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ORIGINAL RESEARCH OPEN ACCESS

An observational study of gastrointestinal stromal tumors by histopathology and immunohistochemistry

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Abstract

Introduction: Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract and their diagnosis is mainly based on histopathology and immunohistochemical study with CD117 marker. However, there are many GIST tumors that are CD117 negative and for such cases come the role of other IHC markers. The study aimed to observe the various histological features and demographic profiles of GISTs and the role of various immunohistochemical markers in the confirmation of diagnosis.

Methodology: A hospital-based observational study was conducted on 40 tumor resection materials diagnosed as GIST from April 2017 to February 2023 at tertiary care center K.E.M. Hospital, Pune. All the cases underwent histopathological examination with standard procedure of tissue processing, staining and IHC with CD117. Those cases who were morphologically designated as GIST on HPE were evaluated with a panel of IHC markers like C-KIT, CD34, SMA, desmin, S-100 and vimentin.

Results: 35 out of 40 cases (87.5%) were found to be positive for CD117 while IHC markers like CD34, SMA, desmin, S-100 and vimentin were found to be positive in 60%, 20%, 5%, 2.5% and 80% cases respectively. Also, we found significant relationship between histopathological groups different progressive disease risk groups with necrosis, cytologic atypia, cellularity and mucosal invasion (p-value<0.05)

Conclusion: In a nutshell, a GIST diagnosis should not be precluded on the basis of morphology only. Use of immunohistochemistry is vital to rule out other mesenchymal tumors and confirmation of GIST.

Keywords: GIST; gastrointestinal stromal tumors; IHC; CD 117; histopathology; c-KIT

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract, their incidence being estimated at 14 to 20 cases per million population; they are more frequent in male patients older than 50 years old. The diagnosis of stromal neoplasms is based on immunohistochemical study with CD117 marker, expressed in most such neoplasia's. Noteworthy are also other markers: DOG 1, nestin, theta protein kinase C and carbonic anhydrase II [1].

Ironically, it was one of the most confusing and neglected area of both surgical pathology and clinical oncology until 2001, when a consensus conference held at National Institute of Health provided a solid, evidence-based rationale for diagnosis and prognostication of GIST's [2].

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Gastrointestinal stromal tumors (GIST) account for 1-3% of all gastrointestinal malignancies (ESMO guidelines) [3]. GIST is characterized by a mutation in the c-Kit or PDGFRA gene, and the vast majority (95%) stains positively with CD117 antibody using immunohistochemistry (IHC), however, a small percentage are CD117 negative. Occasionally, GIST may arise outside of the gastro-intestinal tract (EGIST) and has been recognized as an uncommon variant [4].

Before the pathogenesis of GIST was understood, most GISTs were formerly diagnosed as leiomyo-blastomas and gastrointestinal autonomic nerve tumors (GANTs). GIST arises from interstitial cells of Cajal (ICC) and is generally characterized to be immunohistochemically positive for KIT (CD117) and contains KIT-or PDGFRA-activating mutations [5]. Although GISTs display a spectrum of biological behavior from benign to malignant, the pathogenesis of tumor progression is still debated [6].

Mazur and coworkers coined the term gastrointestinal stromal tumors to refer to a group of mesenchymal tumors of neurogenic or myogenic differentiation that lacked immunohistochemical features of Schwann cells and did not have ultrastructural features of smooth muscle cells [7]. Landmark work done by Hirota and colleagues in 1998 demonstrated c-Kit (CD117) (Cluster designation 117) mutations in the pathogenesis of GISTs [8]. GISTs also express CD34 on their surface. GISTs were considered to originate from interstitial cells of Cajal, but are now believed to arise from multipotent mesenchymal stem cells [9].

Approximately 95% of GISTs stain positive for KIT (CD117) by immunohistochemistry (IHC). Epithelioid GISTs tend to have weaker KIT staining than the spindle cell type. Other commonly expressed markers include CD34 (70%), smooth muscle actin (30%) and desmin (<5%). While immunophenotype is an important component in the diagnosis of GIST, it is not sufficient. Other malignancies that can stain positive for KIT include metastatic melanoma, angiosarcoma, small cell lung cancer and Ewing's sarcoma. The diagnosis of GIST is based on concordance between the morphology and IHC [10].

It was concluded in recent years that immunoexpression of CD117 (c-kit) as an IHC marker of intestinal Cajal cells, which are the origin cells of GISTs, is a gold standard for final diagnosis in tumors, revealing locations and morphological findings that are consistent with GIST [11].

The tumors can be positive for KIT (also known as c-KIT or CD 117) which is seen consistently, CD 34 in 60-70%, SMA (smooth muscle actin) in 30-40%, S100 (5%), desmin in 1-2% [12, 13].

GIST spans a wide clinical spectrum ranging from tumors with no metastatic potential to malignant and life-threatening spread diseases [14]. Prognostic factors of GISTs depend on tumor size and mitotic activity per 5 mm^2 [5].

The molecular pathological studies show that most GISTs are immunoreactive for CD34, a marker for dendritic fibroblastic interstitial cells, and CD117, a c-kit proto-oncogene protein, as well as the gain-of-function c-kit gene mutations that cause pathologic activation of the tyrosine kinase of c-kit in many GISTs, seem to support the concept of GISTs as a biologically distinct entity [15]. 15% of GISTs do not display a definable KIT or PDGFRA mutation. These are classified by convention as wild-type GISTs. They represent a variety of different genomic changes but are not clinically distinct from mutant KIT or PDGFR [16].

The aim of the study was to see the various histological features and demographic profile of GISTs and the role of various immunohistochemical markers (c-KIT or CD-117, CD-34, SMA, desmin, S-100 & vimentin) in the confirmation of the diagnosis and to study the relationship between progressive disease risk groups and histopathological features.

Materials and methods

A hospital-based observational study was conducted on 40 tumor resection material diagnosed as GIST from April 2017 to February 2023 at tertiary care center K.E.M. Hospital, Pune. The necessary permission and approval from the ethics committee and authority, prior to initiation of the study was taken.

All the cases were retrieved, evaluated, and analyzed for age, sex, presenting complaints, tumor localization, histopathological parameters and IHC features. Histopathological features included the gross appearance of the tumor, its size etc. The type of material on which histopathological examination (HPE) was done consisted of tumor resection specimens or slides for review received at the institute. Standard procedures of tissue processing, staining and IHC were done.

Light microscopic findings, which include pattern (spindle/ epithelioid /other), differentiation (smooth muscle/neural/uncommitted), cellularity, cytologic atypia, mucosal invasion, and necrosis were noted. Metastasis was also noted if present in any case. The number of mitoses was counted per 50 consecutive high-power fields from the most cellular or mitotically

active areas. H&E stained slides of paraffin blocks representing tumors were classified according to the criteria of AFIP/2006 [9] and the proposed approach for defining the risk of aggressive behavior in GIST, by Fletcher [2] (Table 1).

Table 1: Proposed approach for defining the risk of aggressive behavior in GIST, by Fletcher [2].

Risk	*Size (cm)*	*Mitotic figures (per 50 HPF)*
Very low risk	<2	<5
Low risk	2 to 5	<5
Intermediate risk	<5	6 to 10
	5 to 10	<5
	>5	>5
High risk	>10	Any mitotic rate
	Any size	>10

For the purpose of clinicopathologic correlation, the GISTs were divided into six categories i.e., (1) 2-5 cm with mitosis <5/50 hpf, (2) >5-10 cm with mitosis <5/50 hpf, (3) >10cm with mitosis <5/50 hpf, (4) 2-5 cm with mitosis >5/50 hpf; (5) >5-10 cm with mitosis >5/50 hpf, (6) >10 cm with mitosis >5/50 hpf.

All H&E slides and immunohistochemistry slides were retrieved from the filing system. In cases of lost or broken slides, immunostains were applied to freshly cut sections. Each case was evaluated with an immunohistochemistry panel consisting of CD117 (Rabbit monoclonal antibody clone yr145 ready to use-BIOGENEX), CD34, S-100, desmin, SMA and vimentin. An external positive control was run for each stain. Local infiltration and distant metastasis by the neoplasm were determined along with the exact histological grading of tumor and IHC features.

Statistical method

The data on categorical variables (such as age group, sex, presenting complaints etc.) is presented as n (% of cases) and the values on normally distributed continuous variables are presented as Mean ± SD for non-normally distributed continuous variables Median (Min–Max) is used. The Chi-square/Fisher exact test is used to find the significance of study parameters on a categorical scale between two or more groups. Kruskal Walis H test is used to find the significance of study parameters on a continuous scale between two or more groups. The p values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data was analyzed statistically using Statistical Package for Social Sciences (SPSS version 15.0, Inc. Chicago, USA).

Results and discussion

In our study, the patients' age ranged from 23 to 77 years with a median of 48.5 years with slight male preponderance male: female ratio is 1.5:1. The most common site of tumor was in stomach 17 cases (42.5%) followed by small intestine 12 cases (30.0%) and large intestine 7 cases (17.5%), esophagus and mesentery was found to be rare site (5% each).

26 cases (65.0%) had presenting complaint of pain, 5 cases (12.5%) had lump, 4 cases (10.0%) had bleeding per rectum, 3 cases (7.5%) had hematemesis and 2 cases (5.0%) had altered bowel habit.

The most common histological pattern observed was Spindle pattern of tumor in 80.0% cases followed by mixed pattern in 12.5% cases and epithelioid pattern 7.5% cases.

24 cases had <5 mitosis /50HPF while 16 cases had >5 mitosis /50HPF. Among all these cases, 14 cases (35.0%) had tumor size between 2 – ≤5cm, 14 cases (35.0%) had tumor size between 5.0 – ≤10.0 cm and 12 (30.0%) had tumor size more than 10.0cm. Size ranged from 2 cm to 18 cm with a median of 6.8 cm (Table 2).

Table 2: Showed distribution of cases by size of tumor and mitosis (n=40).

Size of tumor (cm)	*Mitosis /50hpf (<5) (n=24)*		*Mitosis /50hpf (>5) (n=16)*	
	No. of cases	*% of cases*	*No. of cases*	*% of cases*
2.0 – ≤5.0	9	37.5	5	31.3
>5.0 – ≤10.0	9	37.5	5	31.3
>10.0	6	25.0	6	37.5
Total	24	100.0	16	100.0

Note: values are n (% of cases), Chi-square value = 0.714, p value = 0700.

Most of the cases were found to be high risk 17 out of 40 (42.5%) followed by moderate risk 14 (35.0%). 33 (82.5%) did not have metastasis, 5 (12.5%) cases had metastasis present to liver and 2 (5.0%) had metastasis present to lymph node.

We found significant relationship between different progressive disease risk groups with necrosis, cytologic atypia, cellularity and mucosal invasion (p-value<0.05) and but not seen with hemorrhage (p value>0.05) (Table 3).

Table 3: Showed relationship between progressive disease risk and histopathological features (n=40).

Histopathological features		*Progressive disease risk*				*p value*
		Very low risk (n=1)	*Low risk (n=8)*	*Moderate risk (n=14)*	*High risk (n=17)*	
Hemorrhage	Present (72.5%)	0	4 (13.8)	11 (37.9)	14 (48.3)	0.124
	Absent (27.5%)	1 (9.1)	4 (36.4)	3 (27.3)	3 (27.3)	
Mucosal invasion	Present (28.9%)	0	0	2 (18.2)	9 (81.8)	0.035*
	Absent (71.1%)	0	8 (29.6)	11 (40.7)	8 (29.7)	
Cellularity	High (80%)	1 (3.1)	5 (15.6)	9 (28.1)	17 (53.1)	0.042*
	Low (20%)	0	3 (37.5)	5 (62.5)	0	
Cytologic Atypia	High (62.5%)	0	2 (8.0)	11 (44.0)	12 (48.0)	0.037*
	Low (37.5%)	1 (6.7)	6 (40.0)	3 (20.0)	5 (33.3)	
Necrosis	Present (77.5%)	0	5 (16.1)	9 (29.0)	17 (54.8)	0.013*
	Absent (22.5%)	1 (11.1)	3 (33.3)	5 (55.6)	0	

Note: Values are n (% of cases), *p value <0.05 is considered to be statistically significant.

35 out of 40 cases (87.5%) were found to be positive for CD117 while IHC markers like CD34, SMA, desmin, S-100 and vimentin were found to be positive in 60%, 20%, 5%, 2.5% and 80% cases respectively (Table 4).

Table 4: Showed distribution of IHC findings.

CD117		*CD34*		*SMA*		*S100*		*Desmin*		*Vimentin*		*Total*
+ve	*-ve*	*+ve*	*-ve*	*+ve*	*-ve*	*+ve*	*-ve*	*+ve*	*-ve*	*+ve*	*-ve*	
35 (87.5 %)	5 (12.5%)	24 (60.0%)	16 (40.0%)	8 (20.0%)	32 (80.0%)	1 (2.5%)	39 (97.5%)	2 (5.0%)	38 (95.0%)	32 (80.0%)	8 (20.0%)	40 (100.0%)

Note: Values are n (% of cases).

In nutshell, we found 12.5% tumors morphologically designated as GIST stained negatively for CD117. The application of other IHC markers along with histopathology findings helps in the diagnosis of such cases.

Figure 1 shows gross appearance of excised specimen of pedunculated gastric mass and duodenal tumor respectively.

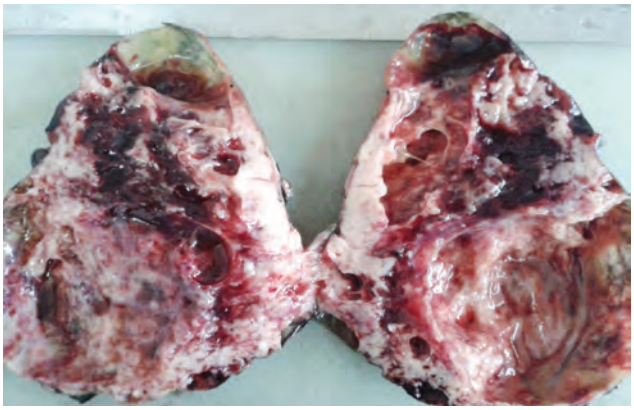

Figure 1a: Macroscopic appearance of excision specimen of pedunculated gastric mass measuring 18 cm in greatest dimension, cut section is grey white, soft to firm with areas of necrosis, hemorrhage and cystic change. No normal gastric mucosa seen.

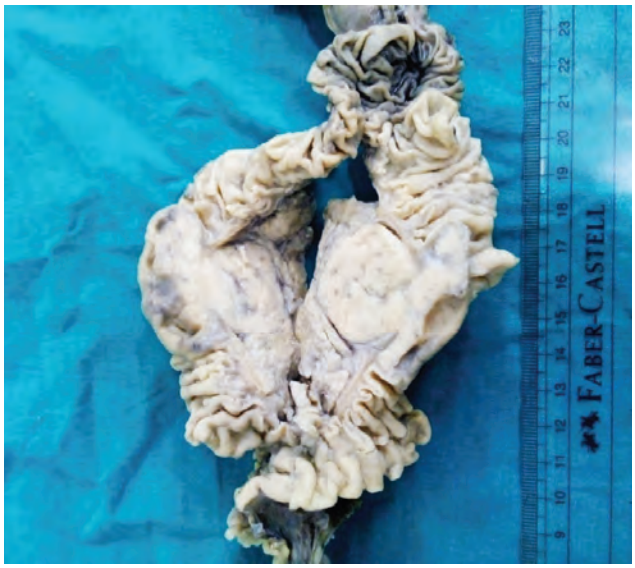

Figure 1b: Macroscopic appearance of a duodenal resection specimen showing a subserosal grey white, firm , lobulated mass with well defined borders measuring 3.5 cm in greatest dimension, sparing the mucosa.

Figure 2 showing cellular spindle cell tumour of stomach. The spindle cells are having benign nuclei and perinuclear vacuoles,the CD117 is diffusely and strongly positive in these spindle cells (both cytoplasmic and membranous positivity) respectively.

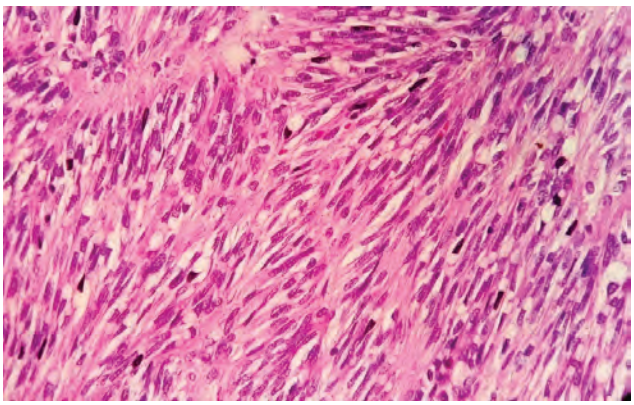

Figure 2a: High power view of a cellular spindle cell tumor of stomach. The cells are cytologically bland. Prominent perinuclear vacuoles are present, which is an artifact of fixation. H& E stain, 40 X.

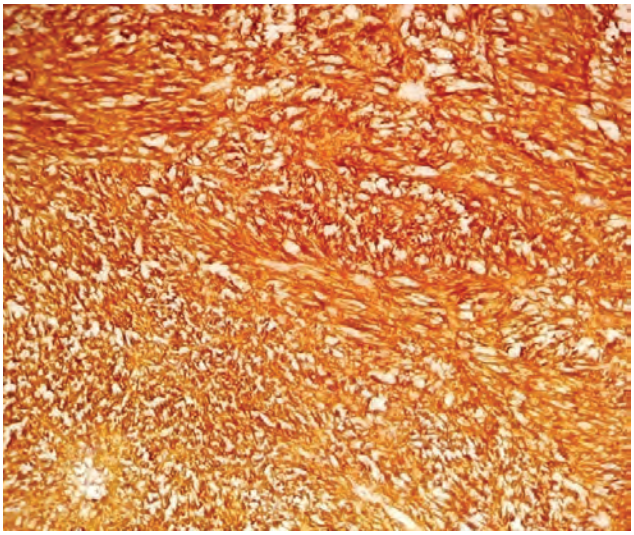

Figure 2b: Diffuse and strong expression of CD117, membranous and cytoplasmic staining in cellular spindle shaped Gastric GIST, 40X.

Figure 3 showing gastric stromal tumour with epitheliod morphology with increased mitosis and CD117 is diffusely positive in these tumour cells respectively.

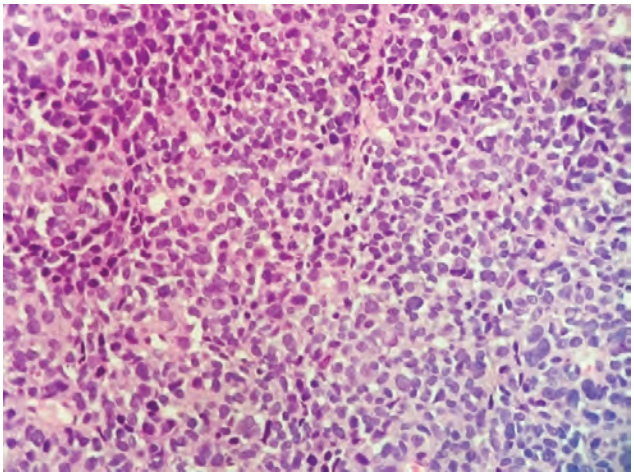

Figure 3a: Malignant epithelioid gastric stromal tumour. H & E Stain, 20X.

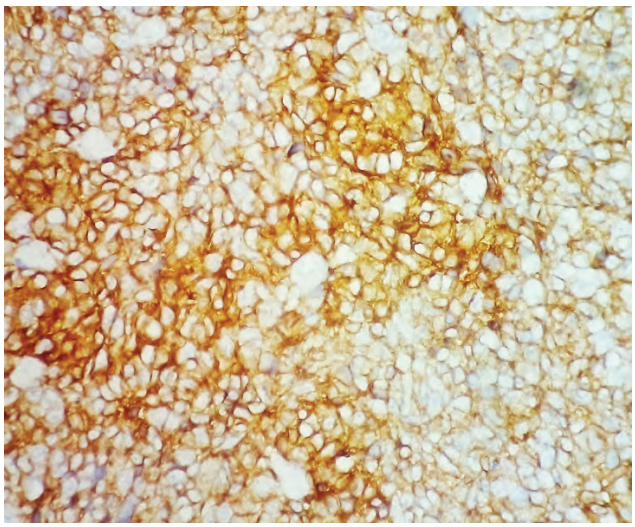

Figure 3b: CD117 positivity in malignant epithelioid gastric GIST, 40X.

Figure 4a showing spindle shaped morphology on microscopy of gastric mass with CD117, S100 and CD34 negativity (Figure 4b,4c,4e) respectively and SMA was focally positive. (Figure 4d).

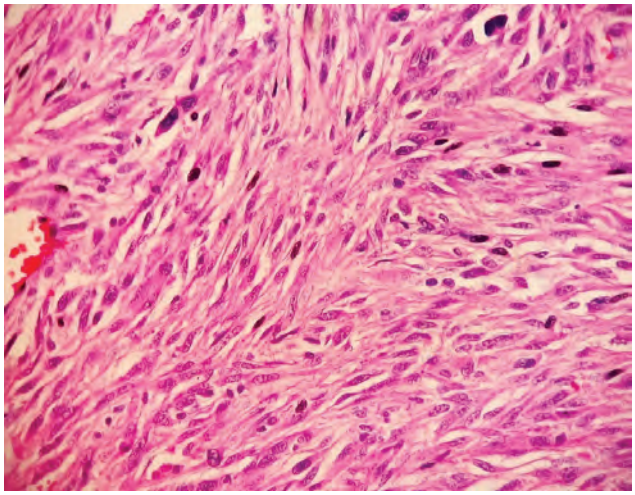

Figure 4a: High power view of spindle shaped GIST, H & E stain.

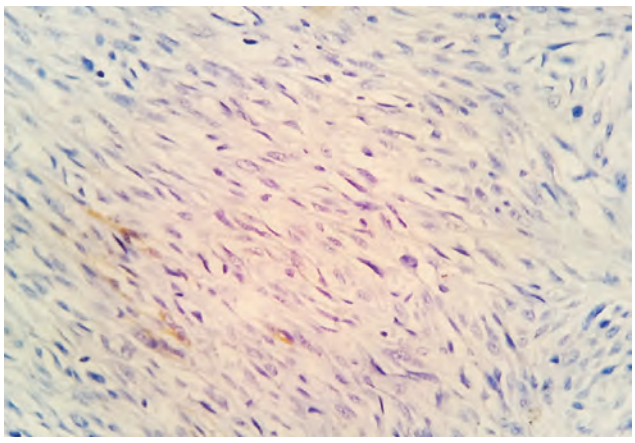

Figure 4b: CD117 negativity in spindle shaped GIST (In same case of figure 4a), 40 X.

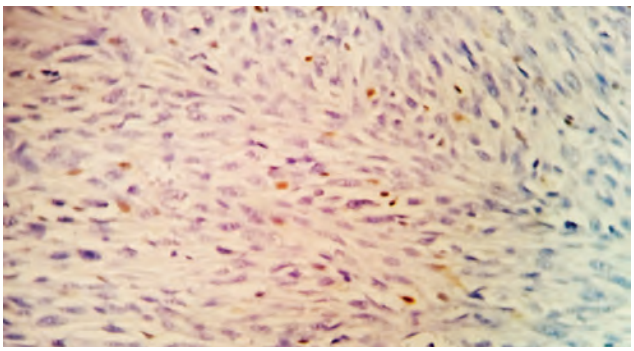

Figure 4c: S-100 negativity in spindle shaped GIST (In same case of image 4a), 40 X.

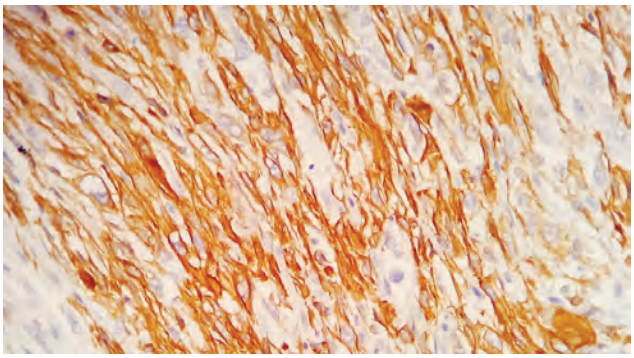

Figure 4d: SMA positivity in spindle shaped GIST (In same case of image 4a), 40 X.

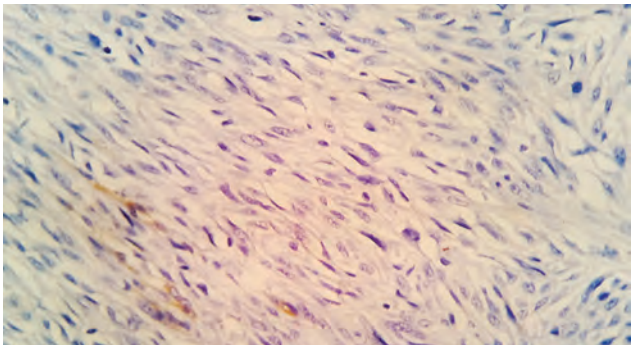

Figure 4e: CD 34 negativity in spindle shaped GIST (In the same case of image 4a), 40 X.

Figure 5a shows spindle-shaped tumor cells metastasize to the liver on light microscopy. Hepatocytes are also seen separately. Figure 5b shows CD117 diffusely positive in spindle cells in the same case.

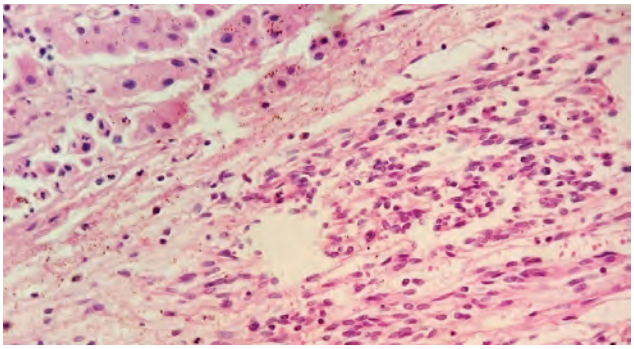

Figure 5a: Metastasis of spindle cell GIST to liver.

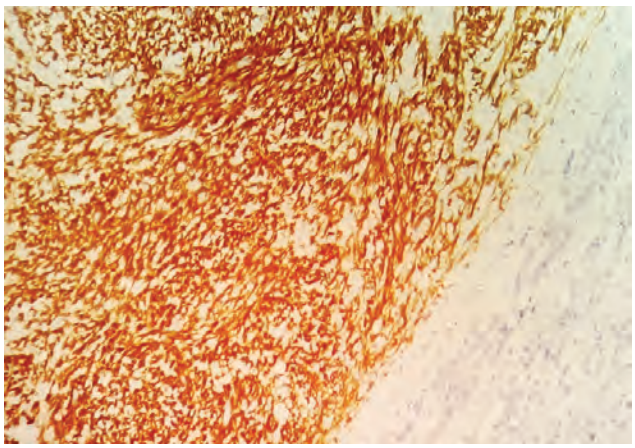

Figure 5b: Diffuse expression of CD117in metastatic (to liver) spindle cell GIST 20x.

Limitations: This is a hospital based study, hence the patients included in the study cannot be considered to be the random sample of the population under study. A longitudinal population based and multicenter study will be required to confirm our findings.

Conclusions

Our study concluded that to demonstrate mucosal invasion proper sampling of tumors involving mucosa needs to be done as it is commonly seen in high-risk groups of GIST and it is advisable to use Fletcher's criteria to demonstrate different progressive disease risk groups, mucosal invasion and atypia. IHC panel plays a vital role in demonstrating GIST. It is important for the pathologist to keep in mind that GIST should not be ruled out solely based on negative staining for CD117, especially when the morphology is otherwise typical. When testing is available, the identification of KIT or PDGFRA mutations can help confirm or diagnose KIT negative GIST. This information can also be important in determining the prognosis for patients who are being considered for Imatinib therapy. We recommend conducting future studies with a larger sample size to determine the correlation between different progressive disease risk groups and mucosal invasion and necrosis.

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Conflicts of interest

Authors declare no conflicts of interest.

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