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CLINICOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF GASTROINTESTINAL STROMAL TUMORS

pathology

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ABSTRACT

(A) Objectives: The prognosis of Gastrointestinal stromal tumors (GIST) largely depend upon the histopathological characteristics and immunohistochemistry marker studies. This study is undertaken to study clinicopathological and immunohistochemical features of these tumors.
(B) Materials and Methods: A 6 years retrospective study (2014-2019) was conducted at a tertiary care hospital. It included all the 15 cases of GIST diagnosed in that period. Histopathology slides and clinical records of all the cases were reviewed. Appropriate blocks were selected and sent for immunohistochemistry marker study which included: DOG-1, CD117, S-100, desmin, smooth muscle actin (SMA), CD34 and vimentin.
(C) Results: Out of 15 cases of GIST, all presented as abdominal masses commonly located in small intestine of adult men with mean age being 56 years. All the GISTs showed positivity for CD117 and vimentin. Immunoreactivity for DOG-1 clone 1.1 was observed in 14 cases and DOG-1 clone k9 was positive in 2 out of 15 cases studied.
(D) Conclusion: This study validates the importance of CD117 in diagnosis of GIST. Out of two clones of DOG-1, clone 1.1 was observed to be more sensitive marker.

KEYWORDS

Cd117, DOG-1, gastrointestinal stromal tumors, immunohistochemistry.

INTRODUCTION

Among all gastrointestinal mesenchymal tumors, Gastro-Intestinal Stromal Tumors (GIST) is the most commonly encountered tumor.[1] It originates from interstitial cells of cajal (intestinal pacemaker cells) or its progenitors which are immunoreactive for CD117, CD34 and DOG-1.[2,3] Histopathologically, GIST is mesenchymal spindle cell or epithelioid cell tumors of GIT showing c-Kit (CD117) positivity.[4] Gain-of-function mutations in platelet-derived growth factor receptor alpha (PDGFRA) and c-Kit receptor of tyrosine kinase gene separately contribute in pathogenesis of GIST.[5,6] Immunoreactivity of CD117 is the most important and sensitive marker in the diagnosis of GIST. With the advent of tyrosine kinase inhibitor therapies against PDGFRA and KIT, previously inoperable or malignant, metastatic GISTs can now be treated successfully.[7]

MATERIALS AND METHODS

We included all 15 cases diagnosed as GIST from department of pathology, at a tertiary care hospital between 2014 - 2019. The age, gender, tumor localization and tumor diameter of the cases were recorded from the surgical pathology records. Hematoxylin-eosin (HE) – stained slides of the paraffin blocks were reviewed in terms of histopathological parameters (number of mitosis/ 50 hpf, cellularity, cell type etc). Risk stratification of the tumors was done using National institute of Health (NIH) criteria. Appropriate blocks were selected and outsourced for immunohistochemistry (IHC) marker study which included: DOG-1, CD117, S-100, desmin, smooth muscle actin (SMA), CD34 and vimentin.

RESULTS-

Table I & II shows clinicopathological and IHC details of the GIST cases.

Clinical Presentation –
All 15 patients of GIST presented with abdominal masses. Mean age of presentation was 56 years (35-75 years) with male preponderance (M:F – 12:3).

Gross pathology - Maximum GIST were commonly located in small intestine (duodenum > jejunum). Average size of GIST was 10.5 cm.

Microscopy – Spindle cell morphology was the commonest microscopic feature in almost all cases **(Fig. 1a).** Only 1 case of GIST showed epithelioid morphology **(Fig. 1b).** There were 7 high risk, 4 intermediate risk and 4 low risk GISTs.

Immunohistochemistry- All cases were positive for CD117 **(Fig. 1c)** and vimentin. CD34 (8 cases) and SMA (6 cases) were most frequently expressed. DOG-1 clone 1.1 **(Fig. 1d)** was positive in 14 out of 15 cases.

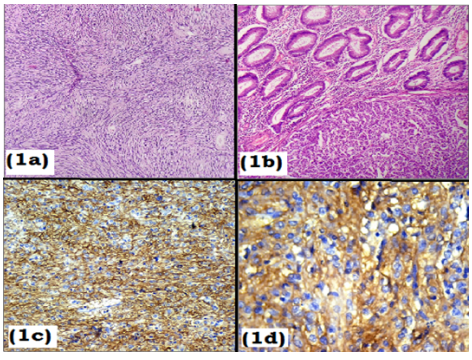

Figure 1- (a) spindle cell GIST (b) epithelioid GIST (c) GIST showing CD117 positivity (d) GIST showing DOG-1 positivity.

Table I – Clinicopathological features of GIST

Sr. No.	features	n = 15	(%)
1	Mean Age	56 years	-
2	Sex: Male female	 12 3	 80 20
3	Tumor site: Stomach Small intestine Colon	 5 8 2	 33.3 53.3 13.3
4	Tumor size: <2 cm 2 to 10cm >10cm	 - 7 8	 - 46.6 53.3

5	Tumor cell type: Spindle Epithelioid Mixed	 14 01 -	 93.3 6.66 -
6	Predominant histopathological pattern	Fascicles	-
7	Mitosis: < 5/50 HPF > 5/50 HPF	 4 11	 26.6 73.3
8	Risk stratification: Low Intermediate High	 4 4 7	 26.6 26.6 46.6

Table II – IHC marker study og GIST cases

IHC marker	n = 15	(%)
Cd117	15	100
CD34	8	40
Desmin	1	6
SMA	6	26.6
S-100	1	6
Vimentin	15	100
DOG-1 Clone k9 Clone 1.1	 2 14	 13.3 93.3

DISCUSSION

GIST are rare mesenchymal tumors constituting less than 1% of the primary tumors of Gastrointestinal (GI) tract.[8] It comprises of spindle cells, epithelioid cells or occasionally pleomorphic cells which express c-kit protein (CD117).[9] Most of the time, GISTs lacking c-kit are immunoreactive for DOG-1, PDGFRA. GIST can show broad spectrum of biological behaviors.[8] An early study by Hirota S et al. identified GIST as a distinct soft tissue tumor with kit immunostaining as its major diagnostic tool.[10] Three years later, GIST became the 1st solid tumor to be given targeted chemotherapy.[11]

Most common sites for GISTs are stomach (50% - 60%) followed by small intestine (20% - 30%) and colorectum (10%). However, it can arise from any site along the GI tract.[12, 13] In our study, most common location was small intestine (53.3 %), followed by stomach(33.3%) and then colon (13.3%). In a study by Rabin I et al. 93 GIST cases were studied, in which male to female ratio was 1.3:1 showing male preponderance and the ages ranged from 36 to 85 years (mean age – 60 years).[13] In this study, this was well correlated with M:F ratio being 4:1 and the ages ranging between 35 – 65 years.

Microscopically, maximum GIST commonly show spindle cell morphology, in few cases epithelioid pattern is seen and very rarely pleomorphic morphology may be observed. Intestinal GISTs with epithelioid morphology is indispensably limited to malignant tumors.[14] Attili SV et al. reported 40% spindle cell morphology, 33% epithelioid morphology and 27% mixed morphology.[15] In the present study, 14 out of 15 cases showed spindle cell morphology and only 1 case of intestinal GIST showed epithelioid morphology.

Now-a-days, almost every GIST is thought to be potentially malignant. For risk stratification, the NIH criteria uses tumor size as well as mitotic rate per 50 hpf as prognostic determinants to categorise these tumors into four risk groups, namely very low risk, low risk, intermediate risk and high risk category GIST. In addition to these, tumor location is also an important determinant of prognosis. For example, Gastric GIST is considered to have better prognosis than intestinal GISTs of similar size and mitotic activity.[16] In present study, maximum GISTs were of high Risk (46.6%) followed by intermediate (26.6%) and low risk (26.6%). Also, maximum intestinal tumors showed high risk GISTs.

Pannel of IHC markers like CD34, SMA (smooth muscle actin), S100, Desmin and CD117 (c-kit) are important for making accurate diagnosis of GIST and also to differentiate it from other mesenchymal tumors. As per literature majority of GIST are immunoreactive for CD117.[17,18] Liu et al. revealed that CD117 and CD34 showed diffuse strong expressions in GISTs, and positive rates were 98.1% and 92.3% in that study.[19] In present study all 15 cases (100%) expressed positivity for CD117. Rabin et al. reported 40% to 70% of GISTs were positive for CD34, 20-30% were positive for SMA, 10% positive for S100 protein and less than 5 % were positive for desmin.[13] In a recent study, the overall sensitivity of DOG-1 and c-kit in GIST was nearly identical : 94.4% and 94.7%. But in intestinal GISTs, c-kit was more sensitive than DOG-1.[8] Our results indicate that out of two clones of DOG-1 studied, clone 1.1 have got better sensitivity.

CONCLUSION-

IHC studies in GIST are important because it impacts treatment with targeted therapy. This study reaffirms the diagnostic importance of CD117 in GIST. Out of two clones of DOG-1, clone 1.1 was observed to be more sensitive marker. However, larger sample sized studies are required for definitive conclusion.

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