Clinicopathologic Spectrum of Gastrointestinal Stromal Tumours; Six Years Experience at King Hussein Medical Center

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ABSTRACT

Objectives: To study the clinicopathologic features of gastrointestinal stromal tumors (GISTs), to identify the frequency of risk categories and to predict prognostic factors for disease outcome.

Methods: This is a retrospective review of gastrointestinal stromal tumor cases that conducted at department of surgery at King Hussein Medical Center between January 2007 to December 2013. A total of 42 cases of c-KIT (CD117) positive GISTs were included in this study. Clinical data and histopathological parameters were reviewed. Categorization of risk groups was done according to the National Institute of Health.

Results: There were 25 males and 17 females. The mean age of presentation was 56.8 years in males and in 51 years in females. The most common origin of GISTs was stomach in 61.9% followed by small intestine 19%, for colon and rectum 4.7% and 14.4% in others (pancreas, ovaries). Abdominal pain was the most common presentation for 42% of cases studied. 21.4% of cases were presented with distant metastasis. Spindle cell morphology was the commonest histopathological pattern observed in (54.7%). Risk categorization based on tumor size and cell proliferation as estimated by mitosis revealed that 59.5% of patients in our clinical settings belonged to high risk group.

Conclusion: Most of the cases in this group of Jordanian patients belonged to high risk group. Certain clinical and histopathological features including tumor size >10 cm, mitotic rate ≥ 10 /50HPF, tumor necrosis, mucosal ulceration and non-gastric site may be predictors for poor outcome in patients suffering from GISTs.

Keywords: Clinicopathologic, c-KIT, GIST.

JRMS March 2016; 23(1): 11-16 / DOI: 10.12816/0023353

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Manuscript received march 4, 2015. Accepted July 28, 2015.

Introduction

Gastrointestinal Stromal Tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract.[1]But still a relatively rare soft tissue mesenchymal tumours arising in the gastrointestinal tract accounting for less than 1% of all gastrointestinal tumours. [1, 2] GISTs can occur anywhere in the gastrointestinal tract, most commonly in the stomach, with extraintestinal involvement as well.[3]

GISTs are originating from interstitial cells of Cajal. These are group of cells which found to be a pacemaker for regulation of peristalsis, express c-KIT (CD117) and are dependent on stem cell factor that is regulated through KIT kinase.[1]

In the past, smooth muscle tumours of gastrointestinal tract were classified into leiomyoma, leiomyoblastoma and leiomyosarcoma. By the discovery of molecular biology and oncogenic role of KIT protein, the term GISTs describe a specific group of mesenchymal tumours characterized by KIT protein expression and gain of function mutations that lead to ligand-independent KIT receptor activation.[1,5] Furthermore, an alternative pathogenesis found in KIT negative GISTs, which is the presence of Platelet-Derived Growth Factor Receptor Alpha (PDGFRA) gene mutations.[6]These findings have highlighted the role of therapeutic target against KIT and PDGFRA in treatment of these mutations-driven tumours.[7] GISTs constitute a broad clinical spectrum of tumours with various clinical presentations, histologic patterns, risk categories and prognosis. The aim of this retrospective study is to describe the clinicopathologic features, frequency of risk categories and to determine prognostic factors of cases of GISTs that were encountered in King Hussein Medical Center.

Methods

This retrospective study was conducted at King Hussein Medical Center over a Period of 6 years (January 2007- December 2013). A search of our oncosurgery and histopathology departments data-base, revealed 42 cases of c-KIT (CD117) –positive cases of GISTs that were diagnosed and underwent surgical resections. All other lesions that were not gastrointestinal stromal tumors such as lipomas of the gastrointestinal tract were excluded from this study.

GISTs were diagnosed on the basis of light-microscope morphologic analysis of hematoxylin-eosin stained slides for each tumor and immunohistochemical (IHC) staining using the following panel of antibodies: CD117 or c-KIT, CD34, Smooth Muscle Actin (SMA) and S100. In addition, desmin was done in some of the cases. As consensus by National Institute of Health (NIH), all c-KIT–positive mesenchymal tumors were considered as GISTs and were included in the current study.[8]

Clinical data, histopathologic parameters and risk stratification of these patients were reviewed, and follow-up details were obtained wherever available. Data including patient's age at diagnosis, gender, clinical presentation, site of the tumor were collected. The presence of recurrences or metastasis of our cases were also determined and documented.

The following histopathologic parameters were documented: cell morphology (either spindle cell, epitheloid or mixed morphology), tumor size, cell proliferation as estimated by number of mitoses per 50 high-power fields (HPF), presence or absence of tumor necrosis and presence or absence of ulceration of the overlying mucosa.

Regarding tumor aggressiveness estimation, we used the consensus criteria as suggested by the (NIH), which assigned each tumor based on tumor size and number of mitoses into 4 groups: very low, low, intermediate and high risk groups[7] ,as shown in Table I.

Table I: NIH risk categorization and staging system for GISTs

Risk category	NIH staging	Size	Mitotic count
Very low	1	<2 cm	≤5 /50HPF
Low	2	2-5cm	≤ 5 /50HPF
Intermediate	3	<5cm	6-10/50HPF
		5-10 cm	≤ 5 /50HPF
		≥5cm	>5/50HPF
High	4	≥10cm	Any mitotic rate
		Any size	>10/50HPF

Results

Out of total 42 cases of c-KIT (CD117)-positive GISTs, there were 25 males (59.5%) and 17 females (40.5%) with a slight male predominance. The median age of presentation was 56.8 years in males and 51 years in females. In our series, the most common primary site of GISTs was the stomach (26 cases 61.9%), followed by small intestine (8 cases 19%), colon-rectum (4.7%) and others including pancreas and omentum (14.4%). Interestingly, there was one case for young female which found to have a bilateral ovarian involvement by malignant GIST, which found to be metastatic.

The study results showed that the most frequent presenting symptom was abdominal pain (42%), gastrointestinal bleeding which was seen in 28 % of cases studied. Overall, 9 cases (21.4%) metastasized and have a malignant clinical behaviour, 2 of whom presented with distant metastasis to the lymph nodes as shown in Table II. Among our patients, 31 cases (73.8%) underwent surgical resection (total and distal gastrectomy, segmental bowel resection, wedge resection), followed by adjuvant treatment for patients of high and intermediate risk categories, non-gastric GISTs and resectable metastatic disease. while 11 cases (26.2%) were unresectable due to overtly metastatic disease at presentation.

Grossly in resected tumors, the median tumor size was 8.2 cm (ranging from 1.5-19 cm). Of all the studied cases, 26.2% were < 5 cm, 42.8% were between 5-10 cm and 31% were more than 10 cm in greatest dimension. Microscopically, spindle cell morphology was the commonest histological subtype observed in 23 cases (54.8%), followed by mixed epitheloid and spindle cell morphology in 13 cases (30.9%) and 6 cases (14.3%) were of pure epitheloid cell pattern. Our study revealed that 17 cases (40.5%) have tumor necrosis, 14 cases of which also showed high malignant behavior.

Regarding cellular proliferation as estimated by mitotic count, we found that 27 cases (64.3%) had mitotic count less than 10/50 HPF, whereas 15 cases (35.7%) with mitoses equal or more than 10/HPF. Furthermore, mucosal ulceration was noticed in 10 cases (23.8%) of which 90% belonged to high risk group as shown in Table III.

Table II: Clinical characteristics of 42 patients with GISTs

	Number	**%**
Age		
<60	25	59.5
≥60	17	40.5
Gender		
Male	25	59.5
Female	17	40.5
Location	26	61.9
Stomach	8	19
Small bowel	2	4.7
Colon and rectum	6	14.4
Others		
Behaviour	9	21.4
Metastasis	33	78.6
Non-metastasis		
Tumor size	11	26.2
<5 cm	18	42.8
5-10 cm	13	31
>10 cm		

In our series, the c-KIT (CD117) positivity was one of the inclusion criteria. Regarding other immunohistochemical markers: CD34, SMA and S100 were positive in 39 cases (92.8%), 2 cases (4.7%) and 1 case (2.4%) respectively. Only 3 cases were focally immunoreactive for desmin.

According to the most commonly used NIH scheme for risk stratification of GIST tumors based on tumor size and mitotic count, we found that about 25 cases (59.5%) belonged to the high risk group, 21.4% to the low risk category, 14.3% to the very low risk group, while only 4.8% fell into the intermediate risk category as shown in Table IV. Regarding the metastasizing tumors, all the 9 cases were fell exclusively in category 4 of NIH criteria.

Table III: Summary of microscopic features of GISTs patients

		Number	%
Cellular type			
	Spindle	23	54.8
	Epitheloid	6	14.3
	Mixed	13	30.9
Mitotic rate			
	<10/50HPF	27	64.3
	≥10/50HPF	15	35.7
Tumor necrosis			
	Present	17	40.5
	Absent	25	59.5
Mucosal ulceration			
	Present	10	23.8
	Absent	32	77.2

Table IV: NIH risk stratification of GISTs patients

NIH risk category	NIH staging	%
Very low	1	14.3
Low	2	21.4
Intermediate	3	4.8
High	4	59.5

Discussion

GIST is a recently categorized entity within the gastrointestinal mesenchymal tumors after a long period of being neglected. This interest was arising after the discovery of gain of function mutation in the c-KIT tyrosine kinase (CD117) that present in approximately 80- 85% of GIST cases and subsequently, the success of targeted therapy against these tumors.[3,6,9,10] The term GIST was first used in 1983 by Mazur and Clark. In 1998, Hirota reported the presence of mutations in the c-KIT proto-oncogene in GISTs that lead to constitutive activation of KIT receptors.[9,11]

GISTs are relatively rare mesenchymal tumors arising from the gastrointestinal tract. Based on the American Cancer Society, the estimated incidence of GISTs in the United States range from about 4,000 to 5,000 cases annually.[12] Recently in the United Kingdom, the estimated annual incidence range from 1.32-1.50 per 100,000 population equivalent approximately to 800-900 new cases per year.[13]

In population based studies, the median age at time of diagnosis is 66-69 years.[14] In our study, the median age was 56.8 years, which was earlier than most have found in the western populations. This is similar to a recent study done in India by Ravikumar G. in July 2014 which also reported an earlier median age of presentation for GISTs patients.[3] Also, by comparison with the western literature that reported an equal sex predilection in GISTs, our study showed a slight male predominance 59.5%.

GISTs can occur anywhere in the gastrointestinal tract. The most common primary site involved by tumor is stomach (40%-60%) followed by small intestine (30%-40%).[9] This is in agreement with our study results which showed that the majority of cases (61.9%) were seen in stomach. In our study, 19% of GIST cases were found in small bowel. Other less common sites were large bowel and peritoneum.

In our series, as also reported in the Swedish and Italian studies,[5,14] the most common presenting symptoms were abdominal pain and gastrointestinal bleeding. Other studies reported that GISTs can presented with gastrointestinal bleeding, dyspepsia, abdominal mass, easy fatigability or it may be discovered incidentally for other reasons.[5,15] In the present study, 21.4% of our patients developed metastatic disease during the study period. The common sites of metastasis were liver, peritoneum, mesentry and omentum. According to literature, lymph node metastases in GISTs are rare.[1,9] In our study, we reported two cases with distant metastasis to the lymph nodes and found to be from gastric origin.

Regarding the histolopathologic features of GIST cases, our results were consistent with the results of Ravikumar G *et al.*[3] ,Mucciarini C *et al.*[5],Tryggvason G *et al.*[6] demonstrated that spindle cell morphology was the commonest pattern 54.8%, 31% of our cases with tumor size more than 10 cm and 35.7% of GIST cases with mitotic count ≥ 10 /50HPF. Ravikumar G *et al,* showed that 55% of studied cases in India have spindle cell pattern.[3] Furthermore, Mucciarini C *et al,* from Italy reported that those tumors with size more than 10 cm in greatest dimension accounted for 33% of GISTs cases.[5]

Tumor necrosis was a common feature in our seies that present in about 40.5% of our

cases. As shown by our study and most studies, tumor necrosis in GISTs is a feature observed mainly in high risk group. Regarding other pathologic variables like mucosal ulceration in GISTs, a population-based study for GISTs in Iceland in which, Tryggvason G *et al*,[6] reported that 33.3% of tumors had ulceration of the overlying mucosa which was approximately similar to our result. And by correlating those variables with the malignant behavior, we found that 90% of cases with mucosal ulceration fell in the high risk category and showed a malignant behavior.

Immunohistochemically, KIT positivity is considered an important method for distinction of GISTs from other mesenchymal tumors which typically lack KIT positivity.[1,5] And as reported in the literature, 80-85% of GISTs are positive for KIT which makes KIT a sensitive and specific marker for GISTs. A small percentage of GISTs lack KIT marker and these found to be either a wild type or having another mutation like PDGFRA.[1,16] However, it is of great significance to demonstrate the expression of KIT protein since the use of tyrosine kinase inhibitor had improved the survival rate of GIST patients dramatically.[17] Also, according to literature, 60-70% of GISTs are positive for CD34, for SMA 30-40%, 5% for S-100 and 2% for desmin.[8] In our series, KIT (CD117) was present in all cases as it is the inclusion criteria in the present study. The percentage of CD34 positive cases in our study was 92.8% which is much higher and the positivity of SMA is much lower that those reported. Low S-100 and desmin positivity was consistent with the other studies.

Risk categorization was done according to the NIH consensus criteria which based on tumor size and mitotic count; we found that most of our cases belonged to high risk category in about 59.5%. This is similar to Ravikumar G *et al*.[3] although other studies reported a lower incidence of this category. The risk categories is presented based on the location of GISTs as shown in Table V, since the location has an important impact in predicting the malignant behavior of GISTs as adapted by Armed Forced Institute of Pathology (AFIP), we observed that 50% of our gastric GISTs fell in the high risk group in contrast to that reported in western literature where gastric GISTs showed a low malignant behavior.[3,18] On the other hand, we found that 75% of non-gastric GISTs showed a much more malignant behavior similar to most published data.

Limitations of the Study

This study had some limitations probably due to lack of real control group because of the retrospective nature of this study. Furthermore, the absence of strict follow-up program for those patients is the reason behind the lack of statistical analysis and calculation of survival rate in this group of GISTs patients.

Conclusion

In conclusion, this study demonstrated the clinicopathologic characteristics of GIST cases in this group of Jordanian patients where most of GIST cases belonged to high risk category, located in the stomach with an earlier age compared to the western population and slight male predominance. Abdominal pain and gastrointestinal bleeding were the commonest presenting symptoms in our cases; it is noteworthy that GIST patients may have distant lymph node metastasis though it is very rare.

Table V: NIH risk category based on the location of 42 GIST cases with

Site	Total (n=42)	High	Intermediate	Low	Very low
Stomach	26	13	3	8	2
Small intestine	8	6	-	2	-
Large intestine	2	2	-	-	-
Others	6	4	-	2	-

Spindle cell morphology is the commonest pattern. In addition, to c-KIT, CD34 positivity is an important marker for the diagnosis of GISTs. A tumor size >10 cm, mitotic rate ≥ 10 /50HPF, tumor necrosis, mucosal ulceration and non-gastric site were considered indicators for worse outcome and more commonly encountered in high risk group.

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