ORIGINAL RESEARCH PAPER

Volume-6 | Issue-10 | October-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

GASTROINTESTINALSTROMAL TUMOURS – HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL ANALYSIS AND CORRELATION WITH PROGNOSIS – A RETROSPECTIVE STUDY.

Pathology

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ABSTRACT

Gastrointestinal Stromal Tumours (GISTs) are the most common gastrointestinal soft tissue malignancies. Most common site is stomach, followed by small intestine, esophagus ,colon ,rectum etc. The symptoms are mainly related to tumor size and site. Mutually exclusive mutations in Kit or PDGFRA receptor tyrosine kinase proteins observed in more than 80% of GISTs are central in sporadic GIST pathogenesis. In this study 50 cases of GISTs were evaluated . We tried to find out the relation of morphology and immunohistochemistry of GISTs, assessed the independent relation of the parameters which are included in this study with prognosis. We also tried to find out the effect of each factor independently on the clinical outcome. We found that the prognosis and survival in GIST patients are dependent on pathological parameters - tumor size and mitotic count. No significant correlation was found between CD117 reactivity/site of origin of tumour with morphology or survival.

KEYWORDS

Gastrointestinal Stromal Tumour, Tumour size, Mitosis, CD117.

INTRODUCTION

Gastrointestinal Stromal tumours are the most common gastrointestinal soft tissue malignancies [1]. Most common site is stomach (60-70%), followed by small intestine, esophagus, colon, rectum etc. Other rare sites are omentum, mesentery and retroperitonium. The symptoms are mainly related to tumor size and site. They usually present with G I bleeding. Other presenting symptoms include palpable masses, pain, gastric outlet obstruction, and dysphagia [2, 3]. In 20% of cases, the tumor is incidentally detected in the gastric wall during laparotomy for other medical reasons.

Grossly they are submucosal, mostly well circumscribed, may project as polypoidal mass into the lumen, or may grow outwards [4]. They are soft to firm in consistency , and show a pale pink, fleshy or whorled cut surface. Areas of necrosis and haemorrhage are common. On histology tumours are very cellular with a whorled or palisaded arrangement of spindle cells [4][5]. Nuclei are oval or cigar shaped and display very little pleomorphism or atypia except in malignant tumours. Some tumours show epithelioid morphology. The spindle and epithelioid patterns can be admixed and often blend together[6].

Mutually exclusive mutations in Kit or PDGFRA receptor tyrosine kinase proteins observed in more than 80% of GISTs are central in sporadic GIST pathogenesis. The most useful parameters which can predict the outcome of GISTs are tumor size and mitotic figures . GISTs are classified as very low risk, low risk, intermediate risk and high risk. By immunohistochemistry, 90% to 95% of GISTs will be diffusely and strongly positive for CD117(c-Kit)[7].Other immunohistochemical markers positive in GIST are CD 34, SMA, S100, PDGFRA and DOG 1. DOG 1 is expressed in GIST irrespective of the mutation type. DOG-1 stains about one third of KIT-negative GISTs, and its utility is greatest in tumors lacking KIT and PDGFRA mutations[8].

The mainstay of treatment for primary GISTs is surgical resection, when possible. Targeted therapy using imatinib is found to be useful for preoperative debulking and to prevent metastasis and recurrence post operatively.

In this study we tried to find out the relation of morphology and immunohistochemistry of Gastrointestinal stromal tumours, assessed the independent relation of the parameters which are included in this study with prognosis. We also tried to find out the effect of each factor independently on the clinical outcome.

AIM

To study the relation of morphology and immunohistochemistry of gastrointestinal stromal tumours with prognosis

MATERIALS AND METHODS

All histopathologically diagnosed cases of GIST during a period of 9 years were included in the study. A retrospective study was done with a minimum follow up of 2 years. Follow up details were obtained from the medical records.

The following parameters were evaluated in each patient

- Patient's age
- Gender
- Clinical manifestation
- Tumor size
- Histopathological findings
- Presence & date of EVENT, if any [Event was defined as - local recurrence/ distant metastasis/death]
- Disease free survival.

In all clinically diagnosed cases a detailed histopathological examination was done on hematoxylin and eosin stained paraffin sections. In each case along with pathology report, electronic medical records were reviewed for clinical information including age, gender, initial clinical presentation, date of surgery and for latest follow up. During the defined period we got 62 histopathologically diagnosed cases of GIST of which 12 were excluded since the follow up period was less than 2 years. In all cases besides the hematoxylin and eosin staining, a standard immunohistochemistry panel was applied.

We used the standard immunohistochemistry panel for GIST which included Cd117,
CD 34,SMA,S100,DESMIN,VIMENTIN,Ki 67.
CD 117 negative cases were evaluated seperately.

For immunohistochemistry paraffin sections were cut at 5 microns. BioGenex ready to use diluted antibodies were used .Antigen retrival was done using microwave method.

For Grading the tumour the standard Fletcher et al criteria was used.

Data entry was done using Microsoft excel programme because it was compatible for further analysis with SPSS. All the datas were analysed using the SPSS 2001 and relevant tests of significance applied wherever necessary.

RESULTS

The study was done by reviewing the medical records and histopathology slides of 50 cases. Initially the clinical and morphological features of all the patients were studied. Later the

prognostic implication of various factors and follow up details were assessed.

The age group ranged from 31-80 years. Majority of the cases were in the 61-80 age group. Males accounted for 42% of the cases and females accounted for 58%. Of the 50 cases, stomach was the commonest site of the lesion followed by small intestine of which jejunum was the most common site. Oesophagus was the least common site. Maleana was the most common symptom followed by pain. Tumour sizes ranged from 2cms to 28 cms with a mean tumour size of 8.37cms. Majority of the tumours were in the 5 – 10cms group. Majority of the patients were in high risk group. Majority of the cases showed spindle cell morphology. Only 4 cases showed epithelioid morphology. Out of the 50 cases CD 117 was positive in 43 cases and CD 34 was positive in 40 cases both were positive in 33 cases.

Figure 1,Gastric GIST.

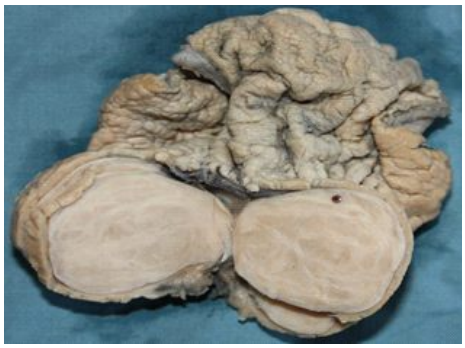


Figure 2 - Small intestinal GIST and Retroperitoneal GIST

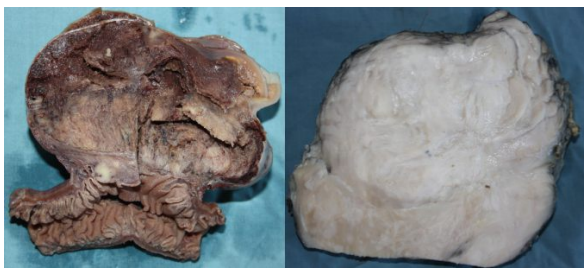


Figure 3-Gastic mucosa with tumour, spindle cell morphology, H & E 100X

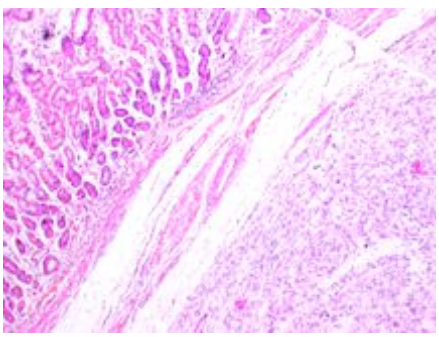


Figure 4 – GIST with epithelioid morphology,H&E 400X

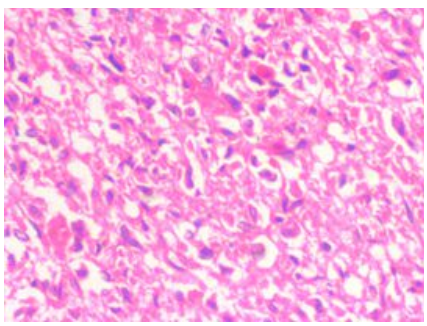


Figure 5 – CD117,400X

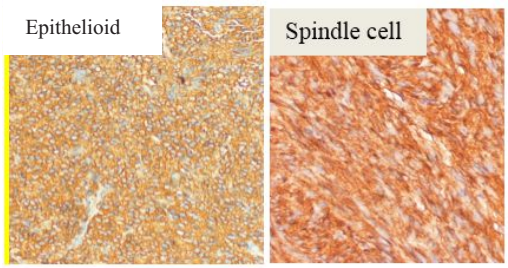
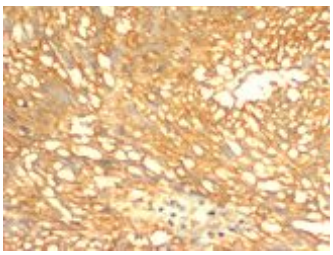


Figure 6 – CD34,400X



Events occurred in 15 out of 50 cases. Maximum number of events occurred in 61-80 age group. Maximum number of events occurred in cases which had > 10 mitosis /50high power field.

The tumours were categorized based on size into< 2cm,2-5cm,5-10cm and>10cm. Events were maximum in case which had a tumour size more than 10cm. Hence the high risk group was associated with increased number of events.

Table 1

Characteristics	Event occurred	Not occurred
	Total no:15/50	Total no:35/50
Mitosis/50 hpf		
<5	4	18
5 -10	4	10
>10	7	7

Table2

	Event occurred	Not occurred
	Total no : 15/50	Total no : 35/50
Size		
<2	0	0
2-5	0	8
5-10	6	20
>10	9	7

13 out of 15 cases with the events showed CD117 positivity.

Within each category Mann - Whitney test was used to compare two groups.

Comparison of the groups showing mitosis < 5 with those having >10 gave a p value of 0.046, which shows that mitosis has a significant effect in outcome. Similarly comparison of the cases showing size between 2 – 5 with those showing size >10 gave a significant p value of 0.009. Between 5 -10 and >10 groups the p value was 0.03.This shows that size also has a significant role in the outcome.

Table 3

Mitosis	Event (total 15)	Mann – Whitney test
<5	4	Bet.<5 and >10
5-10	4	p value -0.046
>10	7	
Size		Bet. 2-5 and >10 -
<2	0	p Value -0.009
2-5	0	
5-10	6	Bet.5-10 and >10,
>10	9	p value -0.03

Kaplan Meier analysis with log rank test used to compare survival of 2 groups, which showed that mitosis and size have significant effect on survival with p value of 0.0099 and 0.0359 respectively. Hence grade is also significant with a p value of 0.0385.

Mean survival period was 5.9 yrs. 2yr disease free survival was -70%.

DISCUSSION

GISTs are the most common mesenchymal tumors of the gastrointestinal tract, yet they continue to pose a challenge with regard to prediction of their behaviour as well as to controlling their spread within the peritoneal cavity. One of the reasons for the difficulty in predicting the clinical outcome for GIST patients has been the lack of consistency in the definition of GIST and in setting up strict criteria for categorization.

We tried to stratify cases according to the different parameters and found that the criteria followed by Fletcher et al hold good for risk categorization.

As well documented, stomach was the most common site of GIST location, followed by small bowel and other sites. Similar results were obtained by Skandalakis JE et al [9] Luigi Boni et al [10] in their study on surgical resection of Gastrointestinal stromal tumours .

There was a female preponderance noted in our study, as against many other studies which showed that male female ratio is equal.

Although they arise over a wide age range, from paediatric to elderly patients, 75% of GISTs occur in individuals over the age of 50[11]. In the present study group, maximum number of patients were in 61-80 age. This is in agreement with Claudia Mucciarini et al'S study on the incidence and clinicopathologic features of GIST [12] and another study by Tadashi Terada [13].

The most common presentation of GIST is GI bleeding. We also found that majority of the patients presented with malena. This supports the observations obtained by Markku Miettinen et al [14].

There are difficulties to classify benign or malignant GIST using the standard criteria commonly used for other tumors and most authors agree that tumors size and the number of mitoses per HPF are the most important factors related to prognosis [13, 15]. These findings allowed Fletcher et al [5], to propose a "risk of aggressive behavior" classification of GIST considering only size and mitotic count per HPF. We have categorized the cases according to the Fletcher et al risk stratification criteria and found that majority of the patients were in the high risk category closely followed by intermediate risk group. The size of tumours ranged from 2cm to 28cms with a mean tumour size of 8.37 cms. Majority of the cases were in the 5 – 10 cms group.

There were no events for cases with size less than 5cms in our study, while the maximum number of events occured in cases with size >10cms . Patients suffering from GISTs , which are less than 5 cm in diameter have a significantly longer survival than patients with bigger tumours. Similarly maximum number of events occurred when the mitosis was >10/50HPF

With these findings this study confirms that size of the tumour and mitosis are highly related to the prognosis. In other words the tumour grade is the most important factor in determining the prognosis. This observation is in agreement with the results obtained by Brennan et al [16]. Luigi Boniet al [17] in their study on surgical resection of Gastrointestinal stromal tumours also have obtained similar results. According to Mack et al [18] and Haque S et al [19], tumour size more than 5 cms is associated with poor prognosis. Similar result was obtained by Franquement D et al [20].Most workers considered unfavourable out come if the number of mitosis is more than 5 per 50 hpf.

On statistical analysis using Mann -Whitney test a significant difference in the occurrence of events was observed between the groups mitosis less than 5/50hpf and more than 10/50 hpf with a p value of 0.046. Therefore our study reveals that the mitosis has significant effect on the prognosis and the survival .

Similarly there was a significant difference in the occurrence of events between the groups showing size between 2- 5cms and more than 5cms with a p value of 0.009 and between the groups showing size between 5 -10cms and >10cms with a significant p value of 0.03.This is in concordance with the study by Luigi Boni et al [17]. So size of the tumour also has got significant effect on the prognosis and survival. In our study no difference in term of survival was observed considering different tumour locations.

According to literature 70% of GISTs are of spindle cell morphological type, 20% of epithelioid type and the remainder have a mixed cellular composition. Epithelioid tumours occur far more commonly in the stomach than in the small bowel. In the present study there were only 4 cases which showed epithelioid cell morphology, 2 from stomach and 2 from small intestine. All were in the high risk category. Due to the low sample size, no statistical correlation was possible with the survival.

By immunohistochemistry, 90% to 95% of GISTs will be diffusely and strongly positive for CD117 (c-Kit), with a cytoplasmic, membranous, or paranuclear "dotlike" distribution pattern [8]. Approximately 80% of CD117 negative GISTs harbour PDGFRA mutations, whereas most of the remaining cases will prove to harbour KIT mutations [21].

The extent and pattern of CD117 immunostaining cannot be used to predict the type of mutation present in any given tumor [22]. According to the consensus approach, CD117 should be performed in every case, as a confirmatory measure, to improve diagnostic standardization and to help determine patient eligibility for the therapeutic drug imatinib mesylate.

As per our study 86% of cases were positive for CD 117. Since the number of cases which were negative for CD117 were less, in those cases correlation with the survival was not possible. The mainstay of treatment for primary GIST is surgical resection, whenever possible. The overall 5 year survival rate for resectable GISTs has been shown to range from 46% to 78.5% [23,24]. However, predicting the recurrence rate of primary resectable GISTs has been very challenging.

Targeted therapy using Imatinib is found to be useful for preoperative debulking and to prevent metastasis and recurrence post operatively. Imatinib has got good oral bioavailability and has been found to dramatically improve the survival of patients with advanced and metastatic GIST [25]. In this study only 5/43 CD 117 positive cases received imatinib due to financial constraints. Since the sample size is very less no correlation is possible with the survival.

CONCLUSION

Prognosis and survival in GIST patients are dependent on pathological parameters - tumor size and mitotic count.

No significant correlation was found between CD117 reactivity/site of origin of tumour with morphology or survival.

We recommend that in all clinically suspected cases panel of IHC for GIST should be done.

Ideally in all CD 117 negative cases immunohistochemistry for DOG1 & mutation analysis should be done.

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