Gastrointestinal stromal tumours: a clinico-pathological study

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ABSTRACT

Introduction: Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Histologically, it can be categorised into spindle cell, epithelioid cell or mixed spindle and epithelioid types. This study assesses the clinico-pathological features of GISTs encountered in Brunei Darussalam. **Material and Methods:** The Department of Pathology registry from 1999 to 2009 was reviewed for cases of GISTs. **Results:** There were 594 cases of gastrointestinal malignancies encountered during this period and GISTs accounted for 4.5% (n=27). Men and women were equally affected and the ethnic breakdown consisted of Malay (70.4%), Chinese (14.8%), Filipino (11%) and other races (3.7%). The clinical presentations were abdominal pain/mass (51%), upper gastrointestinal bleeds/melaena (30%), dyspepsia/vomiting (11%) and anaemia (4%). One patient (4%) had GISTs as an incidental finding on imaging study for other indication. The tumours were located in the stomach (59.3%), small intestine (33.3%) and one case each involving the colon/rectum (3.7%) and omentum (3.7%). The majority occurred between the fourth and seventh decade (range 16 to 83 years). Histologically, 66.7% were categorised as spindle cell, 18.5% epithelioid and 14.8% mixed cell types. On immunohistochemistry studies, 59% were positive for C-KIT (CD117), 66% for CD34, 48% co-expressed CD117 and CD34, 70% for Smooth Muscle Actin (SMA), 41% for S100 protein, 81% for Vimentin and 26% for Desmin. Based on tumour size and mitotic count, 3.7% was categorised as very low, 7.4% as low, 11% as intermediate and 77.8% high risk respectively. **Conclusion:** GISTs accounted for 4.5% of all GI malignancies and more than 70% were categorised as high risk. Accurate diagnosis is important as complete surgical resection is currently the first-line of therapy for resectable tumours. For unresectable disease targeted therapy with tyrosine kinase inhibitors is an option.

Keywords: Immunohistochemistry, interstitial cells of Cajal, leiomyosarcoma, proto-oncogene protein C-KIT

INTRODUCTION

Gastrointestinal stromal tumours (GISTs) are now recognised as a distinct entity and are thought to arise from the interstitial cells of Cajal (ICC) or their stem cell-like precursors located around the myenteric nerve plexus of the muscularis propria. [1] In the past, GISTs were regarded as tumours of smooth muscle cells such as leiomyomas, leiomyoblastomas

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and leiomyosarcomas. In 1983, Mazur and Clark were not able to demonstrate any immunohistochemical and ultra-structural evidence of smooth muscle or Schwann cell differentiation in most gastric mesenchymal tumours (GISTs). [2] The definite cellular origin or pathogenesis of GISTs was not determined until 1998 when Hirota *et al*. discovered that there was mutation of the C-KIT proto-oncogene and type III tyrosine kinase receptor protein KIT (CD117) was highly expressed in GISTs. They also showed that majority of GISTs were positive for KIT (CD117) by immunohistochemistry. [1]

To date, there is no published data available on GISTs in our local setting. This study assesses the clinico-pathological profiles of GISTs encountered between 1999 and 2009.

MATERIAL AND METHODS

GISTs reported in the Department of Pathology, Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital during period from 1999 to 2009 were retrieved with the aid of Laboratory Information Service (LIS) utilising Systematised Nomenclature of Medicine (SNOMED) code for topography for GI tract and morphology for leiomyoma, epithelioid leiomyoma and leiomyosarcoma. Patients' case notes were retrieved from the Department of Medical Records, RIPAS Hospital and were reviewed in detail.

Diagnosis of GIST was established based on the distinctive histomorphologic features of spindle cell, epithelioid cell and mixed spindle cell and epithelioid cell patterns and supported by CD117 immunoreactivity as part of an immunohistochemical panel including CD34, SMA, S100 protein and Desmin as described. [8, 14] CD117 (KIT), a tyrosine kinase growth factor receptor protein structurally related to platelet-derived growth factor is expressed by ICC and tumour arising from these cells. CD117 is regarded as immunohistochemical marker for GISTs. CD34, a haematopoietic progenitor cell antigen is also expressed in subset of ICC. GISTs may also show immunopositivity for smooth muscle actin (SMA), S-100 protein (utilised as neural cell marker) and uncommonly for Desmin (a marker for tumours of smooth muscle or skeletal muscle origin). None of these latter antigens are specific markers for GISTs.

The prediction for the behaviour was based on the diagnosis and morphologic prognostication consensus developed at the GIST workshop convened by National Institute of Health (NIH) in April 2001 in Bethesda, Maryland, United States (Table 1). [14]

Table 1: The NIH risk catergorisation of GISTs. [14]

	Size (largest dimension)	**Mitotic Count**
Very low risk	<2 cm	<5 / 50 HPF
Low risk	2-5 cm	< 5 / 50 HPF
Intermediate risk	<5 cm	6-10 / 50 HPF
	5-10 cm	< 5 / 50 HPF
High risk	>5 cm	> 5 / 50 HPF
	>10 cm	any mitotic rate
	Any size	> 10/50 HPF

RESULTS

The total number of GI malignancies encountered during the study period was 594 and GISTs accounted for 4.5% (n=27). The overall incidence of GISTs in our local setting during the study period was 1.7/100,000 per year.

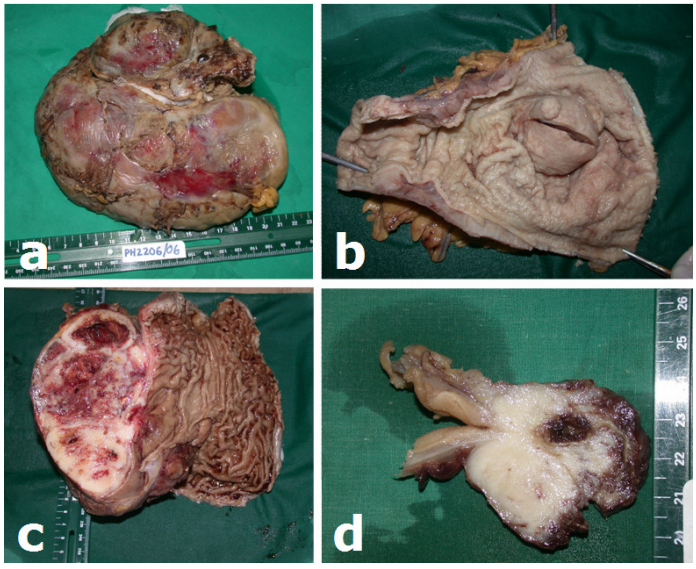
The distribution consisted of gastric 59.3% (n=16), small intestine 33.3% (n=9) and one case each for colon/rectum (3.7%) and omentum (3.7%).

Majority of the tumours occurred in fourth to seventh decade's group with a range of 16 to 83 years. Males and females were almost equally affected (14 males: 13 females). The ethnic breakdown was 19 Malay (70.4%); four Chinese (14.8%), three Filipinos (11%) and other races had one case (3.7%).

The common presenting signs and symptoms were pain and or mass in abdomen 51% (n=14), upper GI bleeds and or melaena 30% (n=8), dyspepsia/vomiting 11% (n=3), anaemia 4% (n=1) and incidental finding on imaging studies 4% (n=1).

Grossly, tumour size varied from microscopic to large with the largest measuring 28 cm in diameter. The only case of omental GIST measured 17 cm in greatest diameter. The microscopic to small GISTs were located in wall of the GI tract and some were found to be protruding into the lumen as polypoid mass covered by intact mucosa. Large tumours showed exophytic growth pattern as nodular masses over the serosal surface.

The cut surface generally showed grayish white fleshy appearance. The large tumours also exhibited areas of haemorrhage and cystic change (Figures 1a-d). Histologically, 66.7% (n=18) cases were of spindle cell type, 18.5% (n=5) were of epithelioid type and 14.8% (n=4) cases were of mixed cellular type (Figures 2a-d). The spindle cell type was composed of monomorphic spindle cells arranged into interlacing fascicles, whorls and storiform pattern. The nuclei were relatively uniform, round to elongated with fine granular to vesicular chromatin and inconspicuous nucleoli. The cytoplasm was pale



Figs 1: a) Large resected exophytic gastric GIST b) Gastric GIST protruding into the lumen as a polypoidal mass, c) Cut section of gastric exophytic GIST showing multiple haemorrhagic foci, and d) Cut section of ileal GIST showing whitish fleshy appearance with a single haemorrhagic focus.

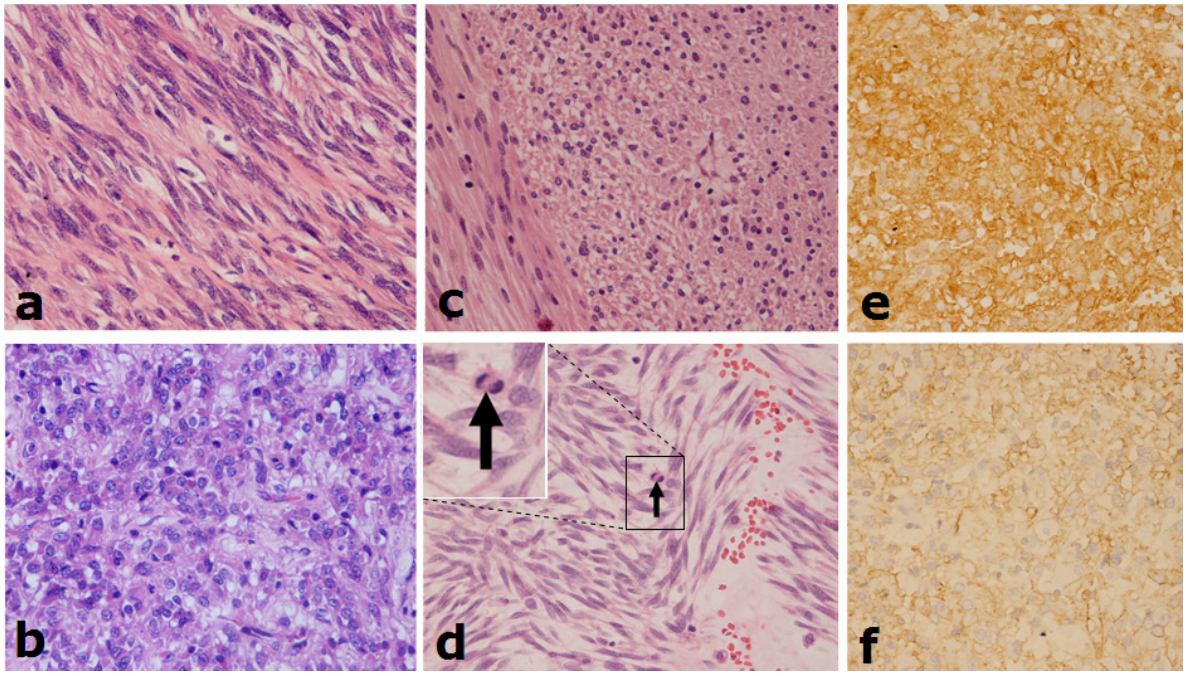
pink and fibrillary in appearance with indistinct cell margins. Prominent peri-nuclear cytoplasmic vacuolation and nuclear palisading were also seen. The epithelioid cell type was composed mainly of cohesive nests and diffuse masses of round to polygonal cells. The nuclei were rounded, vesicular and contained small nucleoli. The cytoplasm was quite abundant and amphophilic appearance. The stroma in both types was scanty to moderate with variable hyalinisation, myxoid and microcystic changes. The mixed cell type was characterised by presence of variable component of spindle and epithelioid cells with abrupt transition between two cell components. Mitotic count was variable (occasional to more than 50/50 high power field [hpf]) depending on the biologic behaviour of tumours (Figures 2a-d).

Immunohistochemistry studies showed that 59% (n=16) were positive for C-KIT (CD117), 66% (n=18) for CD34, 48% (n =13) co-expressed CD117 and CD34, 70% (n =19) for SMA, 41% (n=11) for S100 protein, 81% (n=22) for Vimentin and 26% (n=7) for Desmin (Figures 2e and 2f).

Based on tumour size and mitotic count, 3.7% (n=1) was categorised as very low risk, 7.4% (n=2) low risk, 11% (n=3) intermediate risk and 77.8% (n=21) high risk respectively.

DISCUSSION

GIST is a term applied to KIT (CD117) positive and mutually exclusive KIT or PDGFRA mutation-driven, mesenchymal tumours that can occur anywhere along the GI tract. [3, 7, 8] GISTs are uncommon and constitute approximately two percent of all GI neoplasms. However, they are the most common mesenchy–



Figs 2: a) Gastric GISR of spindle cell type (H & E, x40), b) Gastric GIST of epitheloid cell type (H & E, x40), c) Ileal GIST of mixed cell type, d) Gastric GIST of spindle cell type showing a single mitotic figure (H & E x40), insert showing magnified image, e) Gastric GIST tumour cells showing dark brown membranous and cytoplasmic positive immuno-reaction for CD117 (Immunoperoxidase x40), and f) Gastric GIST tumour cells showing dark brown membranous positive immuno-reaction for CD34 (Immunoperoxidase stain, x40).

mal tumour of GI tract. [3]

In our study, GISTs accounted for 4.5% of all GI tract malignancies (27 out of 594 cases of GI malignancies) with an annual incidence of 1.7 per 100,000 (17 per million). This is comparable to the annual re–ported rates in other countries; 10-14.5/million per year in European countries and 6.8/million per year in the United States (age-adjusted) [9], 13.74/million per year in Taiwan [10] and 16-22/million per year in Korea. [11]

The demographic and clinicopathological profiles of our patients are similar to published series. [3, 7, 8, 12, 13] It has been reported that 75% of GISTs have a predilection to occur in adults over 50 years of age with median age of 58 years. [12] GISTs rarely occur in children. [8] Both males and females were equally affected. [8] In our study, majority of patients were in the four to seventh decade age group with the youngest patient aged 16 years old. There was no significant gender predilection (14 males: 13 females).

The common presenting symptoms include early satiety, bloating, GI bleeding manifesting as haematemesis or melaena, sign and symptoms of iron deficiency anaemia following chronic bleeding. Large gastric tumours may present with GI bleeding in 55% of cases, upper abdominal pain or discomfort or palpable mass in 17%. GISTs arising from the small bowel may also present with GI bleeding, intestinal obstruction or palpable mass. [3] The clinical presentations in our study were pain and or mass in the abdomen 51%, upper GI bleeds and or melaena 30%, dyspepsia and vomiting 11% and anaemia 4%. In one patient the GIST was an incidental finding while undergoing imaging for other reason.

GISTs can occur anywhere along the GI tract. The stomach (39-60%) and the small intestine (30-42%) are the most commonly affected sites. The rest of the bowel is infrequently affected; oesophagus (<5%), colon, rectum and appendix (5-11%). [13] GISTs can also occur in the gallbladder and pancreas. Approximately 10% of GISTs arise outside the GI tract occurring within mesentery, omentum, retroperitoneum or in the pelvis and are referred to as extra-GI GISTs. [12] In our group of patients, 59.3% were located in stomach, 33.3% in small intestine and 3.7% in colon/rectum. One case (3.7%) was extra-GI occurring in the omentum. Again, our findings were consistent to what has been reported earlier.

Microscopically, GISTs may display one of the three characteristic histolomorphologic features; spindle cell (70%), epithelioid (20%) or mixed cellular (10%) pattern. [14] In our study, 66.7% of cases were of spindle cell type, 18.5 % were of epithelioid type and 14.8% cases were of mixed cellular type. These findings were also comparable to other reported series. [8, 13, 14]

Reported studies on immunohistrochemistry have shown that around 95% of GISTs are positive for CD117 (KIT) and 60-70% positive for CD34. Approximately 30-40% also shows immunopositivity for SMA and 5% are positive for S-100 protein. Desmin positivity is quite rare. Approximately 5% of GISTs are immunonegative for CD117. [3, 7, 14] Utilisation of DOG1 (Discovered on GIST1), PKCθ (protein kinase C theta) and Nestin im-

munohistochemical studies or mutational analysis may be helpful in the diagnosis of CD117 negative GISTs. [3-6] Cases with CD117 immunopositivity was less in our study as compared to other published studies. [3, 7, 8, 12, 13] The exact reason is unknown but small sample size may be a factor. Immuno–histochemical studies for DOG1, PKCθ, Nestin as well as mutational analysis for C-KIT and PDGFRA were not done in our study.

KIT activating mutation is identified in 85-95% of GISTs. Five to 10% of GISTs result from activating mutation of the closely related tyrosine kinase, platelet derived growth factor receptor alpha (PDGFRA). [3] Approximately 5% of GISTs do not have KIT or PDGFRA mutation and are designated as wild-type GISTs. [3] It has been reported that less than five percent of GISTs are associated with neurofibromatosis type 1 (NF1), Carney triad and familial GIST syndrome. [7] These associations were not identified in our cases.

GISTs have a variable spectrum of biologic behaviour from small incidentally detected low grade to high risk or overtly malignant tumours; the latter constitutes 20-45% of all GISTs. [13] Various criteria including tumour size, mitotic count, cellularity, immunohistoschemical markers of proliferation (Ki-67, PCNA), DNA flow cytometry, mucosal involvement with ulceration have been proposed to distinguish between benign and malignant GISTs. It is generally regarded that all GISTs are potentially malignant and tumour size and mitotic count are the most important prognostic factors. [14] (*Refer to supplementary text for the AFIP classification and AJCC staging of GISTs*) In our study, the majority of the patients were categorised as high risk (77.8%) compared to those reported by Joensuu *et al* (20-45%). Eleven percent of our patients were categorised as intermediate risk and only one patient (3.7%) was categorised as very low risk.

In conclusion, GISTs accounted for 4.5% of all GI malignancies occurring almost equally in men and women. More than 70% were categorised as high risk. Recognition and correct diagnosis of these tumours is important as complete surgical resection is currently the first-line of therapy for patients with resectable tumours. Locally unresectable, recurrent or metastatic tumours respond generally well to targeted therapy with tyrosine kinase inhibitor imatinib mesylate (Gleevec/Glivec). [15] GISTs in Brunei Darussalam essentially shows similar clinicopathological characteristics to what have been reported.

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World AIDS Day (1st December 2011)

	Theme
1988	**Communication**
1989	**Youth**
1990	**Women and AIDS**
1991	**Sharing the Challenge**
1992	**Community Commitment**
1993	**Act**
1994	**AIDS and the Family**
1995	**Shared Rights, Shared Responsibilities**
1996	**One World. One Hope**
1997	**Children Living in a World with AIDS**
1998	**Force for Change: World AIDS Campaign with Young People**
1999	**Listen, Learn, Live: World AIDS Campaign with Children & Young people**
2000	**AIDS; Men Make a Difference**
2001	**I care. Do you?**
2002	**Stigma and Discrimination**
2003	**Stigma and Discrimination**
2004	**Women, Girls, HIV and AIDS**
2005	**Stop AIDS. Keep the Promise**
2006	**Stop AIDS. Keep the Promise – Accountability**
2007	**Stop AIDS. Keep the Promise – Leadership**
2008	**Stop AIDS. Keep the Promise – Lead – Empower – Deliver**
2009	**Universal Access and Human Rights**
2010	**Universal Access and Human Rights**
2011	**Getting to Zero** *(3 targets: Zero new HIV infections. Zero discrimination. Zero AIDS-related deaths)*