Original Research Paper

Volume - 7 | Issue - 6 | June - 2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Pathology

DIAGNOSTIC SIGNIFICANCE OF THE MARKER DOG-1 IN GASTROINTESTINAL STROMAL TUMORS

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ABSTRACT

Background: Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors that arise predominantly in the gastrointestinal tract (GIT). With the recent developments in the field of management of GISTs in the form of targeted therapies like Tyrosine Kinase Inhibitors (TKIs), the correct diagnosis of these tumors has a considerable clinical impact and great importance. In the vast majority of GISTs, high levels of CD117 expression are accompanied by a c-KIT gene mutation. A subset of GISTs has been found to have PDGFRA mutations rather than c-KIT mutations. Immunohistochemical marker CD117 will be positive in about 90-96% of GISTs. DOG-1 ("discovered on GIST") is a calcium dependent, receptor activated chloride channel protein expressed in GIST and has been reported to be highly sensitive for GIST, for both KIT- and PDGFRA-mutated GISTs. The utility of DOG-1 is greatest in tumors lacking KIT and PDGFRA mutations. The present study evaluates the expression of the marker DOG-1 in gastrointestinal stromal tumors of GIT and correlates this with CD117 expression and various histomorphological features.

Materials and methods : The study was a cross sectional study done in Department of Pathology Government Medical College Thrissur, Kerala, India. Study period is from January 2010 to December 2014 (5 years). All the cases of Mesenchymal tumors of GIT during the same period received in the Department of pathology Govt Medical College Thrissur were included in the study. The various morphological parameters studied include gross dimensions of the tumour, predominant histological type, cellularity, presence or absence of tumour cell necrosis, mitotic Index and grade of the tumour along with Immunohistochemical staining for CD117 and DOG-1.

Results : There were a total of 33 cases. The age group ranged from 41-76 years. The mean age was 57 years. Males accounted for 54.5% of the cases with a male to female ratio of 1.2:1. Of the 33 cases, stomach was the commonest site of the lesion and accounted for 51.5 % of the cases followed by small intestine of which jejunum was the most common. Grossly, tumours with less than 10 cm and more than 10 cm size accounted for 60.6 % and 39.4 % respectively. In microscopy the predominant pattern of the tumors was spindle which constituted 57.6% followed by epithelioid pattern (27.3%). Mixed pattern was present in 15.2% of cases. 51.5 % of the cases showed a mitotic index of less than 5 per 50 HPF. 21.2 % of cases showed a high mitotic index of >10 per 50 HPF. Out of the 33 cases, CD 117 was positive in 23 cases which accounted for 69.6%. 10 cases were negative for CD 117 (30.3%). Out of the 33 cases 24 were positive for DOG-1(72.72%) and 9 (27.27%) were negative. The cases positive for CD117 or DOG-1 were considered as GIST. Those cases negative for DOG-1 and CD 117 (9 cases) were positive for other markers like SMA, Desmin and S-100. They were diagnosed as leiomyoma, leiomyosarcoma and schwannoma.

Discussion: The current study, evaluated DOG-1 antibody as a diagnostic marker for GISTs. The results demonstrated that DOG-1 is a specific and sensitive marker for GIST, as it stained all cases of GIST ie, 24 cases (100%) included in the study and didn't stain any of the other mesenchymal tumors tested. In the present study, a statistically significant concordance was found between the results of CD117 and DOG-1 immunoreactivity with perfect agreement between the two markers (K= 0.918). Twenty three (95.84%) cases of GISTs were positive for both markers. In our study DOG -1 was found to be more sensitive than CD117 (100 % and 95.8%). Negative predictive value of DOG -1 was higher than CD 117(100% and 90%). But the diagnostic accuracies of both DOG-1 and CD 117 were found to be equal (96.96%).

Conclusion : DOG-1 is a more sensitive immunohistochemical marker for GIST than c-KIT and we recommend using DOG-1 as the first choice antibody for the diagnosis of GIST. This study concluded that DOG-1 is a better IHC marker than c-KIT (CD117) in diagnosing GIST due to better sensitivity and negative predictive value. Since the diagnostic accuracy is the same for CD 117 and DOG-1, a combination of both must be considered in all the suspected cases of GISTs.

KEYWORDS : Gastrointestinal stromal tumor, CD117, DOG-1, Background

BACKGROUND

Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors that arise predominantly in the gastrointestinal tract (GIT). In 1998, after the discovery of gain-of-function mutations in the c-KIT proto-oncogene, these tumors were reliably distinguished from other histopathological subtypes of mesenchymal tumors [1, 2]. With the recent developments in the field of management of GISTs in the form of targeted therapies like Tyrosine Kinase Inhibitors (TKIs), the correct diagnosis of these tumors has a considerable clinical impact and great importance. In the vast majority of GISTs, high levels of CD 117 expression are accompanied by a c-KIT gene mutation [3, 4]. A subset of GISTs has been found to have PDGFRA mutations rather than c-KIT mutations [4, 5].

The annual incidence of GIST is 1.5/100,000/year. The median age at diagnosis is 60 years. There is usually no predilection for either gender but some series suggest a slight male predominance [6].

GISTs can develop anywhere along the GI tract from the esophagus to the rectum; however, stomach (60%) and small intestine (30%) are the most common locations for GIST. Only 10% of GISTs are found in the esophagus, mesentery, omentum, colon or rectum [6].

Only 70% of the patients with GISTs are symptomatic and the rest are detected incidentally. Bleeding (30%-40%) comprises the most common symptom after vague abdominal discomfort (60%-70%). Up to 30% of GISTs exhibit high-risk behaviour such as metastasis and infiltration [7-10]. GISTs with indolent (low-risk) behaviour are typically found as small submucosal lesions.

GISTs vary greatly in size from a few millimetres to more than 30 cm. The median size is between 5 and 8 cm. Macroscopically, GISTs usually occur as exophytic growth [4, 5, 8, 11]. Others are endophytic polypoid submucosal growth with surface ulceration and bleeding; a few grow in both directions to produce a dumb-bell appearance. They are usually well circumscribed, nodular or bosselated masses that lack a true capsule. GISTs may be single or multiple. The cut surface of GIST is grey to pink with a rubbery or soft consistency. Larger tumors often undergo cystic degeneration, infarction, haemorrhage, and necrosis. The gross feature suggesting malignancy is tumor size; metastasis is relatively infrequent from neoplasms measuring less than 5 cm but occurs in the majority of lesions over 10 cm [11].

Histologically GISTs show mainly two patterns, spindle and epithelioid. Typical spindle cell tumors are composed of interlacing bundles or whorls of uniform spindle shaped cells with ovoid or elongated blunt ended nuclei and fibrillary eosinophilic cytoplasm. The nuclei are usually monotonous and uniform. Epithelioid GISTs, most often consist of round vacuolated or clear cells, typically arranged in cohesive sheets or nests that impart the epithelioid pattern.

Most of the tumors in this category will have areas of spindle cells with epithelioid foci. Usually these tumors are seen as sheets rather than in fascicles [11].

Most GISTs can be identified based on the combination of tumor location, histological appearance, and the presence of CD 117 by immunohistochemistry. The most useful parameters which can predict the outcome of GISTs are tumor size and mitotic figures (expressed per HPF). In this era, GISTs are being classified as very low risk, low risk, intermediate risk and high risk for predicting the recurrence and metastatic potential.

Immunohistochemical marker CD 117 will be positive in about 90-96% of GISTs. Other than the consistent positivity for KIT (Cd117), about 60% to 70% of GISTs show positivity for CD34, 30% to 40% show positivity for smooth muscle actin (SMA), and around 5% show positivity for S-100. [12]. But none of these markers are specific for GIST.

DOG-1 ("discovered on GIST") is a calcium dependent, receptor activated chloride channel protein expressed in GIST and has been reported to be highly sensitive for GIST, for both KIT- and PDGFRA-mutated GISTs. DOG-1 stains about one third of KIT-negative GISTs, and its utility is greatest in tumors lacking KIT and PDGFRA mutations [13, 14]. Recent studies have suggested that antibodies against it has a better sensitivity and specificity compared with KIT (117) and CD 34 and these antibodies could serve as specific immunohistochemical markers for GIST irrespective of the mutation or the immunophenotype status.

The present study evaluates the expression of the marker DOG-1 in gastrointestinal stromal tumors of GIT and correlates this with CD117 expression and various histomorphological features.

MATERIALS AND METHODS

The study was a cross sectional study done in Department of Pathology Government Medical College Thrissur, Kerala, India. Study period is from January 2010 to December 2014 (5 years). All the cases of Mesenchymal tumors of GIT during the same period received in the Department of pathology Govt Medical College Thrissur were included in the study.

All the specimens were grossed and the tumor dimensions were measured. Formalin fixed paraffin embedded blocks from these tumors were taken and four micrometre 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.

In each case the following parameters were recorded:

1. Gross dimensions of the tumour

All three dimensions of the tumour were measured with emphasis given to the maximum tumour size.

2. Predominant Histological type

It was categorized as spindle, epithelioid or mixed based on the cellular features. Mixed pattern is assessed if both spindle and epithelioid components comprised more than 25% of the tumor.

3. Cellularity

Cellularity was judged to be either cellular or hypocellular, with the highest levels of cellularity in each tumour recorded. Normal muscularis propria was used as the standard for comparison.

4. Presence or absence of Tumour cell necrosis

Defined as tumour cells with coagulative necrosis associated with karyorrhectic debris.

5. Mitotic Index

The mitotic index was counted in the most mitotically active area of the tumour. 50 consecutive high power fields were counted using 40x objective and 10x ocular. This corresponds to a total area of 5 mm^2. Only unambiguous mitotic figures were counted in the process.

6. Grade of the tumour

All the tumours were graded to very low risk, low risk, intermediate risk or high risk depending on the maximum tumour size and the mitotic index.

7. Immunohistochemical staining

3 micron sections of formalin fixed paraffin embedded tissue blocks were taken on Poly L lysine coated or APES coated slides. Antigen retrieval was done by pressure cooker method.

Immunohistochemical staining was performed in all cases with CD 117 and DOG- 1.

DOG-1 immunopositivity was scored quantitatively for the percentage of positive tumour cells

Staining (% of positive tumor cells) -- 0 ,<10, 11-25,26-50 >50

Intensity — 0- negative; 1+ --weak staining⁄ trace; 2+ --moderate staining; 3+ --strong staining

Subcellular location —cytoplasmic, membranous and luminal

In addition, the clinical presentations of the patients were analysed by referring to the case records. The site of the tumour was determined by the gross morphological features and also by referring to the operative notes in ambiguous cases.

All the data were collected, tabulated and analysed using a personal computer with Statistical Package for the Social Sciences" version 19 program.

Chi-square tests were used for the comparison between qualitative variables.

p values were calculated between different variables and $p \leq 0.05$ was considered significant.

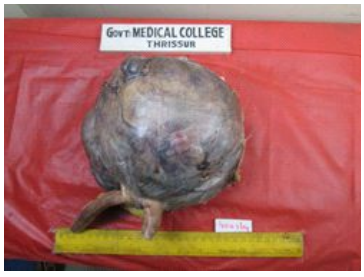
RESULTS

There were a total of 33 cases

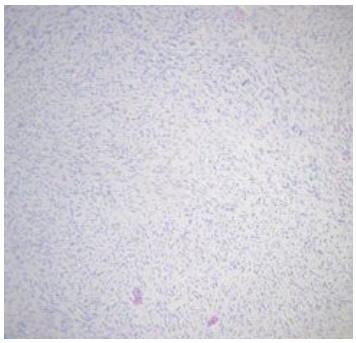
The age group ranged from 41-76 years. The mean age was 57 years. Males accounted for 54.5% of the cases with a male to female ratio of 1.2:1. Of the 33 cases, stomach was the commonest site of the lesion and accounted for 51.5 % of the cases followed by small intestine of which jejunum was the most common (Table-1).

	Table-1	
Site	Frequency	percentage
Stomach	17	51.51
Duodenum	11	33.33
Jejunum	4	12.12
Colon	1	3.03
Total	33	100

Grossly, GISTs were categorized based on tumour size, into less than 10 cm and more than 10 cm, to aid the grading of the tumour. Tumours with less than 10 cm and more than 10 cm size accounted for 60.6 % and 39.4 % respectively (Figure-1). In microscopy the predominant pattern of the tumors was spindle (Figure-2)which constituted 57.6% followed by epithelioid pattern (27.3%). Mixed pattern of spindle and epithelioid morphology was present in 15.2% of cases. 97% of the tumours were cellular. Hypo cellular tumors accounted for only 3% of tumours. Hypocellularity was more common in smaller tumours. 51.5 % of the cases showed a mitotic index of less than 5 per 50 HPF. 21.2 % of cases showed a high mitotic index of >10 per 50 HPF. All the cases were studied for the presence of tumour cell necrosis microscopically, which was present in 42.4 % of cases. On grading, majority of the tumors were in the high risk category (41.66%). 37.55% were intermediate risk and 20.83% were low risk. None of the tumors were in the very low risk category.

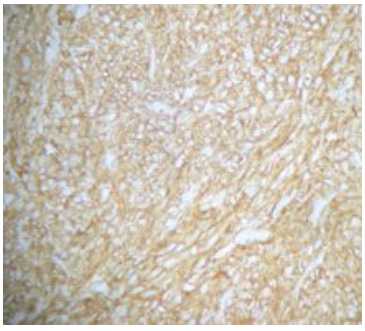


Figure—1 GIST-small intestine Gross morphology

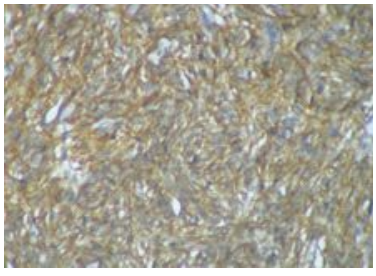


Figure—2 GIST—spindle cell hematoxylin- eosin x10

Out of the 33 cases, CD 117 was positive in 23 cases which accounted for 69.6%. 10 cases were negative for CD 117 (30.3%) (Figure—3). Out of the 33 cases 24 were positive for DOG-1(72.72%) (Figure—4) and 9 (27.27%) were negative. There was one case which was CD 117 negative but positive for DOG-1. The cases positive for CD 117 or DOG-1 were considered as GIST. DOG-1 staining was cytoplasmic in majority of cases constituting 75.75%. 15.15% showed membranous positivity and 9.09% showed a mixed staining pattern. Those cases negative for DOG-1 and CD 117 (9 cases) were positive for other markers like SMA, Desmin and S-100. They were diagnosed as leiomyoma, leiomyosarcoma and schwannoma.



Figure—3 Cd117—x40



Figure—4 DOG—1 x40

We defined Gastrointestinal stromal tumor as a mesenchymal tumor of gastrointestinal tract with spindle or epithelioid morphology with either CD 117 or DOG- 1 positivity.

DISCUSSION

The invention of TKIs (Imatinib) has led to a dramatic improvement in the survival rates of GIST patients, in addition to improving their quality of life [15]. In majority of GISTs, the high levels of CD 117 expression are accompanied by a c-KIT gene mutation [16, 17]. A subset of GISTs has been found to have PDGFRA mutations rather than c-KIT mutations [17, 18]. These patients may still benefit from imatinib therapy, but they often fail to react with antibodies against CD 117 and hence may remain undiagnosed as GIST [18]. In addition, some GISTs with c-KIT mutations may have low c-KIT expression by IHC, yet will still respond to imatinib therapy [19]. Screening for c-KIT and PDGFRA mutations can be helpful in this setting, but this approach adds to the time and cost of diagnosis and only a few centres worldwide perform this analysis clinically. What is needed to aid in routine diagnosis is a marker that reliably stains GIST that is CD 117 weak/negative [20].

In an Egyptian study by Hala Said et al in 2014 showed that DOG-1 is a more sensitive immunohistochemical marker for GIST than c-KIT and they recommend using DOG-1 as the first choice antibody for the diagnosis of GIST [21].

DOG-1 is a calcium regulated chloride channel protein that is expressed in GIST independent of c-KIT/PDGFRA mutation status [20, 22, 23]. The aim of this study was to evaluate immunohistochemical (IHC) expression of DOG-1 as a diagnostic marker for GIST. We also compared IHC staining and diagnostic efficacy of DOG-1 with that of CD 117 in GIST.

In the current study, we evaluated DOG-1 antibody as a diagnostic marker for GISTs. The results demonstrated that DOG-1 is a specific and sensitive marker for GIST, as it stained all cases of GIST ie, 24 cases (100%) included in the study and didn't stain any of the other mesenchymal tumors tested.

Hirota et al reported c-kit (CD 117) expression in 94% of GIST cases [17]. In our work, CD117 was positive in 23/24 GISTs which accounts for 95.84%. 4.16 % of GISTs were found to be negative for c-KIT. The definition of CD117 negativity in GIST was to some extent controversial. This may explain the variable range of GIST tumor positive for CD117 in the literature which range from 74% to 98.1% [20, 23, 24, 25].

Cd117 positivity in other studies depends mainly on staining intensity rather than percentage. They considered positivity if any moderate or strong complete membranous CD117 staining is noticed whether focal or diffuse in tumor [20]. In our study also we followed the same criteria.

West et al studied 149 cases and reported that DOG-1 was superior in sensitivity and specificity to KIT/CD117 being expressed in 97.8% of GISTs, whereas CD117 positivity was 94% [22]. In the present study also DOG-1 proved to be a more sensitive marker than CD 117 for the diagnosis of GISTs (100 % for DOG-1and 95.84% for CD 117). In the study of Espinosa et al in 425 cases, they showed that DOG-1 has a high specificity and sensitivity in the diagnosis of GIST with DOG-1 positivity 87% and 74% for CD 117. In the study of Miettinen et al on 1168 GIST cases DOG-1 positivity was 94.8%, the c-kit positivity was 94.9%. Abdel-Hadi et al. (2009) found that DOG-1 identified only one case that was c-KIT negative [25].

In the present study, a statistically significant concordance was found between the results of CD117 and DOG-1 immunoreactivity with perfect agreement between the two markers (K= 0.918). Twenty three (95.84%) cases of GISTs were positive for both markers.

In a study by Haid et al showed, DOG -1 with high sensitivity (94.1%) and high negative predictive value (81.3%). Also showed that the diagnostic accuracy of DOG-1 was better than CD117, which is 95.3% and 75% respectively [21]. In our study DOG -1 was found to be more sensitive than CD117 (100 % and 95.8%). Negative predictive value of DOG -1 was higher than CD 117(100% and 90%). But the diagnostic accuracies of both DOG-1 and CD 117 were found to be equal (96.96%).

The sample size in our study was 33 (which included all mesenchymal tumors of GIT).The age group ranged from 41 to 76 years. Generally, the 5th and 6th decade is the most commonly diagnosed age group of patients. In parallel to the literature, the median age in our study group was found to be 57.

Males accounted for 54.5 % of the cases with a male to female ratio of 1.2:1. This is in contrast with the study by Haid et al which showed a female predominance. In our study and in several studies reported that there is no significant difference in gender distribution between patients [21].

In our study, stomach was the most common site of the lesion and accounted for 51.5 % of the cases. Other sites were duodenum (33.33%), jejunum (12.12%) and colon (3.03%).This finding was in concordance with the other studies which showed stomach as the most common site. Miettinen et al in their study of 1765 cases of GIST also showed stomach as the most common site involved [26].

In the current study majority of the tumors were of spindled cell

morphology which constituted 57.6%. Haid et al also showed spindle cell morphology as the commonest pattern which was found to be 85.4% [21]. A study by Didem Sozutek et al in 2014 also showed spindle cell morphology as the most common pattern [27].

The relevance of DOG-1 score Vs Age, site, size, sex, patterns, risk stratification, cellularity and necrosis were studied and found to be statistically not significant.

In our study, DOG-1-positive staining was observed in 100 % of GISTs, including the stomach, small intestine and colon. Staining in spindle cells was mainly found in the cytoplasm. Strong membrane staining generally appeared in the epithelioid cells. There were no statistically significant differences between DOG-1 staining and anatomical site distribution. Although the difference in the intensity of staining between DOG-1 and CD117 was not statistically significant, DOG-1 expression was slightly higher than CD117 expression.

When considering GIST risk classification, DOG-1 was found in 5 out of 5 cases in the low-risk group, 9 out of 9 cases in the intermediate-risk group, and in 10 out of 10 in the high-risk group. The statistical analysis showed that DOG-1 did not show any significant difference between DOG-1 expression and risk classification in concordance with the study done by Chao wang et al which showed no significant difference between DOG-1 expression and risk stratification [28].

Mesenchymal tumors other than GIST (9/33 cases), we have encountered in our study were leiomyosarcomas, leiomyomas and schwannoma. None of these showed positivity for CD 117 or DOG-1. Other markers used in these cases were Smooth muscle actin (SMA), desmin, vimentin and S-100. According to Fletcher, SMA can be positive in 25%, desmin in about 5 % and S 100 in <1%. But in our study none of these markers were taken up by GISTs.

In summary, we demonstrate that detection of a novel gene, DOG-1, identifies the vast majority of both KIT- and PDGFRA-mutated GISTs. This may be of clinical value in identifying candidates for Imatinib (TKI) therapy. As a cell membrane-associated protein, with markedly elevated expression in GISTs, DOG-1 may also be a potential therapeutic target.

CONCLUSION

DOG-1 is a more sensitive immunohistochemical marker for GIST than c-KIT and we recommend using DOG-1 as the first choice antibody for the diagnosis of GIST.

This study concluded that DOG-1 is a better IHC marker than c-KIT (CD117) in diagnosing GIST due to better sensitivity and negative predictive value. Since the diagnostic accuracy is the same for CD 117 and DOG-1, a combination of both must be considered in all the suspected cases of GISTs.

The importance of this study is that, approximately 5% of GISTs are CD 117 negative which can be DOG-1 positive. A significant proportion of DOG-1 positive GISTs also respond to Imatinib therapy

In cases that fail to stain for either CD117 or DOG-1 further immunostaining with broader panel of antibodies, including muscle (SMA and desmin) and neural markers (S100), together with molecular analysis, should be considered, to make the diagnosis of other mesenchymal tumors.

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