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Study of Histomorphological Spectrum of Mesenchymal Tumors of GIT at Tertiary Care Centre

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ABSTRACT

Introduction: Mesenchymal neoplasms of gastrointestinal tract are a group of rare tumors with overlapping histological features. There is significant morphologic overlap among diagnostic entities on the differential of mesenchymal lesions. So, use of a panel of immunohistochemical antibodies is necessary for accurate characterization of mesenchymal lesions of gastrointestinal system.

Aim: The study was conducted in a tertiary care hospital in western India between January, 2019 to June 2020 to study the histomorphological spectrum and utility of IHC in the final diagnosis of mesenchymal tumor of GIT.

Material & Methods: The cases were selected on the basis of inclusion & exclusion criteria defined and thereafter a panel of IHC antibodies was applied to diagnose mesenchymal tumors of gastrointestinal tract.

Results: The study included 92 cases with a clinical and provisional morphologic diagnosis of mesenchymal tumors of GIT, mesentery and omentum. 25.00% cases of MT of GIT and were diagnosed on morphology alone. While, 75.00% required IHC for final diagnosis. Tumors with spindle cell morphology 61.95%, epithelioid cell morphology 5.80%, with mixed (spindle+epithelioid) cell morphology 10.14% and pleomorphic cell morphology 1.45%. Using" WHO 2013 of soft tissue tumors" MT of GIT were classified according to clinical behavior in to Benign tumors in 44.57% cases, lipoma being the commonest tumour diagnosed 34.15% cases. Intermediate tumors in 8.70% cases, all cases 100% being fibromatosis. Malignant tumors in 46.74% cases. Using "WHO 2019 of MT of Digestive System", tumors were classified based on cell type. The commonest phenotype was "GIST" with 42.39% cases, followed by the second common phenotype "Adipose and Myofibroblastic tumor" with 33.69% cases, "Smooth and Skeletal Muscle tumors" with 9.78% cases. "Neural Tumors" with 7.63% cases, "Vascular and Perivascular" with 5.43% cases.

Conclusion: GIST are the commonest MT of GIT. The availability of targeted chemotherapy warrants confirmation and ruling out GIST amongst all MT on priority basis. IHC panel should be applied in stepwise manner over "morphologically suspicious" cases Mesenchymal Tumors of GIT to diagnose and rule out GIST with first panel being CD117 and DOG1. These optimize the use of antibodies and make it cost effective.

Key words: Mesenchymal tumors, GIST, CD 117, DOG 1 antibody

INTRODUCTION

Mesenchymal neoplasm of gastrointestinal tract is a group of rare tumors with overlapping histological features. Gastrointestinal stromal tumor (GIST) is the most common (80%) mesenchymal tumor of the alimentary canal[1] GISTs are rare, accounting for 1% to 2% of gastrointestinal neoplasms.[2] It is crucial to detect GIST

among mesenchymal tumors to consider the patients for potential targeted chemotherapy in form of tyrosine kinase inhibitors (imatinib).

Mesenchymal neoplasm affecting the gastrointestinal (GI) tract typically present as subepithelial neoplasm. They are divided broadly into four histomorphological groups on the basis of cell types spindle, epithelioid, mixed and others. The most common group consists of neoplasms that are known as gastrointestinal stromal tumors (GISTs). The less common group of mesenchymal GI tract neoplasms comprise a spectrum of tumors that are identical to those that arise in the soft tissues in other parts of the body including lipoma, liposarcoma, leiomyoma, leiomyosarcoma, desmoids tumor, schwannoma and peripheral nerve sheath tumor[2], inflammatory fibroid polyps, fibromatosis etc. Leiomyoma, a benign pure smooth muscle tumor, is the second most common mesenchymal tumor of the GI tract after GIST. Leiomyoma is the most common spindle cell neoplasm of the esophagus followed by colorectum[3].

The WHO classification of digestive system tumor presented in the first volume of the WHO classification of tumors series, 5th edition, reflects important advancements in our understanding of tumors of the digestive system. Since the publication of the 4th-edition digestive system tumor volume in 2010, there have been important developments in our understanding of the aetiology and pathogenesis of many. Change in 2019 WHO classification of tumors of digestive system for mesenchymal tumors is that they are grouped together in separate chapters, to ensure consistency and avoid duplication tumor.[4]

There is significant morphologic overlap among diagnostic entities on the differential of mesenchymal lesions. So, use of a panel of immunohistochemical antibodies is necessary for accurate characterization of mesenchymal lesions of gastrointestinal system.

The present study is designed with the purpose to study the histomorphological spectrum of mesenchymal tumors of gastrointestinal tract according to recent The WHO 2019 classification of mesenchymal tumors of digestive system. Having a well established immunohistochemistry laboratory in the department, the present study also focuses on evaluation of mutation among mesenchymal tumors by using CD117 and DOG1 antibodies for an accurate diagnosis to initiate appropriate therapeutic decision. The treatment of GISTs includes surgery and imatinib therapy. Accurate diagnosis and treatment in GISTs prolong the survival of GIST patients.

MATERIAL AND METHOD

This is a hospital based cross-sectional study and was conducted in the Histopathology unit of the Pathology Department, Santokba Durlabhji Memorial Hospital cum Medical Research Institute, study was conducted after obtaining approval from scientific and research committee followed by approval from the institutional Ethical Committee.

- Study Area: The source of data for the study were the specimens from IPD, OPD, and outside specimens received at the Histopathology unit of the Pathology Department of Santokba Durlabhji Memorial Hospital cum Medical Research Institute, Jaipur (Rajasthan)
- Study Design: This is a hospital based cross-sectional study and was conducted in the Histopathology unit of the Pathology Department, Santokba Durlabhji Memorial Hospital cum Medical Research Institute, Jaipur (Rajasthan).
- Study Period: This study was conducted over a period of 18 months, extending from January. 2019 to June. 2020.
- Study Population: Patients whose specimens received at the Histopathology unit of the Pathology Department of Santokba Durlabhji Memorial Hospital cum Medical Research Institute, Jaipur (Rajasthan).
- Sample Size: The Sample size was calculated at 95% confidence level assuming 90% GIST among all

mesenchymal tumors as per results of reference study[5]. A total of 101 cases were received in the department during the 18 months study period. 92 cases satisfied the inclusion criteria. 9 cases were excluded as 4 cases had no tumor size available and in 5 cases material for IHC was inadequate

Inclusion Criteria

Cases diagnosed as mesenchymal tumor of GIT on light microscopy, seen in GIT, irrespective of age and gender. Tumor involving mesentry and omentum are also included as a significant overlap was found at these sites.

Exclusion Criteria

1. Cases with no or incomplete clinical details.
2. Cases with inadequate material for IHC.

METHODOLOGY

A written informed consent and clinical details were recorded. After fixation for 12-24 hours grossing was done. Processing, paraffin embedding, section cutting was done by standardized methods. Haematoxylin-Eosin staining [6] was done and slides were mounted and labeled. Representative block was selected for IHC staining.

Immunohistochemistry Analysis was done using:

- Antigen retrieval method: Heat Induced Epitope Retrieval method by BIO GENEX-EZ-Retriever systemV.3.
- Antibodies: Following antibodies were used:

Antibodies and Their Localization

Name of Antibody	Clone	Company	Positive Control	Type of Antibody	Localization
CD34	QBEND/10	Biogenex	Endothelial cells	Mouse monoclonal antibody	Membranous/cytoplasmic
CD117/c kit	A4502	Dako	GIST	Rabbit polyclonal antibody	Membranous and/or cytoplasmic
DOG1	DOG 1.1	Biogenex	GIST	Mouse monoclonal Antibody	Membranous and/or cytoplasmic
SMA	1A4	Biogenex	Colon	Mouse monoclonal antibody	Cytoplasmic
Desmin	33	Biogenex	Muscle	Mouse monoclonal antibody	Cytoplasmics
CK (Cytokeratin cocktail)	AE1 & AE2	Biogenex	Skin	Mouse monoclonal antibody	Cytoplasmic
EMA	E29	Dako	Breast	Mouse monoclonal antibody	Cytoplasmic/ Membranous
S-100	15E2E2	Biogenex	Melanoma	Mouse monoclonal antibody	Cytoplasmic/Nuclear
Beta-catenin	Beta-catenin	Dako	Colon or Breact carcinoma	Mouse monoclonal antibody	Nuclear/Membranous/Cytoplasmic

Continuous variables were summarized as mean and standard deviation while nominal/categorical variables will be expressed as proportions(percentage). Descriptive statistics was used and online free medical software MedCalc 16.4 version used.

The sections were checked for adequacy and categorization of cases of GIST was done according to morphological types followed by application of IHC panels in step wise manner as shown in Fig 1,2 & 3.

Fig -1 Cut surface of tumor is fleshy with hemorrhage & necrosis

Fig-2 H & E section showing spindle cell tumor (40 x)

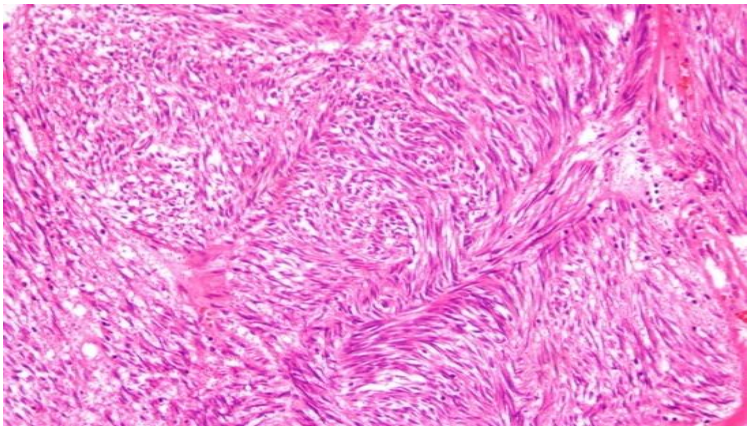


Fig -3 H & E – Epithelioid GIST (40 X)

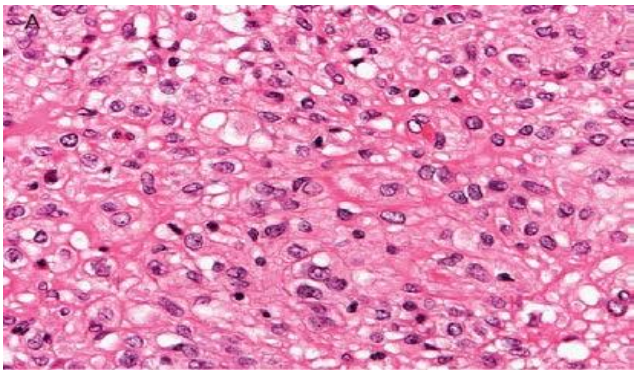
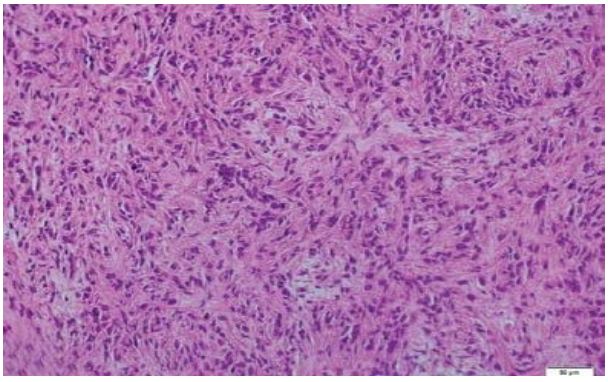
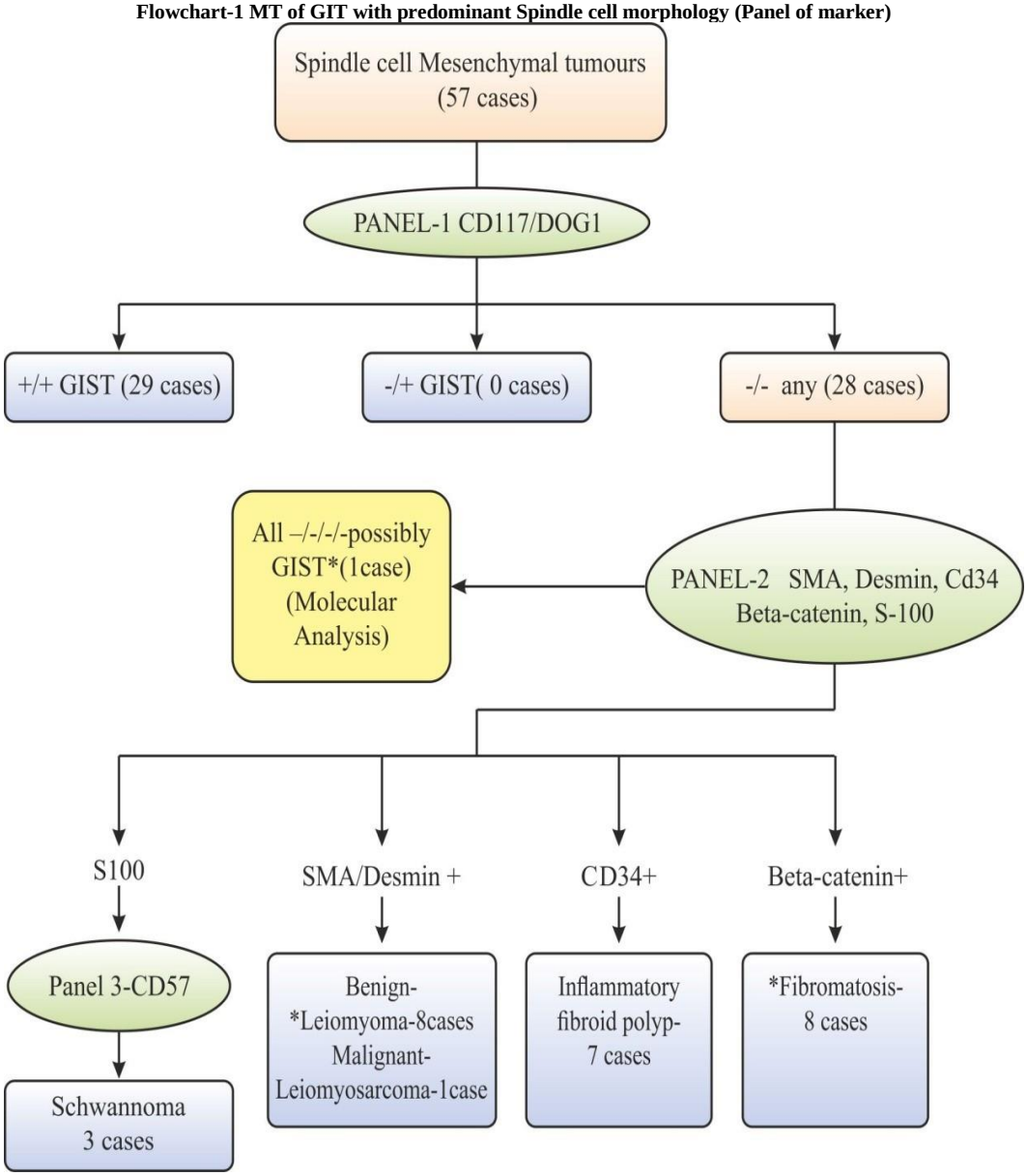


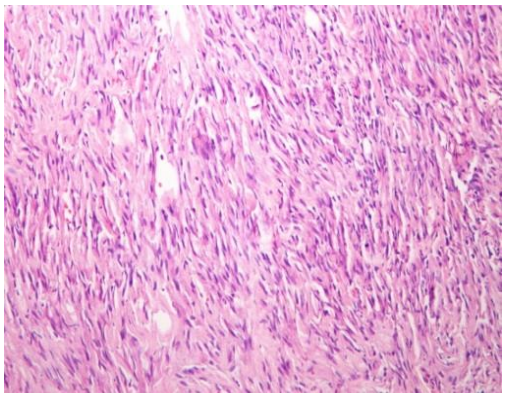
Fig -4 H & E – Mixed GIST (40 X)



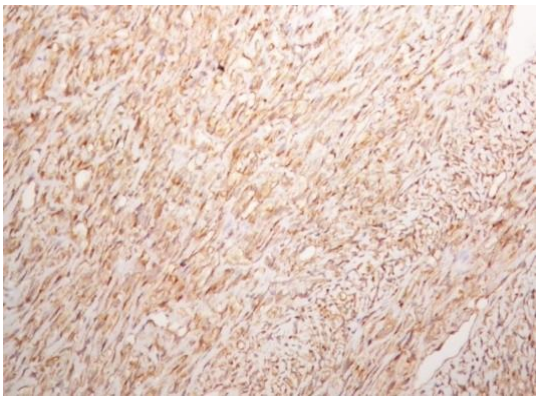
Flowchart-1 MT of GIT with predominant Spindle cell morphology (Panel of marker)



FIBROMATOSIS

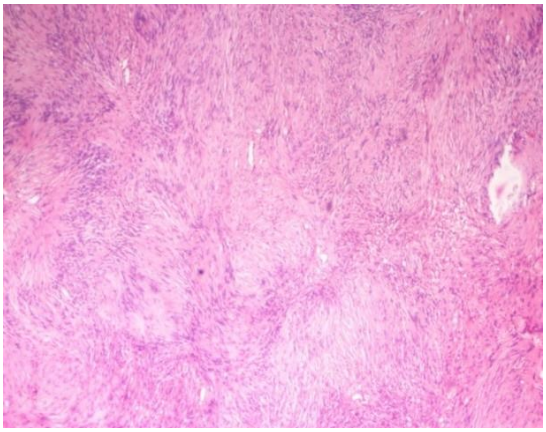


(H&E: 10X)

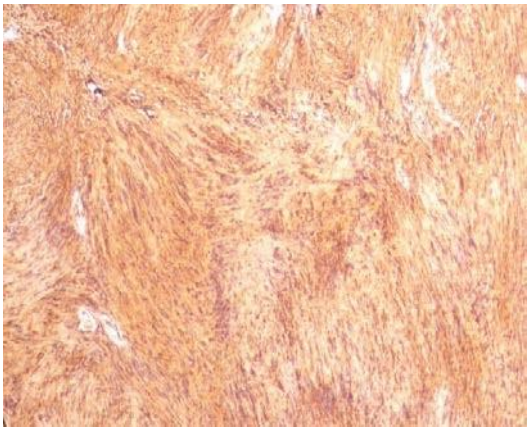


(10X : Beta-catenin strong nuclear staining)

SCHWANNOMA

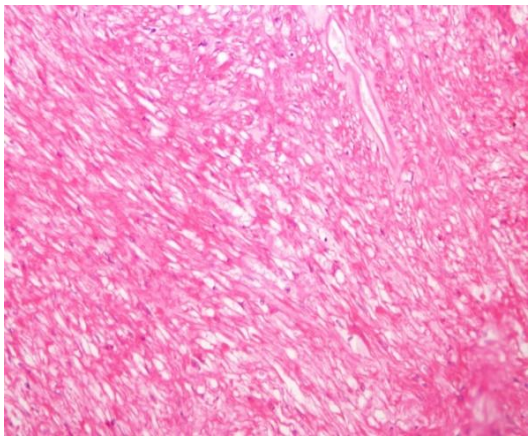


(H&E: 10X)

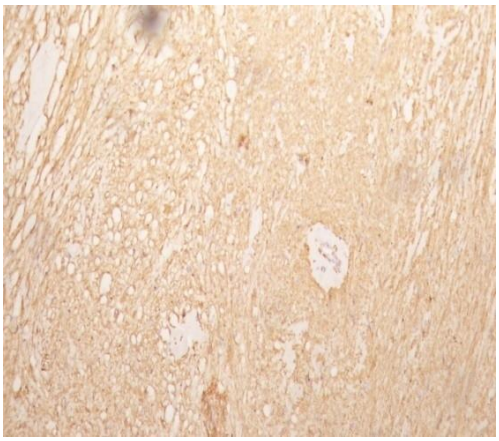


(10X : S100 strong cytoplasmic staining)

LEIOMYOMA

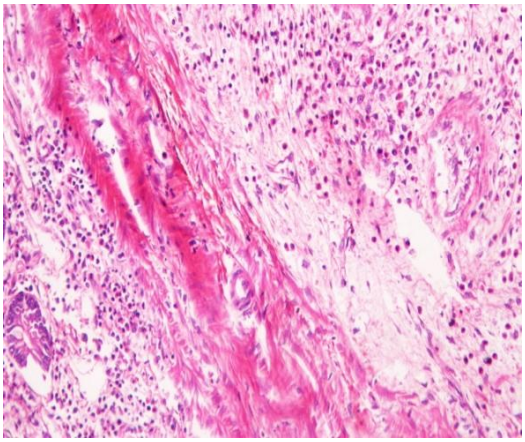


(H&E: 10X)

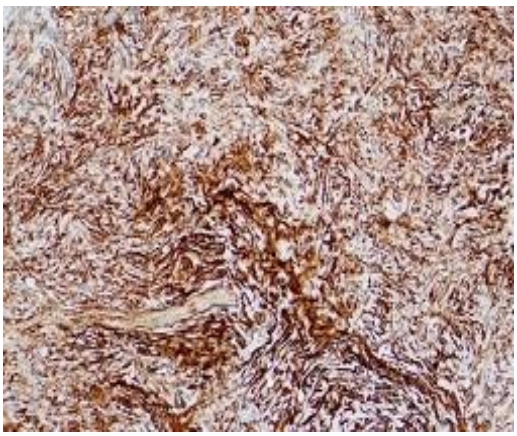


(10X : SMA strong cytoplasmic staining)

INFLAMMATORY FIBROID POLYP



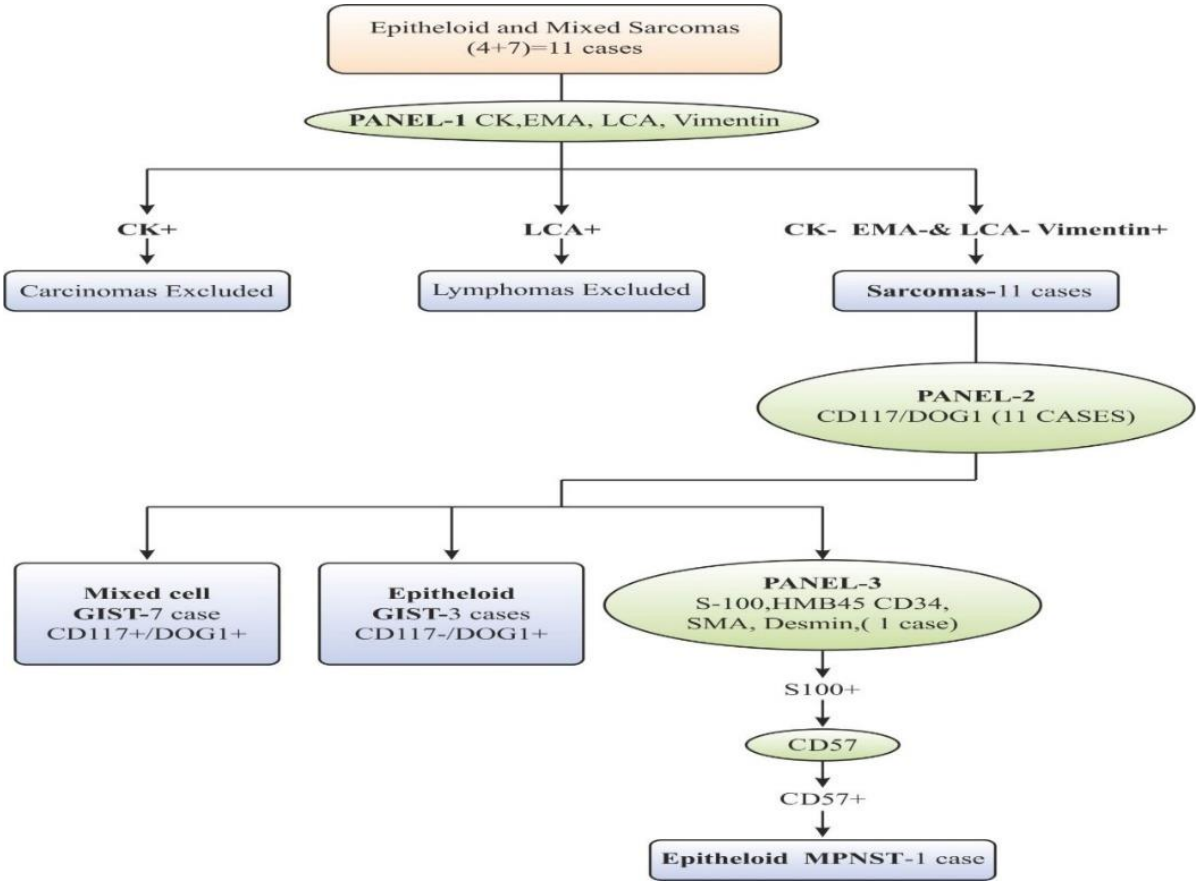
(H&E: 10X)



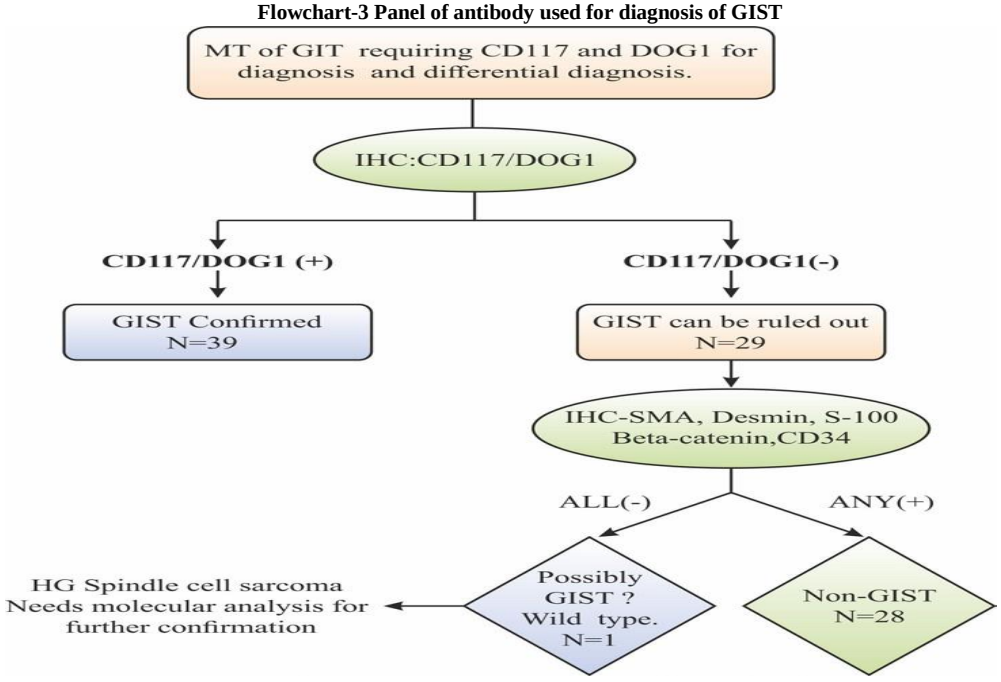
(10X : CD34 strong cytoplasmic and membranous staining)

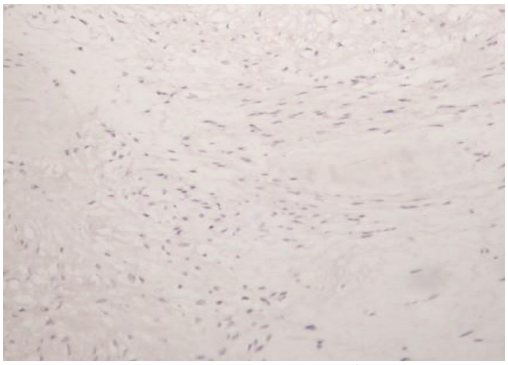
H & E stained section reveals the bland spindle cells, scattered inflammatory cells comprising of mostly eosinophils and lymphocytes which are set in a loose collagenous stroma with prominent small to medium sized blood vessels. On IHC shows strong cytoplasmic staining with SMA.

Flowchart-2 MT of GIT with epithelioid and mixed cell morphology



Flowchart-3 Panel of antibody used for diagnosis of GIST





Tumors Cells are Negative for CD117

Tumour Cells are Negative for DOG1

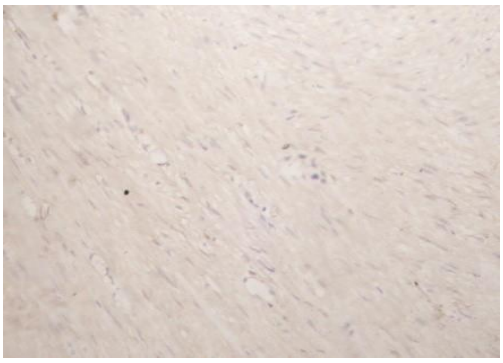


Table No.1 Distribution of mesenchymal tumor of GIT cases Accepted / Rejected N=101

Screened cases	Criteria (inclusion/exclusion)	No. of cases
Accepted	Cases satisfying inclusion criteria	92
Rejected	Tumour size not known (incomplete clinical details)	4
	Suboptimal material for IHC analysis	5
Total		101

Table No. 2 Distribution of cases of MT of GIT on basis of need of IHC for diagnosis (MORPHOLOGIC DIAGNOSIS) N=92

Need for IHC	Morphological Diagnosis	No.	%
IHC Not Mandatory (N=23, 25.00%)	Lipoma	14	60.87
	Lymphangioma	4	17.39
	Haemangioma	1	4.35
	Angiolipoma	1	4.35
	Ganglioneuroma	3	13.04
	Total	23	100
IHC Mandatory For final Diagnosis (N=69, 75.00%)	MT with predominant spindle cell morphology	57	61.95
	MT with predominant epitheloid cell Morphology	4	5.80
	MT with (S+E) mixed cell morphology	7	10.14
	MT with pleomorphic cell morphology	1	1.45
	MT with round cell morphology	0	0
	Total	69	100
	Grand Total	92	100

Table No.3 Distribution of cases of mesenchymal tumor of GIT depicting Final Diagnosis on IHC (Morphology / IHC Diagnosis) N=92

Morphology	IHC Diagnosis	No.	%	Total %
Lipoma	IHC not required	14	60.87	15.22
Lymphangioma	IHC not required	4	17.39	4.35
Haemangioma	IHC not required	1	4.35	1.09
Angiolipoma	IHC not required	1	4.35	1.09
Ganglioneuroma	IHC not required	3	13.04	3.26
	Total	23	100	25.00
MT with predominant spindle cell morphology (N=57, 61.95%)	Leiomyoma	8	30.77	8.70
	Inflammatory fibroid polyp	7	26.92	7.60
	Schwannoma	3	11.54	3.26
	Fibromatosis	8	30.77	8.70

	GIST	29	93.55	31.52
	Leiomyosarcoma	1	3.23	1.09
	HG Spindle cell Sarcoma*GIST	1	3.23	1.09
		57	100	61.95
MT with predominant epitheloid cell morphology (N=4, 4.35%)	Epitheloid GIST	3	75.00	3.26
	Epitheloid MPNST	1	25.00	3.26
		4	100	4.35
MT with predominant mixed (spindle+epitheloid) cell morphology (N=7, 7.60%)	GIST	7	100.00	7.60
		7	100	7.60
MT with pleomorphic cell morphology (N=1, 1.09%)	HG Dedifferentiated Liposarcoma	1	100	1.09
		1	100	1.09
Grand Total		92	100	100

Table No. 4 Classification of soft tissue tumor of GIT on basis WHO 2013 N=92 (Based on biological potential/clinical behaviour)

Clinical Behaviour	Final Diagnosis	No.	%
Benign (41, 44.57%)			
	Lipoma	14	34.15
	Leiomyoma	8	19.51
	Inflammatory Fibroid Polyp	7	17.07
	Lymphangioma	4	9.76
	Schwannoma	3	7.32
	Ganglioneuroma	3	7.32
	Haemangioma	1	2.44
	Angiolipoma	1	2.44
	Total	41	100.00
Intermediate (8, 8.70%)			
	Fibromatosis	8	100.00
	Total	8	100.00
Malignant (43, 46.74%)			
	GIST*	39	90.70
	High Grade Liposarcoma	1	2.33
	HG Spindle cell Sarcoma**	1	2.33
	Leiomyosarcoma	1	2.33
	MPNST	1	2.33
	Total	43	100.00
Grand Total		92	100.00

*Basedon validated risk stratification, behavior in GIST ranges from essentially benign to uncertain malignant potential to malignant.

**High Grade Spindle cell Sarcoma? GIST (wild type) morphologically GIST negative for CD117 and DOG1, needs molecular study for further confirmation.

Table No. 5 Classification of mesenchymal tumor of GIT on the basis of WHO 2019 N=92 (Based on phenotype/cell of origin)

Origin of tumors	Subtype	No.	%	Total %
GIST (N=40, 43.47%)	GIST	40	100.00	100%
Adipose & Myofibroblastic tumors (N=31, 33.69%)	High Grade Liposarcoma	1	3.22	100%
	Inflammatory Fibroid Polyp	7	22.58	
	Fibromatosis	8	25.80	
	Lipoma	14	45.18	
	Angiolipoma	1	3.22	
Smooth & Skeletle Muscle tumors (N=9, 9.78%)	Leiomyoma	8	88.88	100%
	Leiomyosarcoma	1	11.11	
Vascular & Perivascular tumor (N=5, 5.43%)	Lymphangioma	4	80.00	100%
	Haemangioma	1	20.00	
Neural Tumors (N=7, 7.63%)	Ganglioneuroma	3	42.85	100%
	MPNST	1	14.30	
	Schwannoma	3	42.85	
Tumour of Uncertain Differentiation (n=0, 0.00%)	None	0	0.00	

Table No. 6 Distribution of Mesenchymal tumor of Digestive system correlating phenotype and clinical behavior (Phenotype WHO 2019 & Clinical behavior acc to WHO 2013)

Origin of tumour	Total	Benign (N=41, 44.56%)		Intermediate (N=8, 8.70%)		Malignant (N=43, 46.74%)	
		No.	%	No.	%	No.	%
GIST	40	0	0.00	0	0.00	40	93.02
Adipose tissue and myofibroblastic tumor	31	22	53.66	8	100	1	2.32

Smooth muscle and Skeletal muscle tumor	9	8	19.51	0	0.00	1	2.32
Vascular and Perivascular tumor	5	5	12.20	0	0.00	0	0.00
Neural tumor	7	6	14.63	0	0.00	1	2.32
Tumor of uncertain differentiation	nil	0	0.00	0	0.00	0	0.00
Grand Total	92	41	100	8	100	43	100

Percentage of GIST amongst malignant mesenchymal tumor N=43

Total malignant mesenchymal tumor of GIT	**43**	**100.00%**
GIST	40	93.02%
Non-GIST	03	6.97%

DISCUSSION

Mesenchymal neoplasms of gastrointestinal tract are a heterogeneous group of tumors with a wide clinical spectrum ranging from benign incidentally- detected nodules to frank malignant tumors. Individual benign mesenchymal entities range from frequent (e.g. lipoma) to rare (e.g. spindle cell haemangioma) 7Sarcomas are relatively rare subset of GI tumor, far outnumbered by carcinomas and benign mesenchymal GI neoplasms [8]. GIST is the most common sarcoma of GI tract[9,10]. Gastrointestinal stromal tumors (GISTs) are rare tumors with an estimated incidence of 1.5/100,000persons per year [1]. However, these are the most common mesenchymal tumors in the gastrointestinal tract [2].

The present study includes 92 cases with a clinical and provisional morphologic diagnosis of mesenchymal tumor of GIT, mesentery and omentum irrespective of clinical behavior of the tumour. The volume of cases in the study is small being 92 MT of GIT overall, and 40/92 being GIST. Study period is only 18 months, as compared to higher number of cases studied by Wang et al [11], Din et al[12] and Chen et al [13] which were performed exclusively over diagnosed cases of GIST and included 210, 255 and 1303 cases over a period of many years being 11 to 17 years. The short time span affects the no. of cases included. Hence, we realize that the present study has certain limitations.

- Retroperitoneal soft tissue tumor e.g. retroperitoneal leiomyomas, peritoneal leiomyomatosis morphologically resembling GIST where, DOG1 nonspecific positivity is reported by some studies (77) were not in the scope of present study).-expression of CD117 and DOG1 could not be observed on these tumor.
- No case of tumour of "uncertain phenotype" were observed during the study period.
- Aberrant and unusual expression of immunomarkers could not be studied, due to small no. of cases.
- Again for the same reason the percentage of various tumor may not be the actual representation of the frequency of tumor.
- Molecular study facility does not exist in our hospital setup hence, mutation in GIST by molecular studies could not be made as gold standard for comparison. The study limits itself to diagnosis of GIST by IHC technology using CD117 and DOG1 immunomarker.
- To establish specificity of any marker a large volume of cases of various tumor and their subtypes needs to be studied, due to very small no. of cases this has not been a possible scope in the present study.

Spectrum of mesenchymal tumor of GIT: (Table no. 2,3,4,5)

An attempt has been made to study the histomorphological spectrum of tumor (Table 2) and classification of MT on basis of clinical behavior (WHO 2013), phenotype of tumour (WHO 2019) (Table 4, 5) and percentage of tumor requiring IHC for final diagnosis (Table 3). Out of 92 (100%) cases 25 (27.17%) cases were diagnosed with histomorphology alone, while 69 (75%) cases required. IHC for final diagnosis. 68 (58.82%) cases being clinically and

morphologically suspicious of GIST mutations were subjected to stepwise application of antibody panel (Flowchart no. 1, 2, 3) to confirm and separate GIST 40 (58.82%) from non GIST group of tumor 28 (41.17%). Benign MT tumor were 41 (44.57%) cases, lipoma being the commonest benign tumour 14 (34.15%). The intermediate MT 8 (8.70%) consisted of fibromatosis (100%), malignant MT were 43 (46.74%) and the commonest tumour being GIST (93.02%). Also, GIST was the most frequent tumour among all mesenchymal tumor being (43.48%) and the commonest phenotype (43.48%) (Table no. 5).

Table 7: Spectrum of MT in various studies in comparison to present study

Name of study	Total no. of cases	Distribution of GIST and Non-GIST TUMOR (no., %)					
		GIST	Smooth and skeletal muscle tumor	Neural tumor	Adipose and myofibroblastic tumor	Vascular and Perivascular tumor	Tumor of uncertain differentiation
Wang et al [11]	210	127 (60.50%)	33 (15.70%)	18 (12.8%)	none	none	none
Balakrishnan et al [14]	33	24 (72.72%)	7 (21.21%)	2 (6.06%)	none	none	none
Vij et al [15]	133	121(90.98%)	8 (6.01%)	2 (1.50%)	2 (1.50%)	none	none
Varsha et al[16]	39	32 (82.05%)	5 (13.00%)	1 (3.00%)	1 (3.00%)	none	none
Ogun et al [17]	46	24 (52.17%)	9 (19.56%)	none	5 (10.87%)	none	8 (17.40%)
Lakshmi et al[18]	176	92 (52.30)	67 (38.10%)	Others 17 (9.66%)			
Abbas et al [19]	90	77 (85.60%)	Others 13 (14.4%)				
Present study	92	40 (43.48%)	9 (9.78%)	7 (7.63%)	31 (33.69%)	5 (5.43%)	none

GIST remains the most frequent neoplasm amongst all MT included in present study which is concordant with studies done by Wang et al [11], Balakrishnan et al[14], Vij et al [15], Varsha et al [16], Ogun et al [17], Lakshmi et al [18], Abbas et al [19],where GIST was found to be the commonest MT although in percentage varying from as low as 52.67% to as high as 90.98%. Comparing with studies by Abbas et al[19], Varshaetal[16], Vijetal[15], Balakrishnan etal[14] the percentage of GIST in the present study is much lower which can be explained by the selection criteria used. The present study includes all MT irrespective of their clinical behavior or morphology and the above studies included only those cases which were clinically and morphologically highly suspicious of GIST.

Table 8: Percentage of GIST in the present study and comparison with similar studies.

Percentage of GIST amongst all MT (40/92)	43.48%
Percentage of GIST amongst morphologically suspicious cases (40/68)	58.82%
Percentage of GIST amongst malignant MT(40/43)	93.02%

In present study, amongst all cases of MT (92 cases) percentage of GIST was 43.48%, while amongst malignant sarcomas GIST constituted 93.02%.

The percentage of GISTs amongst clinically and “morphologically suspicious group”- the cases which require IHC is (40/68) is 58.82%. This result is now concordant with the studies done by Ogun et al [17], Wang et al [11] and Lakshmi et al [18]. (52.67 to 60%).

The wide range of percentage variation of GIST in series appears to be the result of selection criteria (used in different studies). GIST are known to have a wide spectrum of morphology hence categorization of GIST in” morphological suspicious” cases of GIT may vary amongst histopathologists. In the present study liberal criteria has been used and hence cases of fibromatosis and inflammatory fibroid polyps have also been included to be tested by CD117 and DOG1 panel.

CONCLUSION

GIST are the commonest MT of GIT overall. availability of targeted chemotherapy warrants confirmation and ruling out GIST amongst all MT on priority basis. The IHC

panel should be applied in stepwise manner over "morphologically suspicious" cases Mesenchymal Tumor of GIT to diagnose and rule out GIST with first panel being CD117 and DOG1. Cases negative for all the antibodies should definitely be referred for molecular analysis to detect other mutations of GIST (kit/PDGFRA negative wild type GIST).

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