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Mesenchymal Tumors of Gastrointestinal Tract- The Role of Immunohistochemistry in Characterizing Specific Tumors

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ABSTRACT
Introduction: *Mesenchymal neoplasms of Gastrointestinal tract are a group of rare tumors with overlapping histological features. Characterization and accurate diagnosis of specific tumors is mandatory since many of these tumors have specific targeted therapy*
Aim: *Characterization of specific tumor types in mesenchymal tumors of GIT, based on morphology and immunohistochemistry*
Materials and methods: *33 cases of mesenchymal tumors of GIT were included in the study presented in a period of 5 years (January 2010-December 2010). Immunohistochemistry was done in all the 33 cases with the markers CD 117, DOG-1, SMA, Vimentin, Desmin and S-100.*
Results and Conclusion: *Of the 33 cases, 24 (72.72%) were gastrointestinal stromal tumor. The cells were positive for CD 117 and DOG-1. Other markers were negative. Leiomyogenic tumors accounted for 21.21% (7 cases) which included leiomyoma and leiomyosarcoma. They were positive for SMA, Desmin and / or Vimentin. They were negative for other markers. 6.06% (2 cases) were neurogenic which were positive for only S-100.*
The role of Immunohistochemistry in the specific diagnosis of mesenchymal tumors of GIT is much significant. The specific treatment and prognosis depends on accurate diagnosis.
Keywords: *Mesenchymal tumors, Gastrointestinal stromal tumor, Immunohistochemistry.*

Introduction

Mesenchymal neoplasms of the gastrointestinal tract are very much less frequent than the epithelial neoplasms. Because of the rarity of these lesions and the fact that many have overlapping histologic features, their accurate classification and diagnosis is challenging, especially in the setting of limited endoscopic biopsy material. Mesenchymal neoplasms have favoured anatomic locations within the gut as well as characteristic sites of involvement or origin from the various components of the gastrointestinal tract.

The Gastrointestinal mesenchymal tumors (GIMTs) have been almost uniformly classified as gastrointestinal leiomyomas (LMs). However,

recent evidence indicates that most common mesenchymal tumor of the gastrointestinal tract is gastrointestinal stromal tumor (GISTs)[(1)]. Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors that arise predominantly in the gastrointestinal tract (GIT). Due to their similar appearance by light microscopy, GISTs were previously thought to be smooth muscle neoplasms and most were classified as leiomyomas, leiomyoblastomas, leiomyosarcomas or schwannomas[(1)].

It was in 1998, after the discovery of gain-of-function mutations in the c-KIT protooncogene that, these tumors were reliably distinguished from other histopathological subtypes of mesenchymal tumors[(2)]. Immunohistochemistry (IHC) demonstrated that these tumors lacked features of smooth muscle differentiation and, while some had markers of neuronal different-iation, some had neither. Mazur et al[(3)] coined the term "gastrointestinal stromal tumors" to collectively refer to a group of mesenchymal tumors of neurogenic or myogenic differentiation which lacked the immunohistochemical features of Schwann cells and did not have the ultra structural characteristics of smooth muscle cells[(3)].

Mesenchymal neoplasms affecting the gastrointestinal (GI) tract typically present as subepithelial neoplasms. They are divided broadly into two groups. The most common group consists of neoplasms that are known as gastrointestinal stromal tumors (GISTs). They are most often located in the stomach and proximal small intestine, but can occur in any portion of the gastrointestinal tract including the omentum, mesentery and peritoneum [3-5]. The current view is that the majority of mesenchymal tumors arising in the GI tract belong into the GIST category, and they are identified mainly by expression of KIT protein; as a group, these tumors are more specifically defined by the presence of activating mutations in the *KIT* or platelet-derived growth factor receptor A (*PDGFRA)* genes.

The less common group of mesenchymalGI tract neoplasms comprise a spectrum of tumors that are identical to those that arise in the soft tissues in other parts of the body. These include lipoma, liposarcoma, leiomyoma, leiomyosarcoma, desmoids tumor, schwannoma and peripheral nerve sheath tumor [4].

Gastrointestinal stromal tumor (GIST) includes most tumors previously designated as leiomyoma, cellular leiomyoma, leiomyoblastoma, and leiomyosarcoma. After the discovery of gain-of-function mutations in the c-KIT protooncogene, these tumors were reliably distinguished from other histopathological subtypes of mesenchymal tumors [(4,5)]. It occurs 60% in stomach, 30% small intestine, 10% elsewhere. However, in the esophagus, leiomyoma is the most common mesenchymal tumor. GISTs are composed of spindle (70%) or epithelioid (30%) cells, and 10%-30% are malignant showing intra-abdominal spread or liver metastases. GISTs may be defined as mesenchymal tumors of the GIT that usually express the mast/stem cell growth factor receptor Kit (KIT) protein and harb or mutations of a gene that encodes for KIT or platelet-derived growth factor receptor α (PDGFRA) and probably originate from the interstitial cells of Cajal (ICCs) [(6)]. Since KIT and PDGFRA tyrosine kinase inhibitors (targeted therapy) have become available, the proper identification of GISTs has become clinically important [(6,7)]. Therefore, it is necessary to differentiate other mesenchymal tumors of the GIT from GISTs, particularly those consisting of spindle-shaped tumor cells. GISTs are immunohistochemically positive for c-kit (CD117) or CD34. CD-117 and DOG-1 immunohistochemical staining is a well-known diagnostic tool for detecting GISTs [(8,9)]. DOG-1 is a calcium regulated chloride channel protein that was found to be expressed in GIST independent of c-KIT/PDGFRA mutation status.

The present study aims to assess the role of immunohistochemistry in distinguishing GIST from other mesenchymal tumors of GIT and to

characterize the other less common types of mesenchymal tumors

Materials and methods

Patients and tissue samples: All the cases of spindle and epithelioid cell tumors of GIT over a period of 5 years (January 2010 — December 2014) were included in the present study. Study was done in Department of Pathology, Govt Medical College Thrissur, Kerala, India. The study was approved by the Institutional Review Board at Government Medical College Thrissur, Kerala, after obtaining written informed consent.

These specimens were grossed and tumor dimensions were measured. Formalin fixed paraffin embedded blocks from these tumors were taken and four micrometer thick sections stained by Haematoxylin and Eosin were studied for microscopic features. Sampling of the tumor was done by taking as much tissue blocks as the diameter of the tumor excluding areas of necrosis.

Clinicopathological data, including age, gender, tumor type, tumor size and tumor location, were recorded.

Immunohistochemistry: In all the cases immunohistochemistry was done using the markers—DD 117, DOG-1, Smooth Muscle Actin, Desmin, Vimentin and S-100. Immunohistochemistry was performed on serial 4-µm thick, formalin-fixed paraffin-embedded blocks. Immunostaining was assessed over the range of 0-100% positive staining of cells.

Results

The study population comprised of 33 cases of spindle and epithelioid tumors of GIT. Of the 33 cases, the majority ie, 24 were positive for DOG-1 and CD 117. Those 24 cases were negative for other markers like SMA, Vimentin, Desmin and S-100. All those cases were considered as Gastrointestinal stromal tumors. They accounted for 72.72%. 9 cases (27.27%) were positive for other markers (Table-1). Those were diagnosed as Leiomyoma, Leiomyosarcoma and Schwannoma. Leiomyoma were diagnosed in tumors with interlacing fascicles of spindle cells with low mitotic rate and no pleomorphism. Cells show positivity for SMA, Vimentin and Desmin and negative for CD 117 and DOG-1. Tumors with increased mitosis and pleomorphism with positivity for SMA and desmin were diagnosed as Leiomyosarcoma. Tumors showing strong positivity for S-100 were diagnosed as Schwannoma.

Table-1

Number	CD 117/ DOG-1	SMA	VIMENTIN	DESMIN	S-100	Diagnosis
Case 1	Negative	Strong ++	Focal+	Focal+	-	LMS
Case 2	Negative	++	-	+	-	Leiomyoma
Case 3	Negative	++	-	++	-	LMS
Case 4	Negative	-	-	-	++	Schwannoma
Case 5	Negative	++	+	++	-	LMS
Case 6	Negative	+	+	+	-	Leiomayoma
Case 7	Negative	++	-	++	-	LMS
Case 8	Negative	++	+	+	-	LMS
Case 9	Negative	-	-	-	++	Schwannoma

Of the 33 mesenchymal tumors of GIT, majority of the cases belonged to age group above 60 years (39.4%). There is a slight male predominance in these tumors. Stomach was the commonest site accounting for 51.5%, followed by small intestine (45.45%).in this study group there were no cases diagnosed in esophagus and retroperitoneum. 57.6% of the tumors showed spindle cell morphology. Cells were arranged in interlacing fascicles. Epithelioid morphology accounted for 27.3%. A mixed pattern was seen in 15.2% (Table 2).

Table- 2

		Frequency	Percentage
Age	30-39	2	6
	40-49	6	18.2
	50-59	12	36.4
	60 & Above	13	39.4
Sex	Males	18	54.5
	Females	15	45.5
Site	Stomach	17	51.51
	Duodenum	11	33.33
	Jejunum	4	12.12
	Colon	1	3.03
Size	<10cm	20	60.6
	>10cm	13	39.4
Pattern	Spindle	19	57.6
	Epithelioid	09	27.3
	Mixed	05	15.2
Mitosis	<5/50HPF	17	51.5
	5-10/50HPF	9	27.3
	>10/50HPF	7	21.2
CD 117	Negative	9	27.3
	Positive	24	72.7
DOG-1	Negative	9	27.3
	Positive	24	72.7

Figure: 1 gross appearance

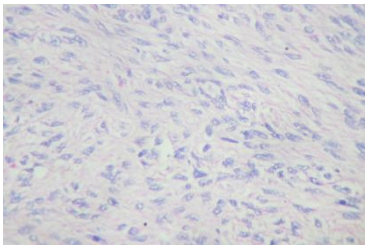

Fig 2: Epithelioid morphology

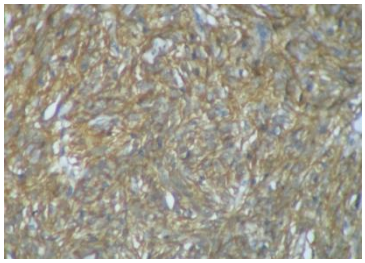

Fig 3: IHC- CD 117

Discussion

The characterization of the specific types of mesenchymal tumors of gastrointestinal tract is mandatory in the management of these tumors. The present study aims to characterise mesenchymal tumors of GIT based on morphology and immunohistochemistry.

With the recent developments in the field of management of GISTs in the form of targeted therapies likeTyrosine Kinase Inhibitors (TKIs), the correct diagnosis of these tumors has a considerable clinical impact and great importance. The invention of TKIs has led to a dramatic improvement in the survival rates of GIST patients, in addition to improving their quality of life (Kang *et al., 2010)* [(11)]. Most GISTs can be identified based on the combination of tumor location, histological appearance and the presence of CD-117 by immunohistochemistry.In an Egyptian study by Hala Said et al in 2014 showed that DOG-1 is a more sensitive immunohisto-chemical marker for GIST than CD-117 and they recommend using DOG-1 as the first choice antibody for the diagnosis of GIST[(12)]. In our study we used both CD-117 and DOG-1 for the specific diagnosis of GISTs.

In our study 72.72% (24 cases) were GISTs. They were positive for CD-117 (Fig 3) and DOG-1 and negative for other markers like SMA, Desmin, Vimentin and S-100. 27.27% (7 cases) were leiomyogenic which included leiomyoma and meiomyosarcoma. Tumor cells were positive for SMA, Desmin and/ or Vimentin and negative for CD 117 and DOG-1. 6.06% (2 cases) were neurogenic tumorsie, Schwannoma. Tumor cells were positive only for S-100. All other markers were negative.

Study by Rudoph. P et al on 244 cases of mesenchymal tumors of GIT state that GISTs were diagnosed when the tumors showed CD-117 positivity[(13)]. SMA and / or Desmin positive tumors were diagnosed as leiomyogenic, S-100 positive tumors as schwannian and vimentin only positive tumors as Gastrointestinal fibrous tumors. In concordance with our study, GISTs were the

predominant tumor. But there were no site predilection for GIST. But our study showed stomach as the commonest site for GISTs and we did not get any fibrogenic tumors. They had a large sample size of 244 cases. One limitation of our study must be the small sample size.

Thomas P et al studied mainly the molecular aspects of gastrointestinal mesenchymal tumors and found that it helps in the precise classification of the tumors, helps to assess prognosis and helps to predict treatment[14]. In contrast to our study, their cases included Inflammatory myofibroblastc tumor, inflammatory fibroid polyp, clear cell sarcoma, synovial sarcoma etc

In the study done by Leona A et al, found that many of the mesenchymal tumors were small and benign and incidentally detected. Some showed distinctive features schwannoma[15]. In contrast, in our study most of the tumors were symptomatic and 39.4% of the tumors were more than 10cm size.

In the study by Dora Lam-Himlinstated that the most common and characteristic mesenchymal lesions in GIT showed specific patterns which include spindle and epithelioidcell morphology [16]. Our findings also were the same. All the cases were spindle epithelioid or a mixture of the two. Of these, spindle pattern was the commonest which accounted for 57.6%. Epithelioid pattern was seen in 27.3% (Fig: 2) cases and mixed pattern seen in 15.2%.

Xuan Zhu, Xiano-Oian Zhang et al in their study on esephageal mesenchymal tumors showed that endoscopicall GISTs and other mesenchymal tumors have similar appearance. Study was done on 29 cases of esophageal mesenchymal tumors. Microscopically GISTs showed spindle and / or epithelioid morphology whereas leiomyomas and leiomyasarcomas showed spindle cell pattern [17]. This is in concordance with our study eventhough there were no esophageal tumors in our study group. Correlating with our study, all the GISTs were positive for CD-117. All cases of leiomyomas and leiomyosarcomas were negative for CD-117 but positive for SMA and Desmin. They conclude their study by stating that most of the esophageal mesenchymal tumors were leiomyomas. GISTs were very less[17].

Zhi-Qiang Wang et al on 210 cases of Gastrointestinal mesenchymal tumors studied the clinicopathologic and immunohistochemical correlation. Among the 210 acses 127 (60.5%) were GISTs, 33 were leiomyomas and leiomyosarcomas (15.7%) and 12.8% were neurogenic tumors (18). In our study also GISTs were commonest (72.72%), followed by leiomyogenic tumors (21.21%). Neurogenic tumors were much less (6.06%). In their study, the incidence of GISTs and Leiomyogenic tumors had equal in males and females but neurogenic tumors were more in males. But in contrast our study showed slight male predominance in all specific categories. In concordance with our study, the predominant pattern was spindle and the comm.-onest site is stomach for GISTs. In discordance with our study, most of the leiomyomas were located in esophagus and neurogenic tumors were located in retroperitoneum. There were no cases in esophagus and retroperitoneum in our study group. They conclude that immunohistochemistry play an important role in the diagnosis of specific tumor types [18].

Conclusion

Mesenchymal tumors of the GIT are rare neoplasms with overlapping histologic features. The accurate and specific diagnosis of these tumors is mandatory because, these tumors respond to treatment differently. Many of these tumors have specific targeted therapy. Apart from morphology, immunohistochemistry must be done for the specific diagnosis since treatment and prognosis depends on accurate diagnosis

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