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A Prospective Study of Assessment of Gastric Tumours Highlighting Gastrointestinal Stromal Tumours (Gist) - A Study of 75 Cases

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Abstract
Introduction: *Gastrointestinal stromal tumors (GISTs) are the most common malignant subepithelial lesions (SELs) of the gastrointestinal tract in the daily clinical setting. GISTs are thought to originate from the interstitial cells of Cajal, which are the pacemaker cells of gastrointestinal movement. GISTs are largely caused by oncogenic mutations in the tyrosine kinase receptor KIT and/or platelet-derived growth factor receptor-α (PDGFR-α).*
Materials and Methods: *The study of patients with gastric tumours attending a tertiary care hospital was conducted in the Department of General Surgery, MIMS, Vizianagaram, Andhra Pradesh for a period of two years (September 2018 to August 2020). It was a descriptive type of study. A total of 75 cases were studied. A detailed clinical history with investigations was collected from each patient using a proper data collection form. Approval from ethics committee was taken, consent from all the patients or guardian of the patient was taken, confidentiality of the findings of the patients was ensured and data was utilised purely for academic purpose.*
Results: *A total of 75 cases were studied during the study period of two years (from September 2014 to August 2016). The age of the patient ranged from 31 years to 80 years. Gastric tumours were more common in age group of 51 - 60 years (38.7%) with a mean age of 57.69 years (Table 1). Gastric tumours are more common in males (76%) than females (24%). Out of the 75 cases included in our study, 54 cases (72%) had gastric tumours located at the body of the stomach. Gastric neoplasms were commonly an ulcerative growth in gross appearance (50.7%). Out of 75 cases studied, 6 cases (8%) were of Epithelioid Cell Variant of GIST (Low Grade), 1 case (1.3%) was suspected to be Fibromatosis or Spindle Cell Variant of GIST (Low Grade), 5 cases (6.7%) were of Infiltrating Poorly Differentiated Adenocarcinoma, 3 cases (4%) were suspected to be Leiomyoma or Spindle Cell Variant of GIST (Low Grade), 44 cases (54.7%) were Moderately Differentiated Gastric Adenocarcinoma, 1 case (1.3%) was of Poorly Differentiated Neuroendocrine Carcinoma, 2 cases (2.7%) were of Spindle Cell Variant of GIST (High Grade- Mitosis > 5/50 Hpf), 4 cases (5.3%) were of Spindle Cell Variant of GIST (Low Grade) and 9 cases (12%) were of well differentiated Gastric Adenocarcinoma.*
Conclusion: *Accurate diagnosis of gastric tumours demands thorough histopathological evaluation. DOG-1 has overall superior and crisply localised staining pattern than CD-117. Histopathological evaluation of gastric tumours must be done carefully, especially for cases of GIST as they are often misdiagnosed. Use of judicious combination of CD-117 and DOG-1 is recommended for diagnosing cases of GIST, as CD117 has got therapeutic importance for administering imatinib.*
Key Words: *Gastrointestinal stromal tumors, DOG, subepithelial lesions, platelet-derived growth factor receptor-α*

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I. Introduction

Gastrointestinal stromal tumors (GISTs) are the most common malignant subepithelial lesions (SELs) of the gastrointestinal tract in the daily clinical setting. GISTs are thought to originate from the interstitial cells of Cajal, which are the pacemaker cells of gastrointestinal movement. GISTs are largely caused by oncogenic mutations in the tyrosine kinase receptor KIT and/or platelet-derived growth factor receptor-α (PDGFR-α). Approximately 10% to 30% of GISTs have a malignant clinical course.[1] Additionally, it has been reported that not only large GISTs with a high mitotic index frequently exhibit a malignant clinical course, but also small GISTs with a low mitotic index rarely show a malignant course with metastasis.[2] Thus, a GIST is considered to be a potentially malignant tumor. GISTs are not classified as either benign or malignant but are rather stratified by their clinical risk of malignancy: Very low, low, intermediate, or high. Mietinenn reported that the metastatic

risk of GISTs increases according to the tumor size irrespective of the mitotic count. Surgical resection is the primary approach to management of localized GISTs.[3] Despite complete resection, postoperative recurrence occurs in at least half of all patients with GISTs. Although tyrosine kinase inhibitors have been shown to provide sustained disease management in patients with metastasis, surgical R0 resection of small GISTs without metastasis is the only promising treatment for a permanent cure.[4] The best treatment strategy for GISTs is early diagnosis and early resection. However, GISTs are frequently detected as SELs during endoscopy. The differential diagnoses of SELs are quite broad and can include extra-gastrointestinal tract compression, varices, an ectopic pancreas, and various tumors including GIST, SEL-like cancer, leiomyoma, schwannoma, and lipoma.[5]

GISTs should be diagnosed by immunohistochemical analysis including assessment of KIT, CD34, and/or discovered on gastrointestinal stromal tumor 1 (DOG1). However, it is more difficult to obtain a conclusive histologic diagnosis of a GIST than gastrointestinal cancer by standard endoscopic forceps biopsy because a GIST is covered by normal mucosa.[6] Although imaging tests including endoscopic ultrasonography (EUS) and computed tomography (CT) are useful for narrowing down the differential diagnoses of SELs, these techniques are unable to provide a conclusive diagnosis. At present, EUS-guided fine needle aspiration (EUS-FNA) is the most accurate, safe, and reliable preoperative immunohistological test to secure a definitive diagnosis of SELs. Aggressive use of EUS and EUS-FNA for SELs is the key to facilitating early intervention of GISTs.[7]

II. Materials And Methods

The study of patients with gastric tumours attending a tertiary care hospital was conducted in the Department of General Surgery, MIMS, Vizianagaram, Andhra Pradesh for a period of two years (September 2018 to August 2020). It was a descriptive type of study. A total of 75 cases were studied. A detailed clinical history with investigations was collected from each patient using a proper data collection form. Approval from ethics committee was taken, consent from all the patients or guardian of the patient was taken, confidentiality of the findings of the patients was ensured and data was utilised purely for academic purpose.

After step-wise grossing, tissue processing, embedding, blocking and microtomy, haematoxylin and eosin (Hand E) stained sections were prepared for light microscopic examination in each case. Immunohistochemistry using DAKO rabbit monoclonal antibody kit by peroxidase-antiperoxidase technique was performed for markers DOG-1 and CD-117 in cases diagnosed as GIST on light microscopy. Antigen retrieval was done using a domestic pressure cooker of 2 litres size filled with one litre of TRIS/EDTA buffer (pH 9.0). The slide cradle with Poly-L-Lysine coated slide bearing the representative section was dipped in this solution. The pressure cooker was removed from heat after 1st whistle and kept under tap water for 30 to 45 mins, i.e. till it reached room temperature. The slides were incubated with primary antibody for 45 minutes to 1 hour in a humid chamber at room temperature. The slides were counterstained with Harris Haematoxylin for 45 seconds followed by dehydration using ascending grades of alcohol, clearing in xylene and mounting with DPX. Categorical variables were expressed as number of patients and percentage of patients and compared using Pearson's Chi-square test for independence of attributes. The statistical software SPSS version 20.0 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p-value is less than 0.05 it has been considered as significant.

III. Results

A total of 75 cases were studied during the study period of two years (from September 2014 to August 2016). The age of the patient ranged from 31 years to 80 years. Gastric tumours were more common in age group of 51 - 60 years (38.7%) with a mean age of 57.69 years (Table 1). Gastric tumours are more common in males (76%) than females (24%). Out of the 75 cases included in our study, 54 cases (72%) had gastric tumours located at the body of the stomach. Gastric neoplasms were commonly an ulcerative growth in gross appearance (50.7%). Out of 75 cases studied, 6 cases (8%) were of Epithelioid Cell Variant of GIST (Low Grade), 1 case (1.3%) was suspected to be Fibromatosis or Spindle Cell Variant of GIST (Low Grade), 5 cases (6.7%) were of Infiltrating Poorly Differentiated Adenocarcinoma, 3 cases (4%) were suspected to be Leiomyoma or Spindle Cell Variant of GIST (Low Grade), 44 cases (54.7%) were Moderately Differentiated Gastric Adenocarcinoma, 1 case (1.3%) was of Poorly Differentiated Neuroendocrine Carcinoma, 2 cases (2.7%) were of Spindle Cell Variant of GIST (High Grade- Mitosis > 5/50 Hpf), 4 cases (5.3%) were of Spindle Cell Variant of GIST (Low Grade) and 9 cases (12%) were of well differentiated Gastric Adenocarcinoma.

Among 75 cases studied, 15 cases (20%) present at pT2N0Mx, 32 cases (42.6%) at pT2N1Mx, 5 cases (6.7%) at pT2N2M0, 18 cases (24%) at pT2N2Mx, 1 case (1.3%) at pT2N3M0, 2 cases (2.7%) at pT3N0Mx and 2 cases (2.7%) at pT3N2Mx. Out of the 75 cases studied, 16 were suspected cases of gastrointestinal stromal tumours (GIST) on light microscopy. They were further evaluated by immunohistochemical analysis using markers CD-117 and DOG-1. Out of 16 GIST cases, 10 cases were positive for both CD-117 and DOG-1.

3 cases were negative for both CD-117 and DOG-1. 1 case was positive for CD-117, but negative for DOG-1. 2 cases were negative for CD-117, but positive for DOG-1. These associations can be corroborated with Table 3. The p-value was 0.029 (significant).

S.No	Age in Years	Frequency	Percentage	Mean Age
1	31-40	10	13.3	38.00
2	41-50	22	29.3	48.36
3	51-60	29	38.7	57.69
4	61-70	13	17.3	61.31
5	71-80	1	1.3	76.00
6	Total	75	100	53.20

Table 1: Frequency Distribution table showing Distribution of Gastric Tumours among different Age Groups

S.No	Gross Appearance	Frequency	Percentage
1	Ulcerative	38	50.7
2	Ulcer proliferative	21	28.0
3	Mass extending from mucosa to serosa, mucosa intact	10	13.3
4	Mass extending from mucosa to serosa, mucosa puckered	4	5.3
5	Mass extending from mucosa to serosa, mucosa erythematous	2	2.7
6	total	75	100.0

Table 2: Frequency Distribution table showing Distribution of Gastric Tumours according to Gross Appearance of the Tumours

		CD-117		Total
		Negative	**Positive**	
DOG-1	Negative	3	1	4
		60%	9.1%	25%
	Positive	2	10	12
		40%	90.9%	75%
Total		5	11	16
		100%	100%	100%

Table 3: Cross-Tabulation showing CD-117 –DOG-1 association in Cases of GIST

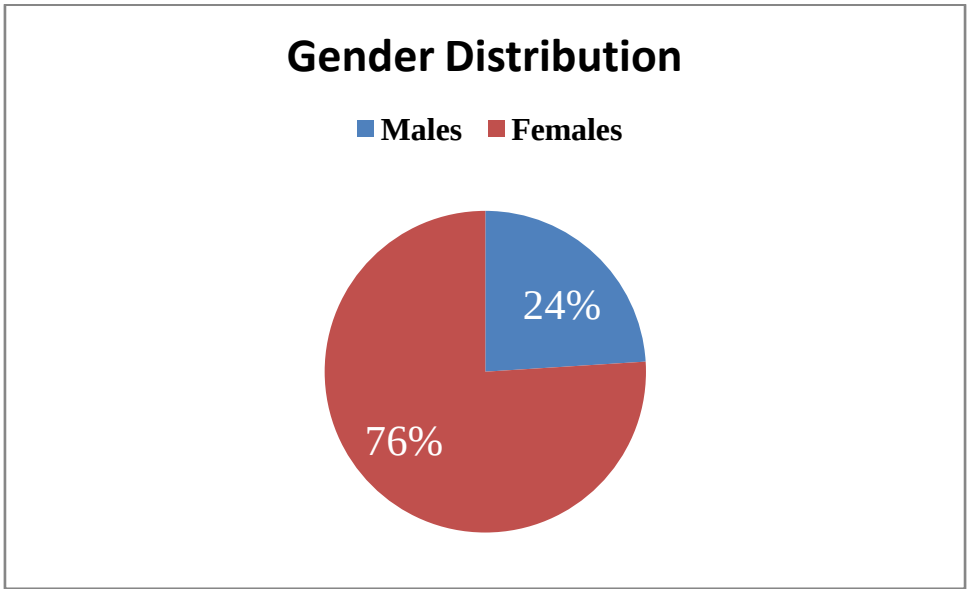

Figure 1: Depicting Sex Distribution of Gastric Tumours.

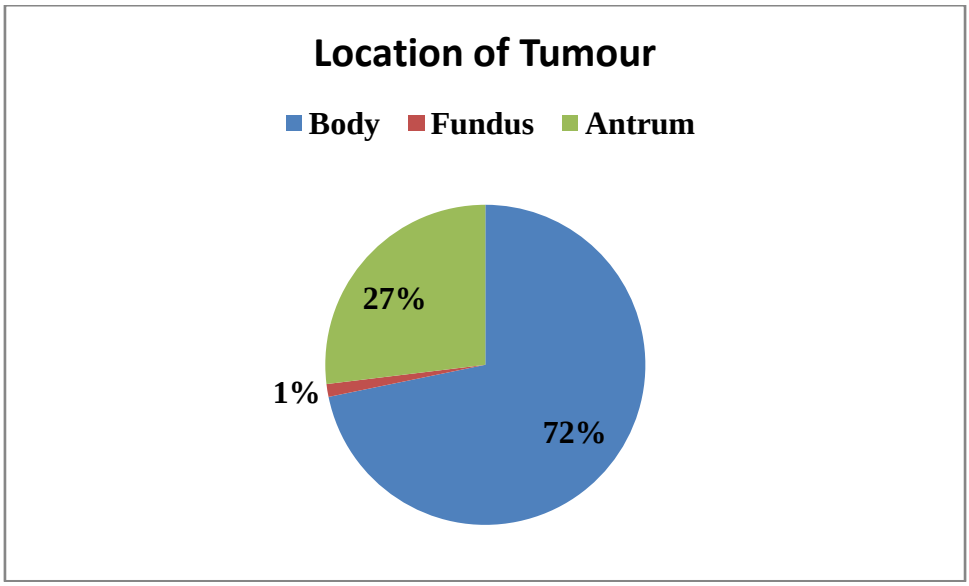

Figure 2: Depicting Distribution of Gastric Tumours according to Location of the Tumour

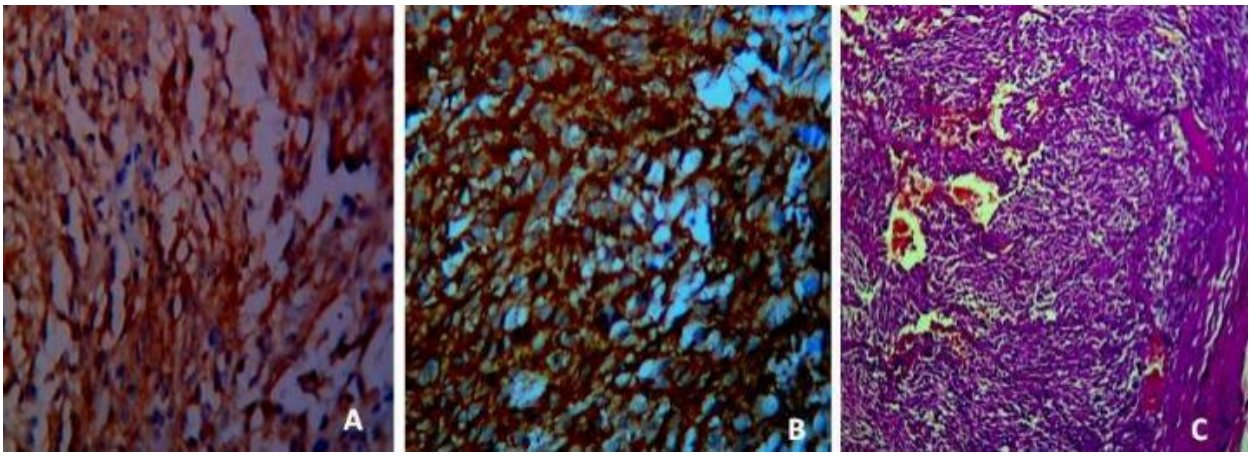

Figure: 3 Epithelioid GIST.
A) CD-117 Diffuse Positive (400X).
B) Corresponding DOG-1 Positive (400X).
C) Corresponding H and E Stain (100X)

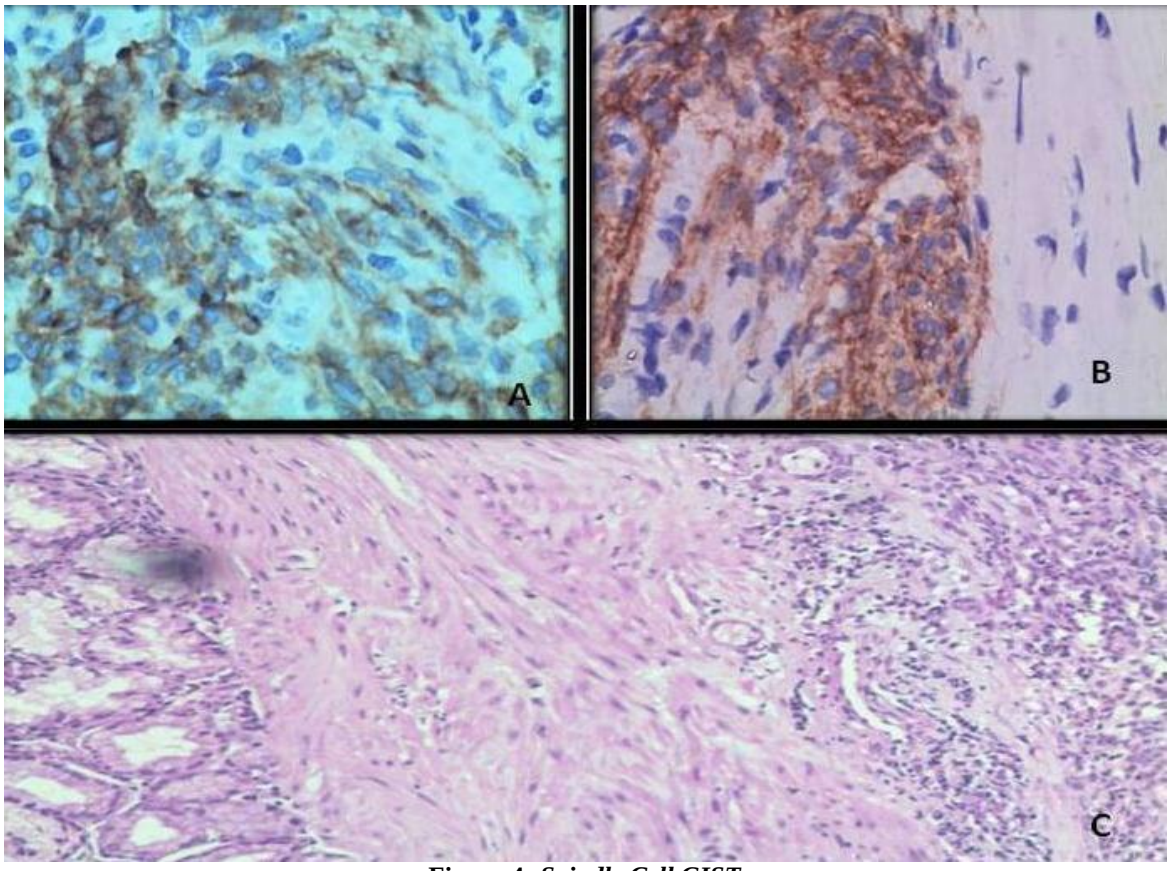

Figure 4: ***Spindle Cell GIST***
A) CD-117 Diffuse Positive (400X).
B) Corresponding DOG-1 Positive (400X).
C) Corresponding H and E Stain (100X).

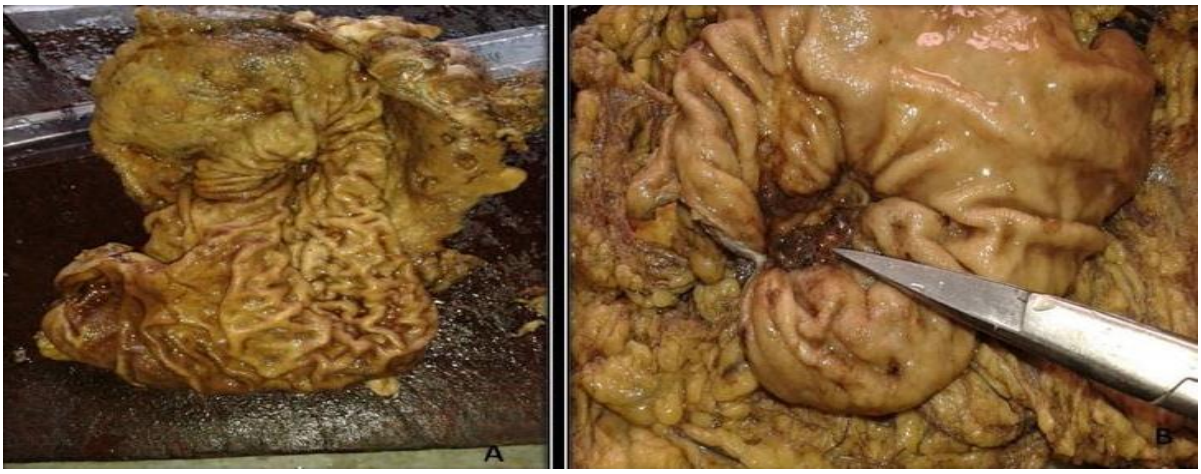

Figure 5: Gross Appearance.
A) Gastric Mass with Mucosa Intact.
B) Ulcerated Growth in Stomach

IV. Discussion

In this study, gastric tumours were found to be more common in males (76%) than females (24%). Throughout the world, gastric neoplasms are observed to be a disease of the elderly population, predominantly in men.

According to this study, gastric tumours were more common in age group of 51 to 60 years (38.7%). There was a spectrum of median age incidence outlined in various studies conducted in different parts of the world. In the western world, it was 71 years in the USA. In Asian countries, mean ages in different countries

were low. For example, in Japan it was 61 years, in Pakistan 48 +/- 4.47 years and in Saudi Arabia 47 years. In this study, the mean age was 57.69 years, which was near similar to the study done in Japan. In Mizoram, male-to-female was 2.3:1, in Saudi Arabia 2.2:1, and in Pakistan 1.5:1. All these show preponderance of gastric neoplasms in elderly male population, which is similar to the findings of our study.[8]

Out of the 75 cases included in the study, 54 cases (72%) had gastric tumours located at the body of the stomach and they were commonly an ulcerated growth in gross appearance (50.7% cases). In the western world according to various studies, there is progressive increase in proximal stomach cancer and concomitant decline in distal stomach cancer. Although, reports from Asian countries were discordant. Japanese and Korean population had preponderance of non-cardia cancer; however, an Iranian study revealed the predominance of cardia cancer. Recently, a report from Kerala in India showed that although predominant site of cancer was antral mucosa, yet the trend was towards proximal shift. Cherian et al revealed no change in site specificity of carcinoma of stomach in South Indian population. Again Qurieshi et al revealed incidences of cancer in proximal, mid and distal stomach to be 42%, 6.2% and 45.7% respectively in the Kashmiri population. Afridi et al in their study found growth at cardiac end in 33%, pylorus and antrum in 40%, linitis plastica in 13.3% and only body and body and pylorus in 6.7% of patients. Qurieshi et al reported 35.5% ulcero-proliferative, 26% proliferative, 31% ulcerative and 7.4% infiltrative lesions during endoscopy performed in Kashmiri patients. Though, in this study, ulcerative growth was the predominant pattern (50.7%) followed by ulcero-proliferative pattern of growth (28%). [9]

In this study, most common histopathological diagnosis was moderately differentiated gastric adenocarcinoma (58.7%). Similar to this study, Peghini et al showed 88% of cases with adenocarcinoma and 7% of cases with lymphoma, thus representing more prevalence of adenocarcinoma than other types of gastric neoplasms. In this study, highest frequency of cases presented at an advanced stage, that is pT2N1Mx (42.6% cases). Stomach cancers are commonly diagnosed in symptomatic patients with advanced disease. Early asymptomatic tumours are detected predominantly in countries following a screening policy such as Japan.

In this study, 16 cases of gastric tumours which were differentially diagnosed as GISTs or leiomyoma or fibromatosis on light microscopy and were further evaluated by immunohistochemistry by using markers CD-117 and DOG-1. Out of these 16 cases, 10 cases which stained positively for both CD-117 and DOG-1. 2 cases which stained positively for DOG-1, but were negative for CD-117 were considered as GIST; as according to a study by Espinosa et al among GISTs bearing PDGFRA mutations 79% stained with DOG-1, 9% with CD-117 and 27% with CD-34. Review of the literature reveals that about one-third of patients who possess PDGFRA mutations, fail to stain with CD-117. Thus, these 2 cases of GIST may have been misdiagnosed to be cases of leiomyoma. 1 case which was differentially diagnosed as fibromatosis or spindle cell variant of GIST (Low Grade) stained positively for CD-117, but negatively for DOG-1, was finally considered as a case of fibromatosis. Immunohistochemically, CD-117 is the protein product of C-Kit gene with a rate of protein expression being 80% - 100% in GIST, but occasionally expressed in non-GIST cells. Thus, this case would have been misdiagnosed as a case of GIST. There were 3 cases, which were differentially diagnosed to be cases of leiomyoma or spindle cell variant of GIST (Low Grade), stained negatively for both CD-117 and DOG-1. These cases were considered as gastric leiomyoma.[10]

V. Conclusion

Accurate diagnosis of gastric tumours demands thorough histopathological evaluation.DOG-1 has overall superior and crisply localised staining pattern than CD-117. Histopathological evaluation of gastric tumours must be done carefully, especially for cases of GIST as they are often misdiagnosed. Use of judicious combination of CD-117 and DOG-1 is recommended for diagnosing cases of GIST, as CD117 has got therapeutic importance for administering imatinib.

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