A Review of Gastrointestinal Stromal Tumours- A Single Centre Experience

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Introduction: Gastrointestinal stromal tumour (GIST) is relatively rare. The clinical behaviour of GIST ranges from benign to frank sarcoma. The diagnosis is established through histopathological examination and immunohistochemistry profile. In Malaysia, the number of publications related to GIST is relatively rare. This study was therefore conducted to examine the demographic, histopathological and immunohistochemical features of GIST cases diagnosed in the Department of Pathology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang from 2009 until 2014. **Methods:** Past histopathological records were reviewed. Demographic and histopathological and immunohistochemical data of patients diagnosed were collected. **Results:** There were 28 cases (14 males and 14 females) diagnosed as GIST. Mean age was 56.4 years, and the majority were above 40 years of age (85.7%). Stomach was the most common location (42.9%), followed by small intestine (28.6%). In 23 cases (82%), the tumours exhibited spindle cell morphology, while epithelioid cell and mixed cell types were seen in 3 cases (11%) and 2 cases (7%), respectively. Five cases were categorised as very low risk to low risk behaviour, while 18 cases were intermediate to high. None of the histological parameters analysed which include tumour morphology, necrosis, haemorrhage, nuclear atypia and mean number of mitoses showed significance difference between the different risk behaviour groups. Positivity with KIT (CD117), considered to be the defining immunohistochemistry feature, was negative in 2 cases. **Conclusion:** Although this study is a retrospective study, the findings contribute to the knowledge on GISTS in Malaysia. Future research related to GISTs in Malaysia should focus on molecular analyses for *KIT* and *PDGFRA* mutations for diagnostic confirmation especially in KIT-negative cases and also for the purpose of therapeutic response correlations.

Keywords: Gastrointestinal stromal tumour, Pathology, Malaysia

INTRODUCTION

Gastrointestinal stromal tumour (GIST) is a relatively rare tumour although it is considered the most common mesenchymal tumour of the gastrointestinal (GI) tract.[1] The condition is seen more commonly in the middle age and elderly and is extremely rare below the age of 20 years.[1] The clinical behaviour ranges from benign to frank sarcoma. GIST occurs predominantly in the stomach (60–70%) and small intestine (20–30%). The large bowel and oesophagus are less frequently involved, and GIST very rarely occurs outside the GI wall. Characteristically, GIST presents as a submucosal neoplasm of the GI wall, which infrequently is associated with mucosal ulcer and rupture of tumour.[2] Patients with tumour growth of less than 2 cm are generally asymptomatic.[3] The clinical features include abdominal pain, nausea, vomiting and abdominal mass.

GIST is believed to arise from interstitial cells of Cajal that function as GI pacemaker and motility regulator.[3] *KIT* and *PDGFRA* genes are thought to play a significant role in the molecular pathogenesis of GIST, and they encode for tyrosine receptor kinases. About 95% of GIST cases harbour mutations in *KIT* or *PDGFRA*, while another 5% are negative for both *KIT* and *PDGFRA* mutations. Others have shown that 10–15% of GISTs exhibit neither *KIT* nor *PDGFRA* mutations.[5] Subsequent studies indicate that *KIT* and *PDGFRA* mutations are mutually exclusive in GISTs.[1, 4-7]

The diagnosis of GIST is basically established through histopathological examination of the tumour tissues and performing relevant immunohistochemistry stains.[1] Morphologically, GISTs can be divided into three principal subtypes: spindle cell morphology (70%) that shows a variety of histological patterns, epithelioid cell morphology (20%) and mixed spindle and epithelioid cell morphology.[4] As for the immunohistochemistry profile, positivity with KIT

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(CD117) is considered the defining feature. Other immunohistochemistry markers include CD34 (70-80%), smooth muscle actin (30-40%) with few (<5%) exhibiting positivity with desmin and S100.[8]

Although immunohistochemistry positivity for KIT is a crucial feature in establishing the diagnosis in addition to the morphological features, it has been shown to be negative in approximately 5% of GIST cases. Tzen and colleagues has suggested that a final diagnosis of KIT-negative GIST would depend on the presence of mutated *KIT* or *PDGFRA* since they have been shown to harbour these mutations.

Mutational analyses for known mutations involving the *KIT* and *PDGFRA* genes are therefore advocated in patients with uncertain diagnosis or atypical morphology or clinical features in whom GIST is a differential diagnosis.[9]

Surgery remains the mainstay of therapy for patients with a local disease.[10,11] Adjuvant therapy with imatinib, a tyrosine kinase inhibitor, has been shown to prolong recurrence-free survival (RFS) following complete tumour resection.[12] In addition to the diagnostic value of mutational analyses of *KIT* and *PDGFRA, KIT and PGFRA* genotypes have been shown to be very closely related with the sensitivity to imatinib and influence the prognosis after imatinib therapy.[2, 13] Recently, regorafenib has been approved as a treatment for patients with a resistant GIST disease.[5,7]

In essence, the standard practice of diagnosing GIST based on the morphological feature and immunohistochemistry profile namely positivity with KIT carries the risk of missing the diagnosis and hence depriving the patients of appropriate and effective treatment.

In Malaysia, the number of publications related to GIST is relatively rare, two of which were by Khoo and colleague and Teong and colleagues.[14,15] Khoo reported on the clinical and immunohistochemical features of 26 cases of GISTs, while Teong performed molecular analyses of 7 cases of confirmed GISTs in addition to immunohistochemical analysis. Others include a case report series by Siam and colleague.[16] Thus, there is a need for more works related to GIST to be undertaken in Malaysia.

In this study, we examined the demographic data and histopathological features of patients diagnosed with GIST from 2009 until 2014 in the Department of Pathology, Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Pahang.

MATERIALS AND METHODS

The histopathological records in the Department of Pathology, HTAA from 2009 to 2014 were all reviewed. Demographic (age, gender and ethnicity), histopathological and immunochemical data of patients diagnosed with GISTs during the period of study were collected.

The histopathological features documented from the reports included the site of tumour, histological type, mitotic count/50 high power fields (HPF), risk behaviour assessment, and presence or absence of necrosis, haemorrhage, nuclear atypia and metastasis. The immunohistochemistry profile of each of the tumours was also noted.

Statistical analysis were performed using Fisher's exact for categorical data whilst nonparametric data were assessed using Wilcoxon signed-rank test available in the statistical programme SPSS version 20.0. A value of $p<0.05$ was considered to be significant.

RESULTS

Gastrointestinal stromal tumours were diagnosed in 28 patients. The diagnosis was made based on the histopathological morphology and immune-histochemistry profile findings. There were 14 males and 14 female patients. The mean age was 56.4 years (range 22–81 years). Majority were above 40 years of age (85.7%). The patients were predominantly Malays (19 patients), and others were 7 Chinese, 1 Indian, and 1 Iraqi patient.

All specimens were resected tumour tissues except in 7, which were tissue biopsy samples. Stomach was the most common location (12 of 28 cases; 42.9%), followed by small intestine (8 of 28 cases; 28.6%). Other sites included anorectal (1 case; 3.6%), omentum (1 case; 3.6%), retroperitoneal (1 case; 3.6%) and 5 (17.9%) cases were reported as abdominal tumour tissue.

The tumours exhibited spindle cell morphology (Fig.1) in 23 cases (82%), while epithelioid cell (Fig.2) and mixed cell types were seen in 3 cases (11%) and 2 cases (7%), respectively.

The epithelioid cell type was only seen in GISTs located in the stomach. Three cases had an evidence of metastasis. Areas of necrosis and haemorrhage were seen in 14 cases (50%) and 2 cases (7%) respectively. Almost half (12 cases; 43%) of the cases exhibited nuclear atypia. The mitotic count ranged from 0–37/50 HPF.

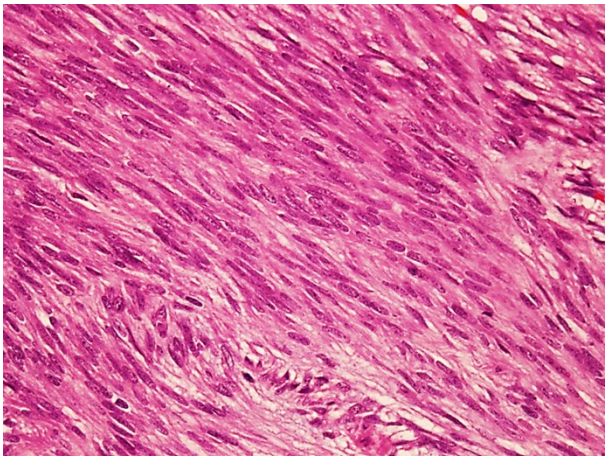

Figure 1. Gastric spindle cell GIST

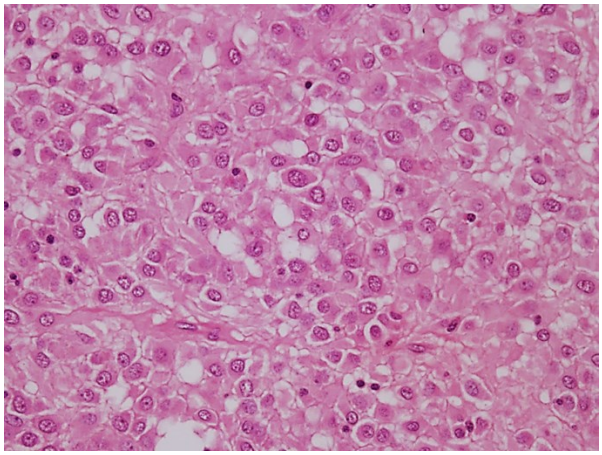

Figure 2. Gastric epithelioid GIST

Based on the GISTs risk behaviour assessment by National Institutes of Health, our series of cases showed 2 (7%) very low risk cases, 3 (11 %) low risk cases, 7 (25%) intermediate risk cases, and 11 (39%) high risk behaviour cases.[17] In 5 cases, the risk behaviour was not assessed as the biopsy samples received were small. The percentage of GIST cases with intermediate to high risk behaviour for tumours located in the stomach verses other sites were 78% (7/9) and 79% (11/14) respectively. Table I shows the demographic data and the features of the tumours according to the risk behaviour.[14] There were no significant difference between the groups for all the parameters analysed.

Table I: Demographic and pathological features of GISTs according to the risk behaviour

	Risk of aggressive behaviour		***P value***
	Very low to low (n=5)	**Intermediate to high (n=18)**	
Sex			
Male	4	7	*P* = 0.155
Female	1	11	
Mean age (years) (SEM)	65 (5.069)	57.8 (3.385)	*P* = 0.315
Site of tumour			
Stomach	2	7	*P* = 1.00
Other sites (small intestine: others)	3 (3:0)	11 (5:6)	
Morphology			
Spindle	3	15	
Epithelioid	1	2	*P* = 0.863
Mixed	1	1	
Necrosis			
Present	2	11	*P* = 0.618
Absent	3	7	
Haemorrhage			
Present	0	2	*P* = 1.00
Absent	5	16	
Mean number of mitosis (no./50 HPF) (SEM)	2 (0.969)	9 (2.491)	*P* = 0.163
Nuclear atypia			
Present	2	10	*P* = 0.640
Absent	3	8	

Notes:

1. *SEM = Standard error of the mean*
2. *In 5 cases, the risk behaviour was not assessed as they were small tissue biopsy samples.*
3. A value of $p<0.05$ was considered to be significant.

Up to 13 types of immunohistochemistry staining were carried out for these cases, but only 3 were consistently performed in all the 28 cases; namely KIT (Fig. 3), CD34 (Fig. 4) and smooth muscle actin.

Another 3 frequently utilised markers were desmin, vimentin, and S100. Table II shows the results of the 6 frequently performed immunohistochemistry study according to the tumour sites.[15]

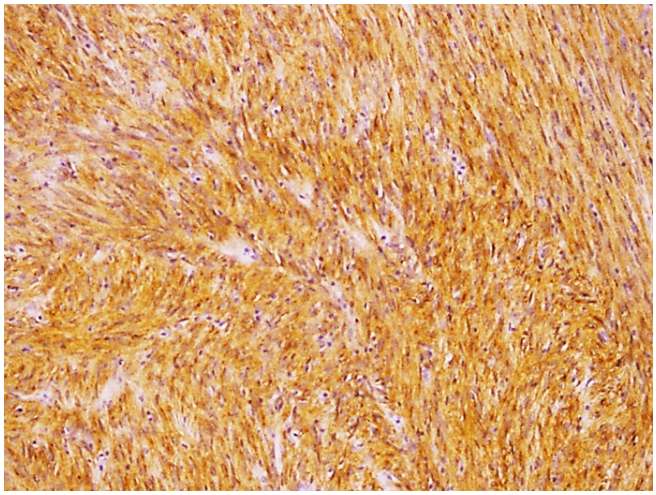

Figure 3. KIT (CD 117)- positive GIST

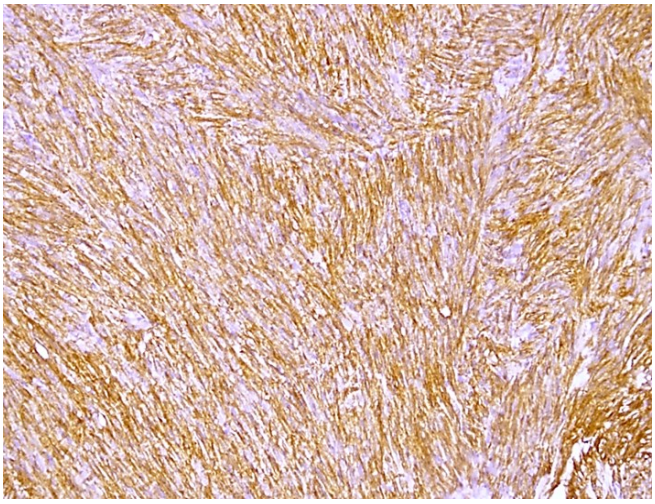

Figure 4. CD 34- positive GIST

There were 2 cases with negative KIT. Both cases showed positivity with CD34. The first case also showed positivity with vimentin and was negative for desmin, smooth muscle actin and S100. The second case was positive for smooth muscle actin and negative for both desmin and S100.

DISCUSSION

There were only 28 cases of GIST in our centre over the 6 years of study period (2009–2014), indicating that this condition is uncommon. Majority of our patients were above 40 years of age. As documented by earlier studies, it is infrequent in patients below 40.[3] The number of male and female patients was approximately equal as noted by others.[14]

Table II: Immunohistochemistry profile according to tumour sites

Immunohis-tochemistry type	Number of positive cases (%)		
	Stomach No. of positivity/ Total no. of test done (%)	**Other sites** No. of positivity/ Total no. of test done (%)	**Total**
KIT (CD117)	11/12 (91.7%)	15/16 (93.8%)	26/28 (92.9%)
CD34	12/12 (100 %)	10/16 (62.5%)	22/28 (78.6%)
Desmin	0/10 (0%)	0/9 (0%)	0/19 (0%)
Smooth muscle actin	2/12 (16.7%)	7/16 (43.8%)	9/28 (32.1%)
Vimentin	6/6 (100%)	7/7 (100%)	13/13 (100%)
S100	2/5 (40%)	6/13 (46.2%)	8/18 (44.4%)

Our study is also in agreement with others in terms of the tumour location where stomach is the most common site followed by the small intestine.[3, 14, 18]

The predominant histological type of GISTs in the 28 cases reviewed was spindle cell type both in the stomach and small intestine. The epithelioid cell pattern was seen only in the stomach. Epithelioid cell pattern is a rare finding in the small intestine, and if present, it is said to be associated with malignancy.[18] Clinicopathologic features of some intra-abdominal tumours are known to simulate GISTS and these include smooth muscle tumours such as intramural leiomyoma, leiomyoma of muscularis mucosae, retroperitoneal and peri-intestinal leiomyoma.

Histologically they however resemble smooth muscle and are smooth muscle actin- and desmin positive with KIT and CD 34-negative. Leiomyosarcomas are rare occurrences in the gastrointestinal tract and immunohistochemically are typically positive for smooth muscle actin and desmin. Spurious KIT-positivity, seen with some polyclonal KIT antibodies, has been a source of confusion leading to probable false-positive results in leiomyosarcomas.[19,20]

Gastrointestinal schwannomas are another important differential diagnosis and usually occur in the stomach. They are composed of bundles of spindle cells with focal atypia, often arranged in a microtrabaecular growth pattern, and are associated with a dense peripheral lymphoid infiltrate. They stain strongly for S100 protein, and the glial

fibrillary acidic protein and are negative for KIT. As for the epithelioid variant of gastrointestinal schwannoma, it occurs exclusively as polypoid lesions in the colon. Other differential diagnosis include fibromatoses, inflammatory fibroid polyps, inflammatory myofibroblastic tumours, desmoid tumour and other types of sarcoma. GIST with epithelioid morphology can also be mistaken for carcinoma, melanoma or other round cell sarcoma.[19,21]

Although GISTs biological behaviour ranges from benign to frank malignancy, it is difficult to confidently differentiate between benign and malignant lesions based solely on histological findings. Hence, Fletcher and colleagues from the National Health Institute have recommended the use of risk assessment.[17] Their risk assessment is defined by a combination of tumour size and mitotic counts. We utilised the same risk assessment to categorise the tumour behaviour. In this study, the percentage of GISTs with intermediate to high risk behaviour was approximately similar for both stomach and other sites. It is worth noting that all the 6 cases arising from locations other than the stomach and small intestine exhibited intermediate to high risk behaviour.

None of the histological parameters analysed which include tumour morphology, necrosis, haemorrhage, nuclear atypia and mean number of mitoses showed significant difference between the different risk behaviour groups. In addition to tumour size and mitotic activity which are generally accepted as independent prognostic factors, other features have been extensively studied in order to predict the potential biological behaviour of these tumours.

Amongst the features examined include necrosis, haemorrhage, cellularity, nuclear atypia, histological type and pattern, immunohistochemical profile, and proliferating index, and no consensus was however being established.[3,22,23] Fujimoto and colleagues showed that male sex, tumour size of 10 cm or more, and cell proliferation as estimated by mitotic index are independent indicators of a poor prognosis in primary gastric GIST while Wang and colleagues revealed that Ki-67 index and cellularity should be used as predictors for the malignant potential of GIST.[22, 23]

KIT positivity, which is considered to be a defining immunohistochemistry feature of GIST, was found to be negative in 2 patients. A minor proportion of GISTs exhibit negative expression with KIT.[18] Most of the KIT-negative cases occur in the stomach and of epithelioid morphology and exhibit *PDGFRA* gene mutation.[2] In our study, both cases had spindle cell morphology. In one of the two cases, the tumour was in the stomach, and the other was a retroperitoneal tumour.

CONLUSION

Although this study is a retrospective study, the findings contribute to the body of knowledge related to GIST in Malaysia as information on GISTS is still lacking in Malaysia. Future research related to GISTs should focus on molecular analyses for *KIT* and *PDGFRA* mutations as there is growing evidence of phenotype-genotype and genotype-therapeutic correlations in GISTs.[2]

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