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GASTROINTESTINAL STROMAL TUMORS: A CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY

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ABSTRACT

Aims:

1. To study the clinicopathological features of Gastrointestinal stromal tumors (GISTs).
2. To study and confirm the diagnosis GISTs by Immunohistochemistry and to establish the correct final diagnosis to help treatment of patient.

Methodology: Thirty one cases of GISTs were diagnosed between January 2010 to October 2015. Their clinical presentations, gross and microscopic features were studied. The surgical specimens were categorized into risk groups based on the National Institute of Health (NIH) consensus criteria. Immunohistochemcal study was done on formalin fixed, paraffin embedded tissue blocks with a panel of five antibodies; CD-117, CD-34, SMA, Desmin and S-100.

Result:

- Peak age of occurrence was between 5th and 7th decade. More cases were diagnosed in males than in females.
- Pain in abdomen was the most common presenting complaint.
- Small intestine was the most common site followed by stomach, colon and rectum. There were 16.1% cases of EGISTs (extragastrointestinal stromal tumors).
- The size of tumor as measured by the maximum diameter ranged from 2.5-30 cm. Average size was maximum for EGISTs.
- Based on the National Institute of Health (NIH) consensus criteria 60.9% (n=14) of cases belonged to the high risk group. 21.7% (n=5) were in the low risk group while 17.4% (n=4) belonged to intermediate risk group.
- Spindle cell type was the most common histological type (90.3%).
- Immunohistochemistry was done in all the cases and 90.3% (n=28) of cases were CD-117 positive. 35.5% (n=11) were positive for CD-34.

Conclusion: Gastrointestinal stromal tumors (GISTs) are rare tumors of the GI tract and account for only 0.1-3% of the gastrointestinal neoplasms. Mitotic rate and tumor size have gained the greatest acceptance as being predictive of outcome. The role of Immunohistochemistry is well known in the diagnosis of GISTs and there has been continuing attempts at finding a more specific and sensitive marker than CD117. New markers like PDGFRA, PKC θ and DOG1 are being analyzed. The combination of a detailed histopathological examination and Immunohistochemistry is important for diagnosis, management and prognostication of patients of GISTs.

Key Words: Gastrointestinal stromal tumors (GISTs), Immunohistochemistry, Extragastrointestinal stromal tumors (EGISTs).

INTRODUCTION

Although far less common than epithelial neoplasms, mesenchymal tumors of the GI tract are not rare. Gastrointestinal stromal tumors (GISTs) constitute approximately 2% of all neoplasms of the GI tract.[1] Over 90% of GISTs occur in adults over 40 years old. GISTs can arise anywhere in the GI tract from esophagus to the colon and rectum. 10% of cases arise outside the tubal gut, in locations such as the mesentery, omentum and retroperitoneum, and have been referred to by

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the acronym EGIST (extragastrointestinal stromal tumors).[1]

The presenting manifestations depend on the site of involvement in the GI tract, the size of the tumor, and the precise portion of the gut wall in which the tumor is located.[2] Clinical symptoms vary and many tumors are discovered incidentally.[3] GISTs show a wide spectrum of histologic features and have distinctive appearances depending on their primary location.[4]

An evidence-based approach for defining the risk of aggressive behaviour in GISTs, based on tumor size and mitotic count, has been presented. Other factors as anatomic location, cellular atypia and necrosis have been shown to be independent prognostic factors.[5] With the discovery of high prevalence of c-Kit mutations and development of STI-571 (Imatinib [Gleevec]), the treatment of GIST has been revolutionized.[6]

MATERIALS AND METHODS

Cases of GISTs morphologically diagnosed on histopathology from January 2010 to October 2015 were included in the study. During this period 23 surgical specimens and 8 biopsies were diagnosed as GISTs.

Histopathological diagnosis was achieved based on gross and microscopic examination of Hematoxylin and Eosin stained slides. The clinical details and pathological findings were obtained from the records available. Clinical data included patient's age, gender, clinical presentation, physical examination and other investigations (hematological, radiological, and endoscopic, FNAC). The pathological findings including tumor location, gross appearance, tumor size (maximum diameter in cm), metastases and microscopic findings were noted.

The surgical specimens were categorized into risk groups based on the National Institute of Health (NIH) consensus criteria (so called Fletcher's criteria- Table a) Based on this system, benign GISTs do not exist and instead the most harmless tumors have been assigned a "very low malignant potential".[7]

Immunohistochemistry (IHC) was performed according to the protocol prescribed Thermo Scientific Immunohistochemistry Solutions, with a panel of five antibodies, CD-117, CD-34, SMA, Desmin and S-100.

Table a: 2002 NIH consensus guidelines risk assessment of GISTs based on tumor size and mitotic frequency

Risk category	Tumor size (cm)	Mitosis/ 50 HPF
Very low risk	<2	<5
Low risk	2-5	<5
	<5	6-10
Intermediate risk	5-10	<5
	>5	>5
High risk	>10	Any
	Any size	>10

Adapted from Fletcher et al

HPF- High Power Field; NIH- National Institute of Health[8,12]

Study was conducted with the prior approval of the subjects and institution, in accordance with the prevailing ethical and legal standards.

RESULTS

Thirty one surgical specimens and biopsies were diagnosed as GISTs on histopathological examination, including twenty three surgical specimens and eight biopsies. Surgical specimens of the biopsies were not recieved.

One case located in small intestine (ileum) was diagnosed on fine needle aspiration cytology (FNAC) and was followed by its specimen which was confirmed to be GIST on histopathology (Figure 1).

Most of the cases of GISTs were between 5th and 7th decade (64.5%). The youngest age was 19 years and the oldest was 80 years. The mean age was 57.8 years. Median age was 60 years. There were 24 (77.4%) cases in males and 7 (22.6%) cases in females. (Male:Female = 3.5:1)

Table 1: Clinical presentation of GISTs

Chief complaint	No of cases	Percentage
GI bleeding	5	16.1%
Abdominal pain	11	35.5%
Lump in abdomen	8	25.8%
Vague abdominal discomfort, fullness of abdomen	3	9.7%
Asymptomatic/ incidental	1	3.2%
Others	3	9.7%
Total	31	100%

Some tumors presented with more than one complaint. The main complaint was taken into consideration. One patient presented with difficulty in deglutition and was diagnosed as squamous cell carcinoma of the oesophagus (Figure 2) with incidentally diagnosed GIST in stomach.

Out of the 31 cases, 7 (22.7%) were located in the stomach, 10 (32.2%) in small intestine, 4 (12.9%) in colon and 5 (16.1%) in rectum. There were 5 (16.1%) cases of EGISTs, 2 in mesentery and 3 in retroperitoneum.

Two cases had liver metastasis. In one case liver biopsy along with the primary tumor in large intestine was received (Figure 3). Two cases, one in large intestine and other in small intestine (duodenum) showed regional lymph node metastases.

The size of tumor ranged from 2.5-30 cm. For biopsies the radiological size was considered. The average size was 8.7cm with no tumor of size less than 2cm. Average size was 9.0cm.

Table 2: Size range and median size of tumor at different sites

Site	Range	Median
Stomach (n=7)	3-9 cm	6cm
Small intestine (n=10)	2.5-10 cm	9.5cm
Colorectum (n=9)	3-12 cm	7cm
Mesentery/Retroperitoneum (n=5)	6.9-30 cm	18cm

The average size was 18.0cm in EGISTs (mesentery and retroperitoneum), which was greater than at other sites (Figure 4)

Table 3: Mitotic index of GIST cases

Mitotic index	No. of cases	Percentage
≤ 5/ 50 HPF	11	35.5%
> 5/ 50 HPF	20	64.5%
Total	31	100%

(HPF- High Power Field)

The surgical specimens (n=23) received were put into risk groups as per the National Institute of Health (NIH) consensus criteria 2002 of risk assessment of GISTs. As 8 were biopsies whose specimens were not received, they were not included.

Table 4: NIH 2002 risk groups of specimens received (n=23)

Risk group	Number of cases	Percentage
Very low risk	0	0%
Low risk	5	21.7%
Intermediate risk	4	17.4%
High risk	14	60.9%
Total	23	100%

(NIH-National Institute of Health)

Table 5: Sitewise distribution of risk groups of specimens (n=23) according to NIH 2002 guidelines

Risk	Size (cm)	Mitotic count (per 50 HPF)	No. of cases			
			G	S	C	A
Very low	<2	<5	0	0	0	0
Low	2-5	<5	2	1	2	0
Intermediate	<5	6-10	0	0	0	0
	5-10	<5	3	1	0	0
High	>5	>5	1	6	2	0
	>10	Any mitotic rate	0	1	0	4
	Any size	>10	0	0	0	0
Total			6	9	4	4

NIH-National Institute of Health

HPF = high power field (x 400 microscopic magnification)
S= small intestinal;

G= gastric;

C= colon/rectum;

A= abdominal (mesentery,retroperitoneum)

* The first line of prognostic assessment was the tumor size. E.g. if a tumor was larger than 10 cm and had mitotic count over 10/50 HPFs, it was stratified to high-risk >10 cm, any mitotic rate group.

All the cases of GISTs presenting in the mesentery or retroperitoneum (EGISTs) belonged to high risk group. In small intestine also a higher percentage of cases belonged to high risk group (77.8%). In stomach most cases belonged to low or intermediate risk group (83.3%) and only 16.7% cases were in high risk group

Out of 31 cases of GISTs, 28 were of spindle cell type (90.3%). Only 1 case arising from colon showed pure epithelioid histology. 2 cases had mixed histology, one in stomach and other in large intestine.

Immunohistochemistry was applied on all cases.

Table 6: IHC findings of GISTs (n=23)

Antibodies	No. of positive cases	Percentage of positive cases
CD-117	28	90.3%
CD-34	11	35.5%
SMA	1	3.2%
Desmin	0	0%
S-100	0	0%

Desmin and S-100 was negative in all cases. So there was no case of GNAT with neural differentiation. Only one case, located in the stomach, was positive for SMA. It was also positive for CD-117 but negative for CD-34.

Three cases were CD-117 negative, two in colorectum (1 in large intestine, 1 in rectum) and one in stomach. Out of these, tumor located in rectum was positive for CD-34. All other markers were negative.

IHC findings of EGISTs were similar to that at other sites. CD-117 was positive in all five cases of EGISTs and CD-34 was positive in only one case.

DISCUSSION

Gastrointestinal stromal tumours (GISTs), despite being rare, pose a relevant medical problem from the viewpoint of diagnosis and management.[9] These tumors are a heterogeneous group of neoplasms, and prediction of clinical behavior requires a multiparametric evaluation. However, the same criteria for malignancy do not apply to stromal tumors from different sites within the gastrointestinal tract, and the relative importance of each of these features is somewhat controversial.[10]

The true incidence may also be rising.[11] As GIST are highly resistant to conventional chemotherapy and radiotherapy[12-15], and carry a high risk of metastatic relapse after initial surgery, survival rates were poor until 2002, when the FDA approved the tyrosine kinase inhibitor (TKI) imatinib mesylate (formerly STI571) for their treatment.[9]

The results of the study were compared with similar studies in India and abroad.

In the present study, the age range was between 19-80 years. Most of the cases (64.5%) were in the 5th and 6th decade. The mean age was 57.8 years. Median age was 60 years. The age was comparable to all other studies. (table 7)

Table 7: Age parameters in different studies

Study	Age range (years)	Mean age (years)	Median age (years)
Ueyama T et al.[15] (1992) [n=96]	17-79	55	-
DeMatteo RP et al.[16] (2000) [n=200]	16-94	-	58
Orosz Z et al.[17] (2005) [n=136]	19-88	59.2	59
Rajappa S et al.[18] (2007) [n=50]	28-73	-	50
Vij M et al.[19] (2010) [n=121]	15-83	50.4	-
Present study (2015) [n=31]	19-80	57.8	60

In most studies done in foreign countries and with more number of cases, the incidence in males and females were comparable with slightly more incidence in males. (table 8) However, in studies done in India, more cases were diagnosed in males than in females. A longer duration study with more cases will be needed to draw definitive conclusion.

Table 8: Sex ratio of GIST cases in different studies

Study	M:F ratio
Ueyama T et al. (1992) [n=96]	1:1
DeMatteo RP et al. (2000) [n=200]	1.3:1
Orosz Z et al. (2005) [n=136]	1.3:1
Rajappa S et al. (2007) [n=50]	2:1
Lakshmi VA et al. (2010) [n=92]	3:1
Present study (n=31)	3.5:1

In the present study the most common site of occurance was colorectum as a group, which represented 29.0% (n=9) of the cases [Colon-12.9%(n=4); Rectum-16.1%(n=5)]. But as a single entitity the most common site was small intestine (32.2%; n=10). In most other studies stomach was found to be the most common site. However, in the study of 50 cases at Hyderabad by Rajappa S et al. (2007)[19] and 92 cases from Tamil Nadu, by Lakshmi VA et al. (2010)[21], small intestine was the most common site.

In the present study cases of EGISTs were slightly more than in other studies. However, in the study done at All India Institute of Medical Sciences, New Delhi, by Iqbal N et al. (2015)[22] which included 13 cases of EGISTs of mesentery and retroperitoneum, similar findings were noted and it was concluded that EGISTs may actually be more frequent, as they were found at a rate of 12% of all stromal tumors.

Table 9: Sitewise distribution of cases in different studies

Study	Oesophagus	Stomach	Small intestine	Colorectum	EGIST	Unknown (unspecified)
Ueyama T et al. (1992)	9.4%	59.4%	29.2%	2.1%	-	-

DeMatteo RP et al. (2000)	-	39%	32%	15%	9%	5%
Orosz Z et al. (2005)	-	44.8%	27.9%	8.1%	-	19.2%
Rajappa S et al. (2007)	-	30%	36%	16%	14%	4%
Lakshmi VA et al. (2010)	2.2%	39%	43%	8.6%+3.3% (anal canal)	-	3.9%
Vij M et al. (2010)	-	55.4%	29.8%	4.1%	10.7%	-
Present study (2015)	0%	22.7%	32.2%	29.0%	16.1%	-

Table 10: Risk groups in different studies

Risk group	Orosz Z et al. (2005)	Lakshmi VA et al. (2010)	Present study (2015)
Very low	3.6%	1.0%	0%
Low	10.7%	8.0%	21.7%
Intermediate	9.8%	20.6%	17.4%
High	75.9%	70.4%	60.9%

In all the studies, most cases belonged to high risk group with minimum frequency of cases belonging to very low risk group.

Spindle cell GIST was most common in the present study (90.3%; n=28). There was 1 case of pure epitheloid histology and 2 cases of mixed histology, similar to other studies.

In the present study 90.3% (n=28) of cases were CD-117 positive and 35.5% (n=11) were CD-34 positive. CD-34 was positive in less percentage of cases in present study as compared to other studies.

Table 11: IHC findings in different studies

Study	CD-117	CD-34	SMA	Desmin	S-100
Orosz Z et al. (2005)	97.8%	70.0%	39.6%	0.9%	5.7%
Lakshmi VA et al. (2010)	94.5%	77.0%	50.0%	17.0%	25.0%
Vij M et al. (2010)	94.2%	59.2%	39.7%	36.4%	4.1%
Present study (2015)	90.3%	35.5%	3.2%	0%	0%

Table 12: Percentage of CD-34 positivity at different sites

Study	Stomach	Small intestine	Colorectum	Retroperitoneum/ Mesentery
Vij M et al. (2010)	73.0%	44.5%	40%	-
Present study (2015)	57.1%	40.0%	22.2%	25.0%

Vij M et al. (2010)[20] observed that frequency of CD-34 positivity varied significantly in GISTs of different locations. Maximum positivity was present in gastric GIST (73%). Similar finding was noted in the present study with gastric GIST showing maximum positivity (57.1%).

CONCLUSION

Gastrointestinal stromal tumors (GISTs) are rare and account for only 0.1-3% of the gastrointestinal neoplasms.[20] Even though a number of studies on GISTs are available from foreign countries, the studies from our country are still limited. The exact incidence, age and sex data of GISTs in our country is not yet available.

Criteria for distinguishing benign from malignant GISTs, or at least to identify those lesions that are more likely to metastasize, have been sought, analyzed and disputed for many

years. Many parameters have been proposed but mitotic rate and tumor size have gained the greatest acceptance as being predictive of outcome.[23] The combination of a detailed histopathological examination and use of Immunohistochemistry is important for diagnosis, management and prognostication of patients of GISTs.

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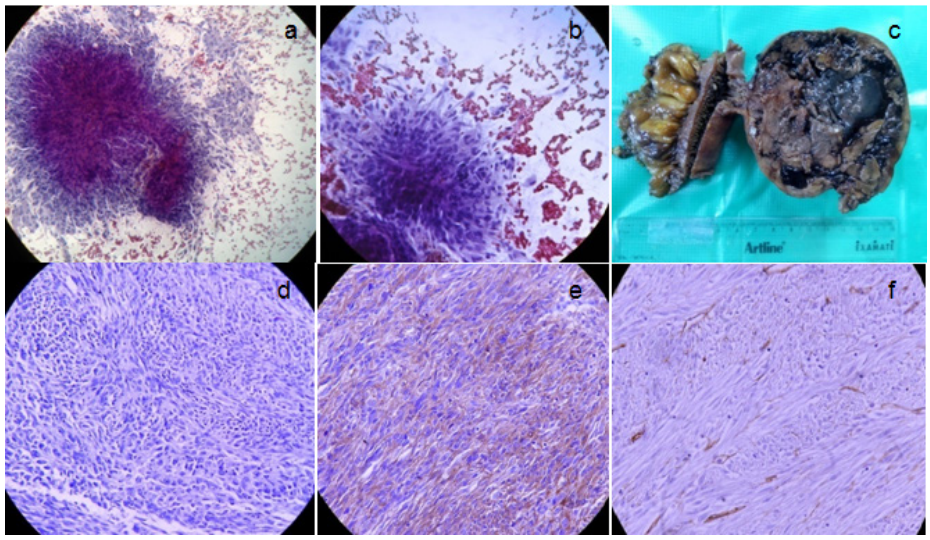

Figure 1:

a] Fine needle aspiration cytology of small intestinal GIST showing high cellularity and closely packed clusters. Spindle cells displaying elongated to wavy nuclei with blunt to tapered ends (pap, x200).

b] Spindle cells with bipolar cytoplasmic processes seen at periphery of the cluster (pap, x400).

c] Gross appearance of small intestinal GIST. The tumor is protruding outside the lumen of the small intestine. Note the fleshy, hemorrhagic cut section.

d] Plump and uniform spindle cells arranged in fascicles (H&E, x400).

e] CD117 positivity in small intestinal GIST (IHC, x400).

f] CD34 negative in small intestinal GIST. Autocontrol positive in vessel wall (IHC, x400)

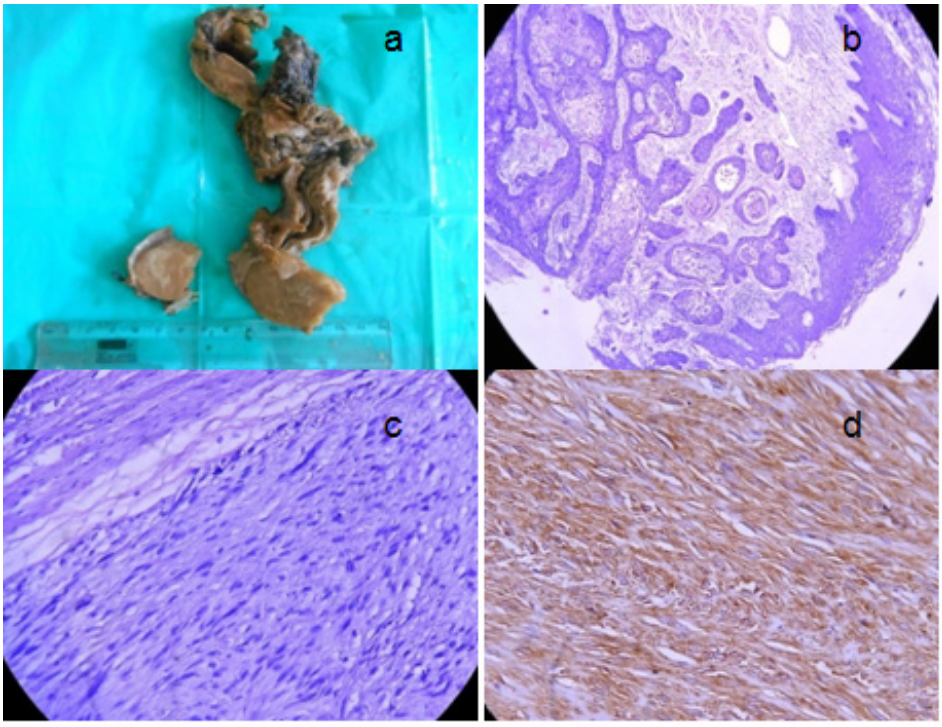

Figure 2:

a] Gross appearance of gastric GIST. Notice thickening of upper part of oesophageal wall.

b] Low power microscopic appearance of concomitant squamous cell carcinoma of oesophagus (H & E, x100).

c] High power microscopic appearance of GIST showing spindle cell histology (H & E, x400).

d] CD117 positivity in gastric GIST- High power view (IHC, x400).

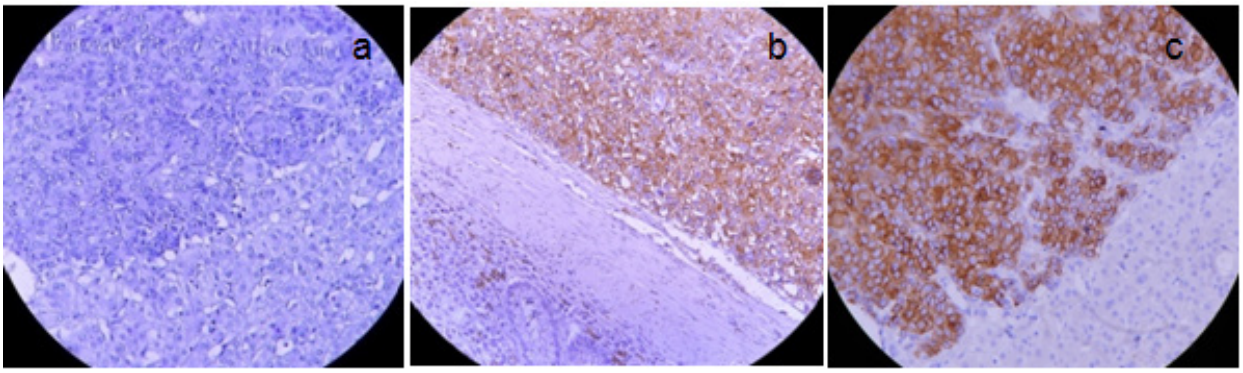

Figure 3:
a] Biopsy from liver metastasis showing round epitheloid cells similar to the primary tumor in large intestine. Tumor with part of liver seen (H & E, x400).
b] CD117 positivity in primary tumor (IHC, x400).
c] CD117 positivity in liver metastasis (IHC, x400).

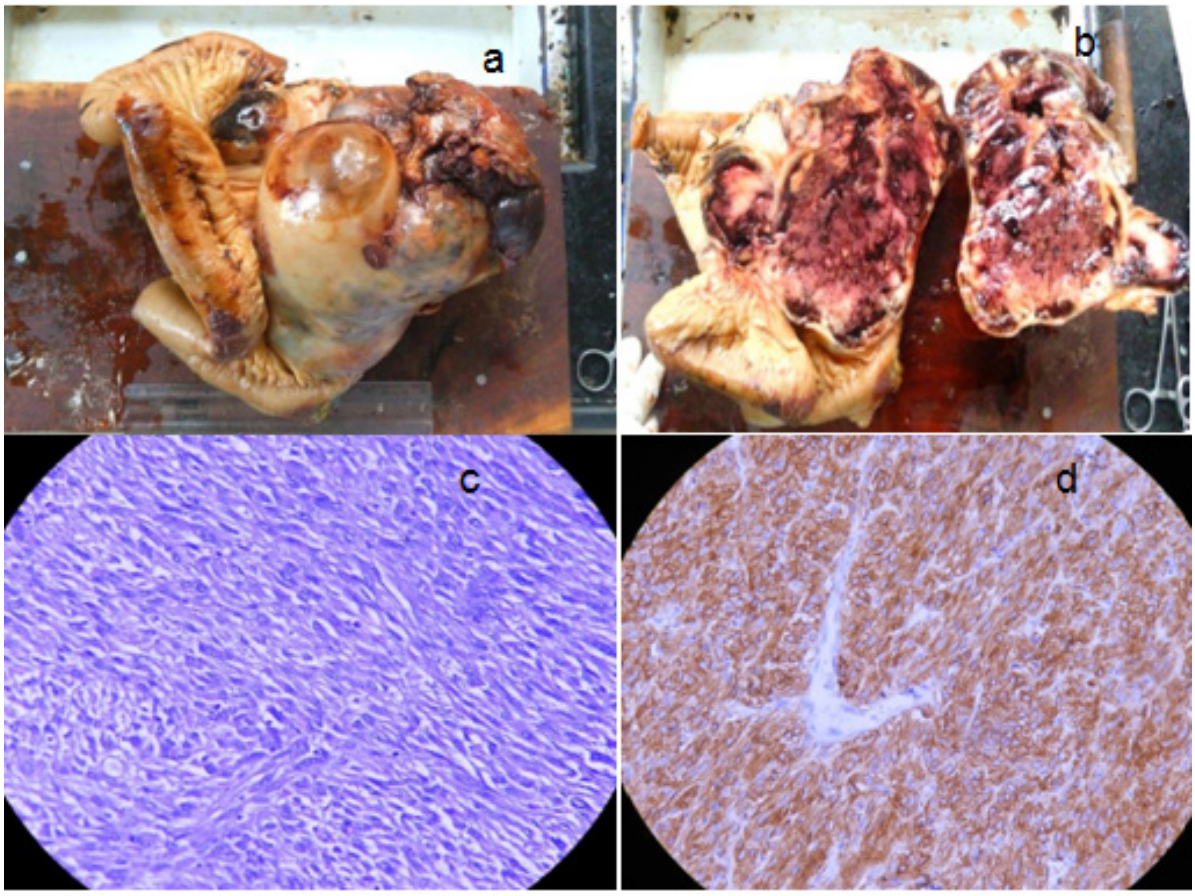

Figure 4:
a] Gross appearance of extragastrointestinal stromal tumor (EGIST) of mesentery. The tumor is large, lobulated and attached to mesentery.
b] Cut section is fleshy with areas of hemorrhages.
c] Microscopic appearance of EGIST showing spindle shaped neoplastic cells having hyperchromatic nuclei. Mitosis is frequent (H & E, x400).
d] CD117 positivity in EGIST (IHC, x400).