval epithelioid cells with vesicular nuclei and moderate amount of eosinophilic cytoplasm were seen, suggestive of epithelioid variant GIST [Table/Fig-2a]. The tumour was graded as G2 with mitosis >5 per 20-25 hpf, high-risk category. CD 117 and vimentin were positive [Table/Fig-2b,c], while S-100 was weakly positive, confirming GIST and excluding neural tumours. Negative Cytokeratin (CK) and chromogranin ruled out carcinoma and neuroendocrine tumour. Follow-up was not possible due to a change in contact number.



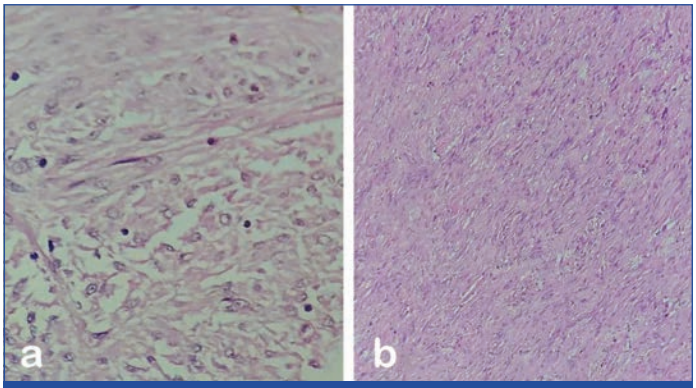
[Table/Fig-2]: a) Small bowel GIST composed of epithelioid cells with abundant eosinophilic cytoplasm and abnormal mitotic activity (H&E stain, 40 X); b) Immunohistochemistry for CD 117 showing diffuse cytoplasmic positivity (IHC, 10X); c) Immunohistochemistry for vimentin showing strong diffuse cytoplasmic staining (IHC, 10X).

Case 3

A 70-year-old female with the complaint of left-side abdominal pain and decreased appetite for 20 days presented to the surgical OPD. For two days she developed a fever and noticed a mass. Clinically, the provisional diagnosis was lymphoma. During the CECT abdomen, a well-defined heterogeneous soft tissue density lesion of 5.4×4.1 cm was seen in mesentery in the left lumbar region with few necrotic areas [Table/Fig-3]. Radiologically, the lesion was suggested as GIST. Intraoperatively, a mass arising from the jejunum was revealed. Part of the small bowel with a 6.0×4.5×4.0 cm size tumour was received for a histopathology examination. The tumour was lobulated, adherent to mesentery with a greyish-white, solid cut surface. Haemorrhagic, cystic areas were also identified. Histomorphologically, diagnosis of spindle cells variant of GIST [Table/Fig-4a] with mitosis >5 per 20-25 hpf, G2, and high-risk assessment was given. IHC for CD117 was positive, S-100 was weakly positive and CD 34 was negative. There was no adverse event during one month follow-up after which the patient lost to follow-up.



[Table/Fig-3]: CECT abdomen showing a well-defined heterogeneous soft tissue density lesion in the left lumbar region.



[Table/Fig-4]: a) Small bowel GIST showing short fascicles of spindle cells (H&E stain, 40 X); b) Small bowel GIST with spindle cell morphology (H&E stain, 10X).

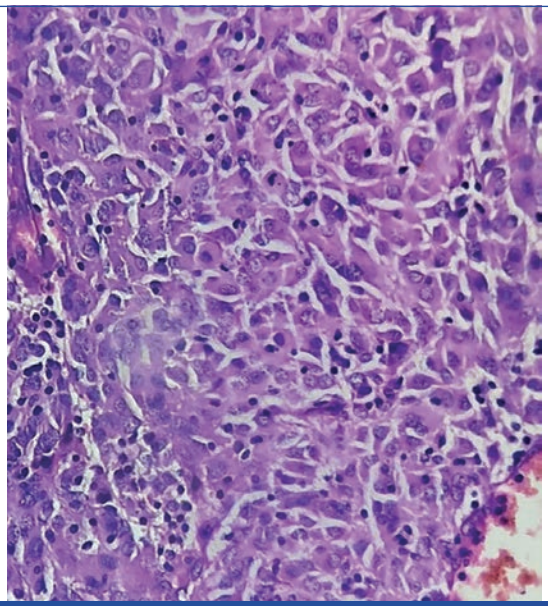
Case 4

A 62-year-old male presented to the Medical OPD with symptoms of abdominal pain for one month, nausea, and vomiting for two days. There was a past history of tuberculosis 15 years ago with anti-Koch's treatment for six months. He was referred to the Surgery Department. The CECT showed a mass measuring 5.0×5.0 cm arising from the ileum, and the possibility of a neoplastic lesion was suggested. The provisional diagnosis was a probability of carcinoma causing intestinal obstruction. Part of ileum with a mass was received for histopathological examination. Grossly, the tumour was well-circumscribed, protruding out from the intestinal wall, 4.5×3.5×3.5 cm in size with a nodular external surface. Cut section was solid with haemorrhagic and focal necrotic, cystic areas. Histomorphologically, it was diagnosed as a spindle cell variant GIST [Table/Fig-4b]. Mitosis was <5 per 20-25 hpf. The tumour

was G1 in grading with a low-risk assessment for recurrence or metastasis. IHC markers CD117, and vimentin were positive, while desmin, actin were negative, ruling out leiomyoma. The patient was followed-up till date with good clinical and radiological outcomes.

Case-5

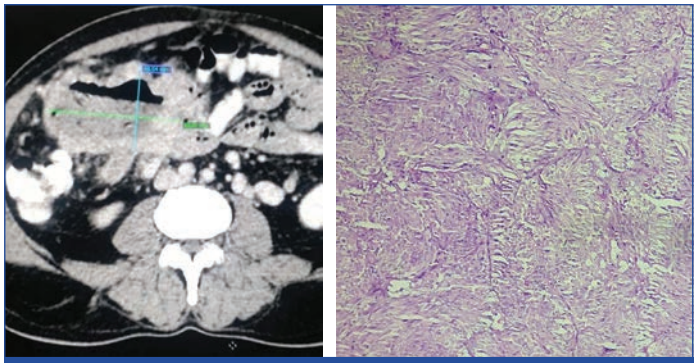
A 65-year-old male came to the Emergency Department with a complaint of severe abdominal pain for two days. He was referred to the surgeon. On CECT, a 13.0×11.0 cm mass was revealed in the right abdomen, suggesting a retroperitoneal mass. The possibility of a carcinoma, sarcoma, or tumour of neural origin was raised. A CT-guided biopsy was taken which was inadequate for evaluation, and was followed by excision biopsy. A single, well-circumscribed mass arising from ileum with adherent mesentery was received for pathological examination. The tumour measured 13.0×11.0×7.0 cm with greyish-white, partially solid, and cystic cut surface with haemorrhagic and necrotic areas. Tumour showed histomorphology of epithelioid GIST with mitosis >5 per 20-25 hpf, G2 and high-risk behaviour [Table/Fig-5]. A diagnosis of epithelioid GIST was confirmed. S-100 and CK were negative. The patient died within a month of the operation.



[Table/Fig-5]: Small bowel GIST composed of epithelioid cells with abundant eosinophilic cytoplasm and abnormal mitotic activity (H&E stain, 40X).

Case 6

A 55-year-old male visited surgery OPD for symptoms of abdominal pain for 20 days with off and on nausea and vomiting. He was operated on for an intestinal mass one month ago in an outside hospital, but documents were not preserved. On per-abdominal examination, the abdomen was soft and a previous operative scar was seen. No obvious lump was found. Postoperative CECT revealed large mass with adherent jejunum and colon with peri-hepatic fluid collection and air in the right sub diaphragm; possibility of pneumoperitoneum was suggested. The peritoneum showed multiple nodules [Table/Fig-6]. Considering the clinical history and radiological findings, recurrence or inadequate excision or metastasis of the mass was suspected. Right hemicolectomy with omentum and peritoneal seeding was received for histopathology examination. On gross examination, 10.0×8.0×5.5 cm size greyish-white tumour in jejunum involving of 3.0 cm segment and infiltrating the adherent colonic wall. Sections studied showed a mixture of spindle cells and epithelioid cells and was reported as mixed variants of small intestinal GIST, G2, mitosis >5 per 20-25 hpf, high-risk behaviour [Table/Fig-7]. Tumour cells invaded the colonic wall with metastasis in the peritoneum. Pericolonic lymph nodes and omentum were uninvolved. IHC CD117 and CD 34 were positive while S-100, CK, and EMA were negative

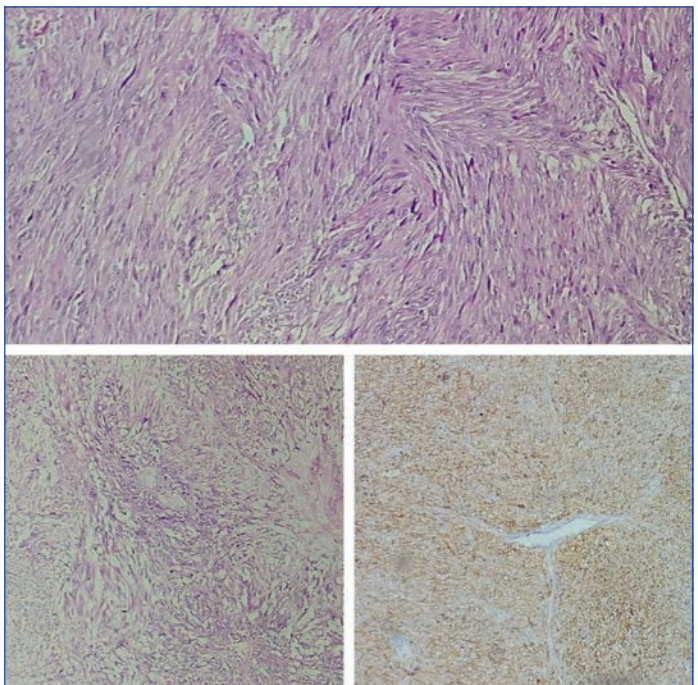


[Table/Fig-6]: Postoperative CECT abdomen showing large tumour adherent to small bowel and colon.
[Table/Fig-7]: Small intestinal GIST, mixed variant, showing both spindle and epithelioid cells (H&E stain, 10X). (Images from left to right)

ruling out epithelial and neural tumour. This patient expired within one month of treatment.

Case 7

A 29-year-old female consulted a general surgeon in the OPD of the hospital for a mass in the right iliac fossa which was found incidentally during routine USG carried out three months ago. There was an operative history of caesarean section and a scar of it was identified during abdominal examination. Repeat USG revealed a well-defined hypoechoic cystic lesion in the right iliac fossa measuring 8.3×5.7 cm in size stating the possibility of a mass. On USG-guided biopsy, a diagnosis of spindle cell neoplasm with the possibility of leiomyoma, neural tumour or GIST was given, and IHC was advised. This was followed by excision of mass with segment of the ileum, colon, omentum and lymph nodes. Grossly, a submucosal, nodular, greyish-white tumour located in the ileum, near the ileocaecal region, adherent to colon, measuring 10.0×9.0×8.0 cm was identified. The cut surface was solid with many necrotic, cystic and haemorrhagic areas. Spindle cell variant GIST, G1, mitosis <5 per 20-25 hpf with moderate risk category was reported [Table/Fig-8a]. Tumour cells invaded adherent colonic wall, however, pericolonic fat, omentum and lymph nodes were uninvolved. The tumour was CD117 positive with negative CD34 and S100. Adjuvant chemotherapy (Imatinib) was given for 3 years. Patient outcome to date has been good without recurrence or metastasis.



[Table/Fig-8]: a) Spindle cell variant of small bowel GIST showing interlacing bundles of spindle cells (H&E stain, 40X); b) EGIST, mixture of spindle and epithelioid cells with myxoid change (H&E stain, 10X); c) EGIST, Immunohistochemistry for CD117 positive shows strong and diffuse membranous staining (IHC, 10X).

Case 8

A 46-year-old male presented to Surgery Department with a complaint of abdominal pain for five months. CECT showed multiple, lobulated, inhomogeneously enhancing solid masses with internal necrosis, scattered throughout the abdomen and pelvis with possibilities of disseminated neoplastic aetiology or lymphoma. The provisional clinical diagnosis was lymphoma or germ cell tumour. Serum alpha-fetoprotein and carcinoembryonic antigen were normal. The USG-guided biopsy showed proliferation of malignant spindle cells as well as round cells with abnormal mitosis, increased vascularity and areas of necrosis suggestive of malignant soft tissue neoplasm. IHC was not performed as tissue was insufficient. Multiple retro and intra peritoneal nodular tumours with the largest measuring 12.0×9.0×7.0 cm were received for histopathology. Cut surface was greyish-white, solid, firm with multiple necrotic and haemorrhagic areas. Extensive IHC panel for malignant soft tissue neoplasm revealed positive CD117, CD34, vimentin, BCL-2 (B-cell lymphoma 2), SMA and focal positivity for S-100 and EMA. Ki-67 proliferative index was 70%. Desmin, HMB-45, calretinin, CD99, Pan CK, and CD45 were negative, ruling out synovial sarcoma, carcinosarcoma, malignant melanoma, and lymphoma. The final diagnosis of a mixed variant of EGIST, G2 with mitosis >5 per 20-25 hpf, high-risk behaviour was given [Table/Fig-8b,c]. Till now one year and six months have passed with no adverse events. A summary of eight cases is depicted in [Table/Fig-9,10].

DISCUSSION

The GISTs have an annual incidence of 10 cases per million populations [1]. In the present study, the majority of cases were observed between the fifth and seventh decades, with a median age of 58.5 years. There was a slight male predominance. Abdominal pain was the predominant symptom. Similar findings were noted by Indian authors as well as western studies and are shown in [Table/Fig-11] [6-12]. This tumour was found incidentally in the case of a 29-year-old female, who was notified at the time of routine USG. Presenting symptoms of GISTs are variable depending upon the site of origin. Upper GIT GISTs produce GI bleeding, while lower GIT GISTs are responsible for symptoms of acute abdomen. EGISTs usually present as an incidental finding or with abdominal mass and anaemia [1].

As per Miettinen and Lasota's algorithm, location is an important prognostic factor. Gastric GISTs have a favourable prognosis as compared to intestinal GISTs [4]. This study showed the small intestine as the most common site (75%) similar to findings of Indian authors, whereas a large study of 76 cases from Bangkok and other studies found the stomach as the most common site [Table/Fig-11] [6-12]. Whether there is a regional difference in location or whether it is related to better imaging and diagnostic modalities in developed countries need to be studied in large studies.

Case no.	Age/Sex	Primary symptoms and duration	Location	Size of tumour (cm)	Histopathology	Mitosis (per 20-25 hpf)	Grade
1	36/M	Abdominal pain, nausea, vomiting, one month	Stomach	4	Spindle cell	<5	G1
2	75/M	Weakness, diarrhoea, mass effect, six months	Small bowel	3	Epithelioid cells	>5	G2
3	70/F	Abdominal pain, mass effect, decrease appetite, 20 days	Small bowel	6	Spindle cell	>5	G2
4	62/M	Abdominal pain, nausea, vomiting, one month	Small bowel	4.5	Spindle cell	<5	G1
5	65/M	Abdominal pain, two days	Small bowel	13	Epithelioid cells	>5	G2
6	55/M	Abdominal pain, nausea, vomiting, 20 days	Small bowel	10	Mixed	>5	G2
7	29/F	Mass effect, three months	Small bowel	10	Spindle cell	<5	G1
8	46/M	Abdominal pain, five months	Bilateral lumbar, iliac fossa, pelvic region	12	Mixed	>5	G2

[Table/Fig-9]: Case-wise clinical presentations and histopathological features of GISTs.

Case no.	Age/Sex	Risk assessment	Positive IHC markers	Postoperative treatment (Imatinib/Sunitinib)	Follow-up and out-come
1	36/M	Very low risk	CD117, Vimentin, S100	NA	NA
2	75/M	High risk	CD117, Vimentin, S100	NA	NA
3	70/F	High risk	CD117, S100	NA	NA
4	62/M	Low risk	CD117, Vimentin,	No	Good
5	65/M	High risk	CD117, CD34, Vimentin, SMA	No	Poor
6	55/M	High risk	CD117, CD34	No	Poor
7	29/F	Moderate risk	CD117	Yes (Imatinib)	Good
8	46/M	High risk	CD117, CD34, Vimentin, S100	No	Good

[Table/Fig-10]: Case-wise risk assessment and immunohistochemical features of GISTs.
IHC: Immunohistochemistry; SMA: Smooth muscle actin

Author name, Country	Median/Mean age (Years)	Predominant sex (%)	Predominant symptom	Most common location	Median/Mean tumour size (cm)
Lopes LF et al. [6], Brazil	59	Female (50.3%)	-	Stomach (38.4%)	-
Alqusous ST et al. [7], Jordan	56.8	Male (56.8%)	Abdominal pain (42.0%)	Stomach (61.9%)	8.2
Ud Din N et al. [8], Pakistan	52	Male (59.2%)	-	Stomach (45.9%)	10.0
Gupta A et al. [9], India	50	Female (57.1%)	Abdominal pain (57.1%)	Stomach and Small bowel (42.9%)	6.0
Sengupta R et al. [10], India	52	Male (57.4%)	Abdominal lump (25.9%)	Small bowel (40.7%)	9.4
Minhas S et al. [11], India	-	-	-	Stomach (41.9%)	-
Jumniensuk C and Charoenpitakchai M [12], Thailand	61.1	Male (50%)	Abdominal bleeding (39.7%)	Stomach (64.5%)	6.8
Present study, India	58.5	Male (75%)	Abdominal pain (75%)	Small bowel (75%)	7.8

[Table/Fig-11]: Comparison of demographic and clinicopathological features of GISTs with various studies [6-12].
†cm: Centimeter

In 5 (62.5%) cases, high mitotic counts of 20-25 per hpf were found, and the average tumour size was 8.8 cm. At the same time, Miettinen M et al., [13] and Jumniensuk C and Charoenpitakchai M [12] correlated high mitotic count with metastasis, while Miettinen et al., [13] found high mitotic activity along with tumour size as the most powerful prognostic indicators. Since GISTs are predominantly intramural lesions, they present late with larger tumour sizes. Large tumours frequently show intra-tumoural haemorrhage, cystic degeneration, and adhesions with intestinal loops [2]. Similar to other studies [7,8,10], present study also found that the majority of GISTs were > 5 cm in size and had intestinal adhesions.

Spindle cell morphology was predominant in this series, where tumour cells were arranged in sheets and short fascicles, followed by epithelioid and mixed types. These findings were similar to the observations seen in other studies [7,10,12,14]. Gastric GISTs have spindle cell morphology and low-risk behaviour [14]. The present study revealed a single case of gastric GIST that showed similar findings. Epithelioid-type morphology is usually common in small intestinal locations associated with high-risk behaviour [15]. Similarly, four out of six cases of small intestinal GISTs in the present study were of high-risk behaviour, with two of them showing epithelioid cell morphology and one showing mixed morphology. Predominant high-risk category was noted in the present study in concordance with other studies [Table/Fig-12] [7,10,12,14].

Author name, Country	Spindle cells (%)	Epithelioid cells (%)	Mixed cells (%)	Very low risk (%)	Low risk (%)	Intermediate/ Moderate risk (%)	High risk (%)
Alqusous ST et al., [7], Jordan	54.8	14.3	30.9	14.3	21.4	4.8	59.5
Ud Din N et al., [8], Pakistan	84.7	12.5	2.7	-	-	-	-
Gupta A et al., [9], India	42.8	42.8		14.2	57.1	-	28.5
Sengupta R et al., [10], India	85.3	13.0	1.63	3.3	4.9	11.5	78.7
Minhas S et al., [11] , India	77.4	6.45	16.1	-	-	-	-
Jumniensuk C and Charoenpitakchai M [12], Thailand	75.0	7.9	17.1	18.4	27.6	22.4	26.3
Gaopande VL et al., [14], India	81.25	-	18.7	-	18.7	25.0	56.2
Present study, India	50.0	25.0	25.0	12.5	12.5	12.5	62.5

[Table/Fig-12]: Comparison ofhistomorphology and risk assessment of GISTs with various studies [7-12,14].

Postoperative follow-up was available in five out of eight cases. Three patients had high-risk factors for progressive disease (G2), of which two expired. Peritoneal metastasis was observed at the time of presentation in one case of small bowel GIST and one case of ExtraGIST, both presenting with high mitotic counts. The liver, peritoneum, and lungs are the most common sites of metastasis and can develop as long as 30 years after the removal of the primary tumour [15]. Langer C et al., reported tumour size >5 cm, small bowel origin, high-grade, and tumour rupture as predictors for recurrence [16]. Tumours that rupture during surgery and GISTs that show mucosal invasion have a worse prognosis. Both these criteria are not currently included in various risk stratification schemes [1]. However, utmost care must be taken to prevent intraoperative tumour rupture.

Due to the advent of targeted therapy for GISTs and tyrosine kinase inhibitor (TKI) molecules, IHC is crucial in the differential diagnosis [1]. Generally, 98% of small intestinal and 95% of gastric GISTs are KIT positive. All cases in this study were positive for KIT (CD117), which was similar to various studies in the literature [8,10-12,14]. Recently, it has been found that the stomach is a common site for SDH-deficient GISTs, which should be confirmed by the loss of expression of SDH by IHC as it guides the treatment protocol [1]. This study showed 37.5% positivity for CD34. The majority of GISTs are positive for CD34 (70%), but it is also immunoreactive in a large group of other tumours, such as solitary fibrous tumours. This marker is no longer included in the primary panel for suspected GISTs [1,15].

Surgical removal of the lesion is the mainstay treatment of GISTs, especially in the Asian region [3]. Unresectable, recurrent, or metastatic GISTs are treated with TKI [1]. Only one case of a young female having a tumour with a high risk of progression and a small intestinal location was treated postoperatively with Imatinib (TKI). The indication of TKI was young age along with high-risk features.

As GISTs are rare tumours and this study was only four years in duration, a limited number of cases could be studied. Also, IHC was not done in some patients due to financial constraints, further leading to exclusion. Further genetic mutation analysis could not be done as infrastructure for molecular studies is not available at our institute. Despite being a case series, authors could establish that, even in resource-constrained settings, morphology, risk assessment criteria, and the basic IHC panel are still the most useful for the final diagnosis, prognostication, and therapeutic guidance.

CONCLUSION(S)

The GISTs can present with varied clinical presentations with indolent to aggressive behaviour. Some regional differences in location and morphology were found, with the small intestine as the most common location, similar to other Indian studies, in contrast to western studies. Accordingly, epithelioid morphology (aggressive behaviour) was more common in small intestinal GISTs. Even if molecular studies are not available in resource-limited countries like India, the basic IHC panel is the most useful in the final diagnosis. Risk stratification criteria are helpful for prognostication and further management with the use of appropriate targeted therapies. Larger studies are required, especially from Asian countries, to look for regional differences that may be helpful in the framing of guidelines specific to the Asian region.

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