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Study from Tertiary Care Centre Elucidating the Role of CD 117 & DOG 1 Antibodies in Diagnosis of Gastrointestinal Stromal Tumors

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ABSTRACT

Introduction: Gastrointestinal stromal tumors are the most common mesenchymal tumors in the gastrointestinal tract. The diagnosis of GISTs becomes much more accurate by using IHC (CD117/DOG1) and molecular analysis (*KIT/PDGFRA*), both of which constitute the gold standard of diagnosis in GISTs.
Aim: The study was conducted in a tertiary care hospital in western India between January, 2019 to June 2020 to evaluate clinic pathological correlation & agreement between CD117 and DOG1 antibodies that are employed in diagnosis of GIST.
Material & Methods: The cases were selected on the basis of inclusion & exclusion criteria defined and thereafter a panel of CD117, DOG1 and other antibodies was applied to diagnose GIST from other mesenchymal tumors of gastrointestinal tract.
Results: The average age of the patient was 53.5 years with male preponderance was noted. (M:F=1.66). The clinical complaints included: GI Bleeding (50%), Abdominal pain (30%), lump abdomen (20%). Most common site for GIST was gastric (50%) followed small intestine (40%), mesentery-omentum (7.50%) and colon (2.50%). Spindle cell morphology (75.00%) was the most common histomorphological subtype. DOG1 antibody diagnosed 97.50 % cases of GIST and CD117 diagnosed 92.50% cases of GIST. DOG1 expressed high staining ratio score in 95% cases while CD117 had high staining ratio score in 87.50% cases. Mostly stronger intensity of immunostaining was observed with DOG1 while CD117 expressed variable intensity of immunostaining. Also, CD117 expressed variable immunostaining amongst different histomorphological variants and risk groups. While immunostaining with DOG1 was not significantly variable. The results demonstrated that DOG-1 was found to be a superior marker with higher sensitivity and specificity as compared to CD117, specificity (100% versus 96.43%) and sensitivity (97.5% versus 92.5%).
Conclusion: The immunohistochemistry panel should be applied in stepwise manner over "morphologically suspicious" cases Mesenchymal Tumours of GIT to diagnose and rule out GIST with first panel being CD117 and DOG1. DOG-1 was found to be a superior marker with higher sensitivity and specificity as compared to CD117. 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).

Key words: GIST, CD 117, DOG 1 antibody

INTRODUCTION

The WHO classification of digestive system tumours presented in the first volume of the WHO classification of tumours series, 5th edition, reflects important advancements in our understanding of tumours of the digestive system. Gastrointestinal stromal tumors (GISTs) are rare tumors with an

estimated incidence of 1.5/100,000 persons per year.[1] However, these are the most common mesenchymal tumors in the gastrointestinal tract.[2] They occur most frequently in stomach (60%) and small intestine (25%) as well as rarely in other gastrointestinal regions (esophagus, colon, rectum), and retroperitoneum.[3]

Risk factors of mesenchymal tumors are determined by age, ethnicity and gender. Sporadic GISTs are most common and familial GISTs with germline mutation of the KIT gene are rare, but have been well described[4]. GISTs present asymptomatically in 18% of cases, especially in cases of smaller tumors of the intestinal tract[5]. Symptomatic patients may present with nonspecific symptoms of nausea, vomiting, abdominal distension, early satiety, abdominal pain, and rarely as a palpable abdominal mass[6].

The diagnosis of GIST depends the integrity of histology, immunohistochemistry and molecular analysis.

Majority of GISTs show somatic mutation of CD117.Some GISTs are also associated with platelet-derived growth factor receptor-alpha (PDGFRA) mutation[7]. Subsequent studies have shown that there is still a small subset of GISTs that are wild type for both KIT and PDGFRA, some of which have been shown to harbor BRAF /RAS/NF-1 mutations[8]. The progress of immunohistochemistry (IHC) and development of CD117 (antibody against c-kit) made the accurate diagnosis of GISTs much easier. Later, it was recognized that c-kit mutation was found in 85%– 90% of the cases; in the remaining 5%–10% of GIST cases, PDGFR-α mutation being noted. Also, CD117 did not show uniform expression in all the c-kit mutation induced tumors, and about 5% of the cases could be missed. Recently, a new specific immunohistochemical antibody DOG1 (discovered on GIST) was discovered which when used in combination with CD117 usually resolves this issue.[9]

DOG1 is considered a sensitive and specific antibody of GISTs regardless of CD117 expression. DOG1 is also independent of KIT or platelet-derived growth factor receptor α (PDGFRA) mutation status in GISTs.[10] CD34 is another common marker for GISTs but it is not as sensitive and specific as CD117 and DOG1 The diagnosis of GISTs becomes much more accurate by using IHC (CD117/DOG1) and molecular analysis (*KIT/PDGFRA*), both of which constitute the gold standard of diagnosis in GISTs.

The study was designed to study CD117 and DOG1 antibodies for an accurate diagnosis to initiate appropriate therapeutic decision.

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.

1. **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).
2. **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).
3. **Study Period:** This study was conducted over a period of 18 months, extending from January 2019 to June. 2020.
4. **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).

5. **Sample Size:** The Sample size was calculated at 95% confidence level assuming 90% GIST among all mesenchymal tumours as per results of reference study[11]. 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 tumour size available and in 5 cases material for IHC was inadequate

Inclusion Criteria

Cases diagnosed as mesenchymal tumours of GIT on light microscopy, seen in GIT, irrespective of age and gender. Tumours involving mesentery 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 [12] was done and slides were mounted and labeled. Representative block was selected for IHC staining.

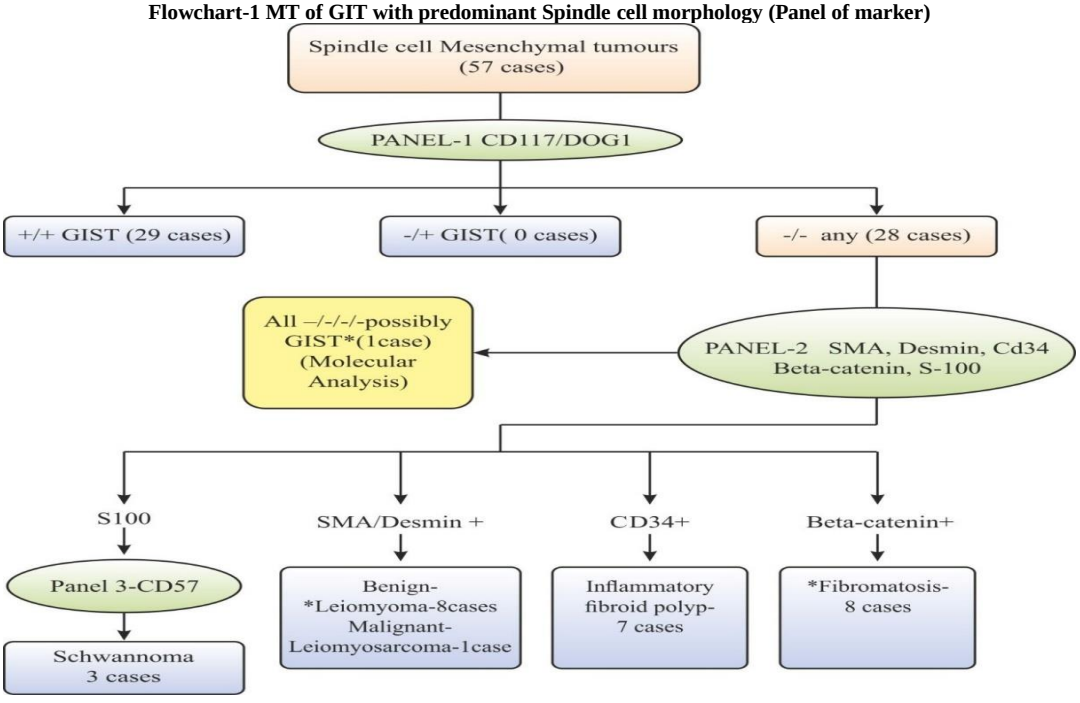
Immunohistochemistry Analysis was done using:

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

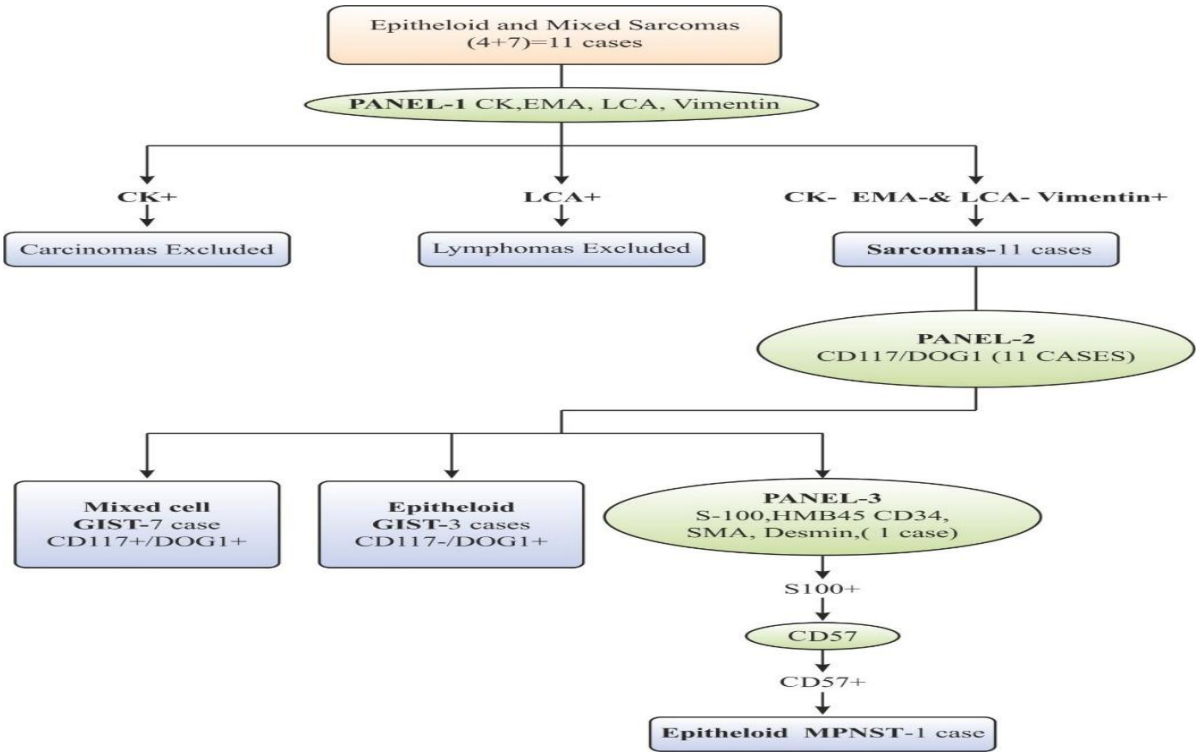
Continuous variables were summarized as mean and standard deviation while nominal/categorical variables will be expressed as proportions (percentage). Unpaired T-test, one-way ANOVA test and other parametric tests was used for analysis of continuous variables whereas chi-square test and Fisher exact test were used for analysis of nominal/categorical variables. The p value < 0.05 was taken as significant. MedCalc 16.4 version software was used for all statistical analysis.

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.

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



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



Flowchart-3 Panel of antibody used for diagnosis of GIST

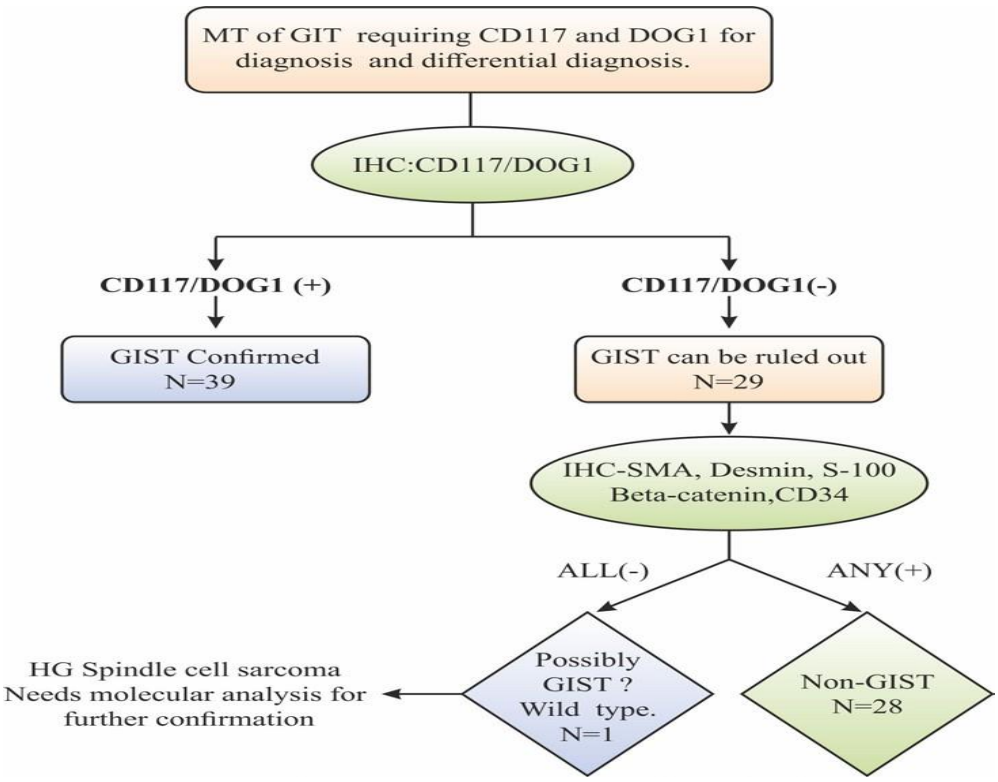


Table No.1 Clinicopathological parameters of cases of GIST N=40

Parameters	Variables	Number	%
Age (in years)	0-20	0	0.00
	21-40	5	12.50
	≥40	35	87.50
Gender	Male	25	62.5
	Female	15	37.5
Clinical feature	GI Bleeding	20	50.00
	Abdominal Pain	12	30.00
	Awareness of Lump	8	20.00
	Intussusception/Obstruction	0	0.00
Site	Gastric	20	50.00
	Esophagus	0	0.00
	Mesentry & Omentum	3	7.50
	Small Intestine	16	40.00
	Colon	1	2.50

.

Table No. 2 Distribution of GIST according to morphology N=40

Histomorphological Group (Based on cell type)	No.(%)
Spindle	30 (75.00)
Epithelioid	3 (7.50)
Mixed	7 (17.50)
Total	40 (100.00)

Table No.3 IHC expression of CD117 and DOG1 in studies of GIST N=40

Antibody CD117		GIST		Antibody DOG1		GIST	
		No.	%			No.	%
CD117	Negative	3/40	7.50	DOG1	Negative	1/40	2.50
	Positive	37/40	92.50		Positive	39/40	97.50
CD117 staining ratio score	Low (0,1,2)	5/40	12.50	DOG1 staining ratio score	Low (0,1,2)	2/40	5.00
	High (3,4)	35/40	87.50		High (3,4)	38/40	95.00
CD117 staining intensity	Negative	3/40	7.50	DOG1 staining intensity	Negative	1/40	2.50
	Weak	4/40	10.00		Weak	1/40	2.50
	Moderate	20/40	50.00		Moderate	8/40	20.00
	Strong	13/40	32.50		Strong	30/40	75.00

Table No.4 Comparison between CD117 and DOG1 staining ratio score expression in GISTs. (Percentage of cells)

DOG-1 staining ratio	CD117 staining ratio						chi-square	
	Low (0,1,2)		High (3,4)		Total			
	N	%	N	%	N	%	X^2	*P*-value
Low (0,1,2)	2	40.00	0	0.00	2	5.00	7.292	0.007
High (3,4)	3	60.00	35	100	38	95.00		
Total	5	100	35	100	40	100.00		

Table No.5 Comparison between CD117 and DOG1 staining intensity in GISTs

	CD117 staining intensity									
DOG-1 staining intensity	Negative		Weak		Moderate		Strong		Total	
	N	%	N	%	N	%	N	%	N	%
Negative	1	2.50	0	0.00	0	0.00	0	0.00	1	2.50
Weak	0	0.00	1	2.50	0	0.00	0	0.00	1	2.50
Moderate	0	0.00	1	2.50	5	12.50	2	5.00	8	20.00
Strong	2	5.00	2	5.00	15	37.50	11	27.50	30	75.00
Total	3	7.50	4	10.00	20	50.00	13	32.50	40	100.00
chi-square	X^2		22.893							
	P-value		0.006							

Table No.6 Expression of CD117 and DOG1 in different Histomorphological groups of GIST n=40

Histomorphological Group	Total	CD117				DOG1			
		Negative		Positive		Negative		Positive	
		No.	%	No.	%	No.	%	No.	%
Spindle	30	1	3.33	29	96.66	1	3.33	29	96.66
Epithelioid	3	2	66.66	1	33.33	0	0.00	3	100.00
Mixed	7	0	0.00	7	100.00	0	0.00	7	100.00
Total	40	3	7.50	37	92.50	1	2.50	39	97.50

Table No. 7 Concordance between Morphological Diagnosis and CD117 and DOG1 in IHC Diagnosis. n=40 (Morphologic Diagnosis and IHC Diagnosis)

Histomorphological Group	Total No	CD117		DOG 1	
		Total +ve	%	Total +ve	%
Spindle	30	29	96.66	29	96.66
Epitheloid	3	1	33.33	3	100.00
Mixed	7	7	100.00	7	100.00
Total	40	37	92.50	39	97.50

Table No. 8 Co-relation between CD117 & DOG1 ratio score expression and Morphologic cell type of GIST

	Histological cell type						Chi-square	
CD117 staining ratio	Spindle GIST		Epithelioid GIST		Mixed GIST			
	N	%	N	%	N	%	X^2	*P*-value
Low	2	6.67	2	66.67	1	14.28	9.001	0.011
High	28	93.33	1	33.33	6	85.72		
Total	30	100.00	3	100.00	7	100.00		
DOG-1 staining ratio							X^2	*P*-value
Low	2	6.67	0	0.00	0	0.00	0.702	0.704
High	28	93.33	3	100.00	7	100.00		
Total	30	100.00	3	100.00	7	100.00		

Table No. 9 Co-relation between CD117 & DOG1 ratio score expression and Risk Stratifications of GIST

	Risk stratification									
	Very low risk		Low risk		Intermediate risk		High risk		Chi-square	
CD117 staining ratio	N	%	N	%	N	%	N	%	X^2	*P*-value
Low	2	66.67	2	18.18	0	0.00	1	5.00	10.258	0.021
High	1	33.33	9	81.82	6	100.00	19	95.00		
Total	3	100.00	11	100.00	6	100.00	20	100.00		
DOG-1 staining ratio	N	%	N	%	N	%	N	%	X^2	*P*-value
Low	1	33.33	0	0.00	0	0.00	1	5.00	5.965	0.149
High	2	66.67	11	100.00	6	100.00	19	95.00		
Total	3	100.00	11	100.00	6	100.00	20	100.00		

Table No. 10 Diagnostic efficacy of CD117

C117	Type of tumor						Chi-square	
	GIST		NON-GIST (Control)		Total			
	N	%	N	%	N	%	X^2	*P*-value
Negative	3	7.50	27	96.42	30	44.12	49.287	<0.001
Positive	37	92.50	1	3.5	38	55.88		
Total	40	100	28	100	68	100.00		
Sens.	Spec.		PPV		NPV		Accuracy	
92.50	96.43		97.37		90.00		94.12	

Table No. 11 Diagnostic efficacy of DOG1

DOG1	Type of tumor						Chi-square	
	GIST		NON GIST(Control)		Total			
	N	%	N	%	N	%	X^2	*P*-value
Negative	1	2.50	28	100.00	29	42.65	60.09	<0.001
Positive	39	97.50	0	0.00	39	57.35		
Total	40	100.00	28	100.00	68	100.00		
Sens.	Spec.		PPV		NPV		Accuracy	
97.50	100.00		100.00		96.55		98.53	

Table 12 Agreement between two markers

		Value	Std. Error	Approx. T	'p' value
Measure of Agreement	Kappa	0.481	0.306	2.225	<0.001

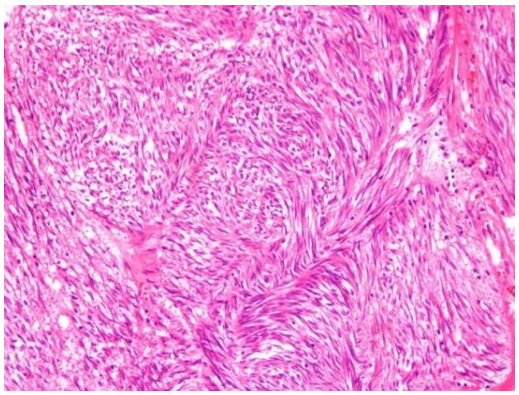
Table 13: Collective evaluation of results of studies using DOG1 and CD117 expressions in GISTs

Name of study	GIST (No.)	DOG1/ Clone	DOG1 +ve (no., %)	CD117 +ve(no., %)	DOG1 +/ CD117 –(no., %)
Espinosa et al [27]	428	DOG1.1/mcl	370 (87%)	317 (74%)	63/111 (57%)
Liegl et al [13]	81	DOG1.1/mcl	61 (75%)	53 (65%)	10/28 (36%)
Lopes et al [25]	668	K9/mcl	642 (96%)	643 (96%)	19/25 (76%)
Abbas et al [16]	77	No information	77(100%)	72(93.5%)	5/5 (100%)
Kang et al [14]	138	K9/mcl	124(89.85%)	112(81.16%)	24/26 (92.31%)
Guler et al [19]	37	SP31/mcl	33 (89%)	37(100%)	No case
Rizk et al [21]	58	SP31/mcl	58 (100%)	54 (93.10%)	4/4 (100%)
Jumniensuk et al [28]	76	No information	76 (100%)	75 (98.70)	1/1 (100%)
Sui et al [20]	63	mcl	53 (84%)	57 (91%)	6/6 (100%)
Rios et al [26]	99	K9/mcl	90 (91%)	94 (94%)	2/5 (40%)
Present study	40	DOG1.1/mcl	39 (97.5%)	37 (92.5%)	2/3 (66.66 %)

DISCUSSION

The age distribution of patients varied from 27 to 80 years with the majority of patients found above > 40 year age bracket. (Table -1) The mean age was 53.5 years in the study which is similar to most of the South Asian studies by Vij et al [11], Abbas et al [16], Varsha et al [17] , Ravi et al [18], Guler et al [19]. On comparing with the studies from West we found that the age of presentation was a decade earlier as in study by Corless et al [3] (mean age range 60 to 70 years). (Table -1) There was males predominance 25 (62.5%) noted with and male to female ratio being 1.66. These results are comparable to most of the studies described by Abbas et al [16], Varsha et al [17] ,Ravi et al [18] in South Asian settings. Most of the patients presented with GI bleeding 20 (50.00%) cases, followed by abdominal pain in 12 (30.00%) and awareness of lump in 8 (20.00%) as clinical presentation which was concordant with studies done by *Ravi et al* [18], *Vij et al* [11], *Abbas et al* [16] . (Table -1) Contrary to our study *Varsha et al* [17] *have* observed abdominal pain as the most common presenting symptom. The variation in presentation was related to tumour location, biological features and disease spread as seen in literature studies. (Fig -1) As far as location of tumor is concerned the most common site was stomach 20 (50.00%) followed by small intestine in 16 (40.00%) cases, mesentery and omentum in 3 (7.50%) cases and colon in 1 (2.50%) case. (Table -1) These results are concordant with most of studies of South Asian settings.

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



In the present study 75.00% GIST were of spindle cell morphology (Fig-2) followed by 17.50% GIST with mixed cell morphology and 7.50% GIST with epithelioid cell (Fig-3) morphology. (Table -2) Spindle cell morphology was commonest in present study and was found commonest universally amongst all the studies in Asian and western setting irrespective of ethnicity and geographical distribution and was concordant with Vij et al.[11], one from China Sui et al [20] , and one from Korea, Kang et al [14] . The possible explanation for this observation is that the distribution of histologic cell type may have some connection with type of mutation (kit/ PDGFRA), could be related to study population i.e. geographical area, ethnicity, since the mixed spindled-epithelioid (Fig-4) histology was found more common than the epithelioid morphology, which mainly occurs in Asian population.

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

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

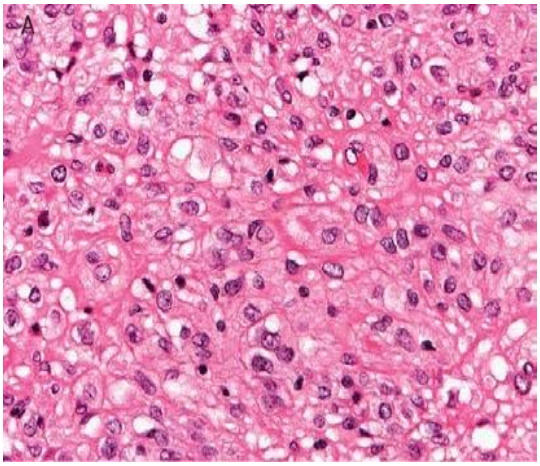
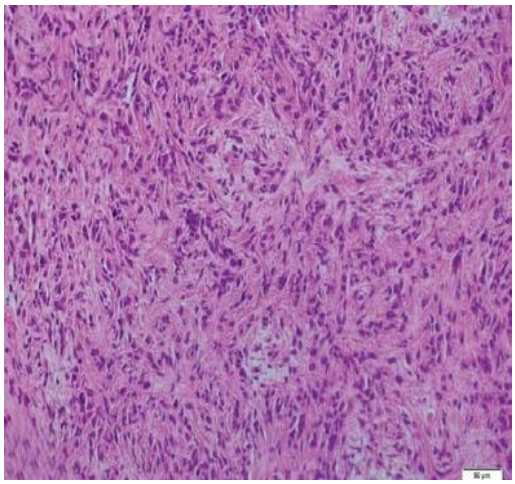


Fig -4 H & E – Mixed GIST (40 X)



In present study out of 40 cases of GISTs CD117 was found positive in 37 (92.50%) cases and negative in 3 (7.50%) cases. (Table 3) These results were concordant with studies by Rizk et al [21] (2017) CD117 was positive in (93.10%) cases, Sözütek et al [22] (2014) reported that CD117 was positive in (93.7%) cases, Sui et al[20] (2012)studies shown CD117 positivity 94.7%, 89.8% and 90.48% respectively. Most of the above studies have concluded that CD117 failed to immunostain 6.90% cases by Rizk et al [21], 6.3% cases by Sozutek et al [22] also reported that between 5% and 10% of GISTs fail to immune-staining for CD117. DOG1 in present study was positive in 39 (97.50 %) cases. These results were in agreement with that done by West et al [10] (2004), and Nakhla et al [23](2012) who reported immunopositivity for DOG-1 in 97.5% and 97.4%respectively, Rizk et al [21] (2017) and Fatima et al [24] (2011) have reported immunopositivity for DOG-1 in 100% cases. In present study immunostaining results were found superior (more positivity) with DOG1 as compared to CD117. Similarly, Abbas et al [16] have found immunopositivity DOG1 superior in 100% cases. On contrary, studies done by Varsha et al [17], Lopes et al [25], Rios et al [26], Sui et al [20], Guler et al [19] have reported to higher immunoreactivity with CD117 than with DOG1.

In present study 35 out of 40 cases with high staining ratio score of CD117 also expressed high staining ratio score of DOG1 which showed statistically significance (p value 0.007) . (Table -4) . Our findings were similar to those by Rizk et a l [21] study.

Table -5 shows the staining intensity of CD 117 & DOG 1 antibody where majority of cases expressed mostly moderate immunostaining with CD117 (50% of cases) i.e. CD117 expressed variable intensity while mostly stronger immunostaining was observed with DOG1 (75% of cases) similar to literature studies by Rizk et al[21] (2017) and Kang et al [14]. Although results of present study demonstrate superiority of DOG1 immunostaining over CD117 for diagnosis of GIST however the use of both the antibodies in combination can compensate for the weakness and limitations in the diagnosis of GIST as supported by literature studies (Table -13). The cases which still remains undiagnosed by using IHC should be referred for molecular analysis to establish the final

diagnosis.

There was concordance in morphological and IHC diagnosis of GIST as shown in table -7. The Correlation of CD117 staining ratio score and histomorphology was statistically significant with p-value <0.05 while this correlation was not statistically significant with DOG1 staining p-value 0.704. (Table-8). CD117 expressed the high staining ratio in majority of cases of spindle cell GISTs (93.33%) (Fig-5-7) and mixed cell GIST (85.72 %) while it expressed low staining ratio score in majority of epithelioid cell GISTs.(Fig-8) While, DOG1 expressed mostly high staining ratio amongst all histological variants of GIST (Fig-9,10) (Table- 8). These results were concordant with studies *by Rizk et al* [21], *Kang et al* [14], which also expressed that most of the CD117 negative GIST or GIST lacking KIT mutations were more likely to have epithelioid cell morphology while performance of DOG1 staining was better in epithelioid morphology too.

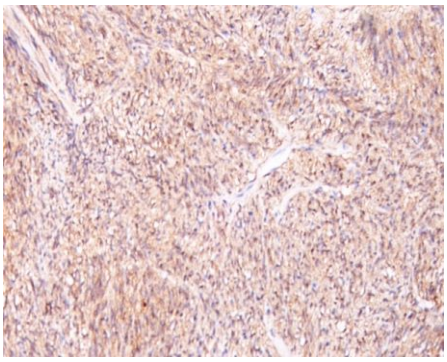


Fig -5 (10X) Spindle cell GIST showing high score (+4) and strong staining with CD117

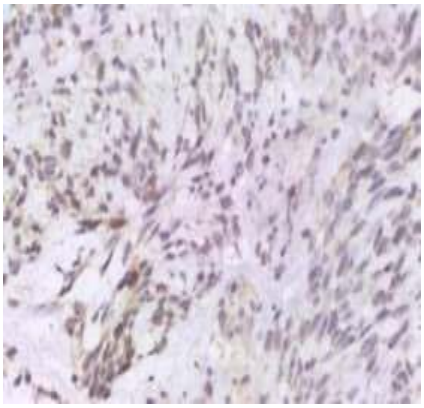


Fig -6 Spindle / mixed cell GIST with low (+2) score & weak staining for CD 117

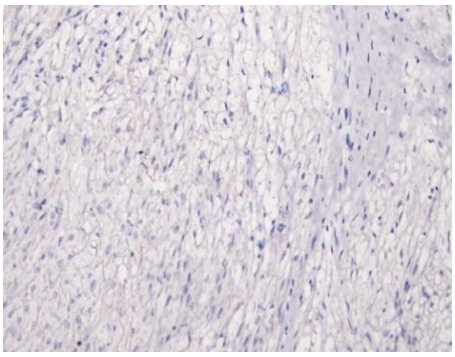


Fig -7 Spindle / mixed cell GIST with low (+1) score & weak staining for CD 117

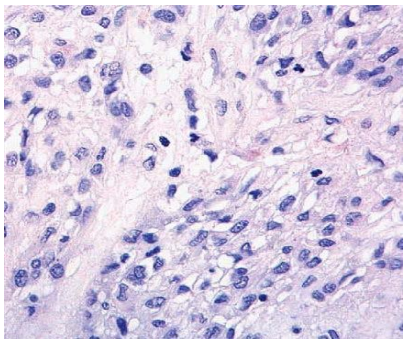


Fig 8 (40X) Epithelioid cell GIST showing low score (zero 0% cells) and negative staining with CD117

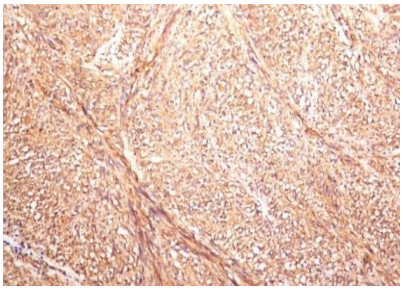


Fig -9 (10x) Spindle cell GIST with high score (+4) & strong DOG 1 staining

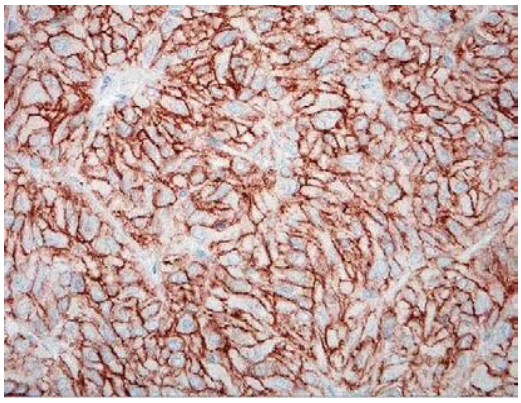


Fig -10 (10x) Epithelioid GIST with high score (+4) & strong DOG 1 staining

The correlation of CD117 staining ratio score and risk category showed p-value <0.05 which was statistically significant while the correlation of DOG1 staining ratio score and risk category was not found statistically significant with p-value 0.149. (Table-9) CD117 staining ratio score expression was variable amongst different risk groups i.e. CD117 expressed high staining ratio score in majority of high risk (95.00%) cases while very low risk cases expressed low staining ratio score (missed on CD117 staining). On other hand DOG1 staining ratio score expression found high in all risk categories and the results of our study were concordant with studies by Rizk et al [21] (2017), Abdel-Hadi et al [29] (2009).

Comparison of diagnostic efficacy of CD117 and DOG1 for GISTs (Table- 10 & 11) shows that the sensitivity, specificity, PPV, NPV and accuracy are superior with DOG1. However diagnostic efficacy of both the markers individually was found statistically significant between GIST and Non GIST groups but comparative analysis of their efficacies in diagnosis of GIST was not found statistically significant in present study as both markers were good but DOG1

was found slightly more superior with higher sensitivity and specificity as compared to CD117, specificity (100% versus 96.43%) and sensitivity (97.5% versus 92.5%). Similar observations were reported in literature by, *Rizk et al [21] (2017), Espinosa et al [27] (2008), Fatima et al [24] (2011), Abdel-Hadi et al [29] (2009), El Rebey and Aiad et al [15] (2014).* While studies by *Varsha et al [17], Liegl et al [13]* demonstrated that similar and compatible sensitivity and specificity of DOG1 with CD117, and both can compensate for the weakness and limitations in the diagnosis of GIST.

The combination of both CD117 and DOG1 in an IHC panel covers more than 98% of GISTs in clinical practice with good agreement as Kappa value in our study was 0.481. Use of proper standardized IHC staining, antibody clone, batch control by well experienced technical staff has huge impact on Immunostaining results which should always be considered for final conclusion.

CONCLUSION

The IHC panel should be applied in stepwise manner over "morphologically suspicious" cases Mesenchymal Tumours 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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REFERENCES

1. Nilsson B, Bümming P, Meis-Kindblom JM, Odén A, Dortok A, Gustavsson B et al. Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. Cancer 2005; 103:821-9
2. Agaimy A, Wünsch PH, Hofstaedter F, Blaszyk H, Rümmele P, Gaumann A, et al. Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol 2007; 31:113-20.
3. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004; 22:3813-25.
4. Nishida T, Hirota S, Taniguchi M, Hashimoto K, Isozaki K, Nakamura H et al. Familial gastrointestinal stromal tumours with germline mutation of the KIT gene. Nat Genet 1998; 19:323-4.
5. Soreide K, Sandvik OM, Soreide JA, Giljaca V, Jureckova A and Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. Cancer Epidemiol 2016; 40:39-46.
6. Scherubl H, Faiss S, Knoefel WT, Wardelmann E. Management of early asymptomatic gastrointestinal stromal tumors of the stomach. World J Gastrointest Endosc 2014; 6:266-71.
7. Tzen CY, Mau BL. Analysis of CD117-negative gastrointestinal stromal tumors. World J Gastroenterol 2005; 11:1052–55.
8. Agaimy A, Terracciano LM, Dirnhofer S, Tornillo L, Foerster A, Hartmann A et al. V600E BRAF mutations are alternative early molecular events in a subset of KIT/PDGFRA wild-type gastrointestinal stromal tumours. J Clin Pathol 2009; 62:613–16.
9. Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: A study of 1840 cases. Am J Surg Pathol 2009; 33:1401-8.
10. West R.B., Corless C.L., Chen X., Rubin B.P., Subramanian S., Montgomery K et al. The novel marker, DOG1, is expressed ubiquitously in gastrointestinal stromal tumors irrespective of KIT or PDGFRA mutation status. Am. J. Pathol 2004; 165:107–13.
11. Vij M, Agrawal V, Kumar A, Pandey R. Gastrointestinal stromal tumors: a clinicopathological and immunohistochemical study of 121 cases. Indian J Gastroenterol 2010; 29:231-6.
12. Bancroft JD, Layton C. The hematoxylins and eosin. In: S. KimSuvarna, Christopher Layton, John D. Bancroft (eds.) Theory and Practice of Histological Techniques. 7th ed. Waltham, USA. Elsevier. 2012; 173-86.
13. Liegl B, Hornick JL, Corless CL, Fletcher C. Monoclonal antibody DOG1.1 shows

higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors including unusual subtypes. Am J Surg Pathol 2009; 33: 437-446.
14. Kang G., Srivastava A, Kim YE, Park HJ, Park CK, Sohn TS et al. DOG-1 and PKCh are useful in the diagnosis of KIT-negative gastrointestinal stromal tumors. Mod Pathol 2011; 24: 866-87.
15. El Rebey HS and Aiad AH. Immunohistochemical Expression of DOG1 as a Diagnostic Marker for Gastrointestinal Stromal Tumors in Comparison to c-KIT. J Am Sci 2014; 10:198-205.
16. Abbas F, Besina S, Farooq S, Bhat G, Ashraf S, Latief M. Role of novel marker discovered on gastrointestinal stromal tumor 1 in evaluation of gastrointestinal stromal tumors. Indian J Med Paediatr Oncol 2019; 40:244-8.
17. Varsha P, Champaka G, Kumar RV, Krishnamurthy S. Pathological Spectrum of Gastrointestinal Stromal Tumors - A 1.5-year Experience at Kidwai Cancer Institute. Int J Sci Stud 2018; 6:38-45.
18. Ravikumar G, Kalegowda I Y, Ananthamurthy A. Clinicopathologic spectrum of gastro intestinal stromal tumours - Experience at a tertiary care center. Indian J Cancer 2011; 48:466-70.
19. Güler B, Özyılmaz F, Tokuç B, Can N, Taştekin E. Histopathological features of gastrointestinal stromal tumors and the contribution of DOG1 expression to the diagnosis Balkan Med J 2015;32:388-96.
20. Sui XL, Wang H, Sun XW. Expression of DOG1, CD117 and PDGFRA in gastrointestinal stromal tumors and correlations with clinicopathology. Asian Pac J Cancer Prev. 2012; 13:1389–93.
21. Rizk MO. Comparative study between c-kit and DOG-1 immunohistochemical expression in GISTs. Cancer Biology 2017; 7:54-62.
22. Sözütek D, Yanık S, Akkoca AN, Sözütek A, Özdemir ZT, Avşar ÇU et al. Diagnostic and prognostic roles of DOG1 and Ki-67, in GIST patients with localized or advanced/metastatic disease. Int J Clin Exp Med 2014;7:1914- 22.
23. Nakhla GA, Hosni HN, Darweesh MF, Morsi DF, Soliman AA. Immunohistochemical study of DOG1 protein expression in gastrointestinal stromal tumors. Acad J Cancer Res. 2012; 5:61-70.
24. Fatima N, Cohen C, Siddiqui MT. DOG1 utility in diagnosing gastrointestinal stromal tumors on fine-needle aspiration. Cancer Cytopathology 2011; 119:202-8.
25. Lopes LF, Ojopi EB, Bacchi CE. Gastrointestinal stromal tumor in Brazil: clinicopathology, immunohistochemistry, and molecular genetics of 513 cases. Pathol Int 2008; 58:344–52.
26. Rios-Moreno MJ, Jaramillo S, Gallardo SP, Vallejo A, MoraM, Garcia- Escudero A et al. Gastrointestinal stromal tumors(GISTs): CD117, DOG-1, and PKCθ expression. Is there any advantage in using several markers? Pathol Res Pract 2012; 208:74-81.
27. Espinosa I, Lee CH, Kim MK, Rouse BT, Subramanian S, Montgomery K, et al. A novel monoclonal antibody against DOG1 is a sensitive and specific marker for gastrointestinal stromal tumors. Am J Surg Pathol 2008; 32:210- 8.
28. Jumniensuk C, Charoenpitakchai M. Gastrointestinal stromal tumor: Clinicopathological characteristics and pathologic prognostic analysis. World J Surg Oncol 2018; 16: 231.
29. Abdel-Hadi M, Bessa SS, Hamam SM. Evaluation of the Novel Monoclonal Antibody against DOG1 as a Diagnostic Marker for Gastrointestinal Stromal Tumors. J Egy Nat Canc Inst 2009; 21:237-47.

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