Clinical research

Clinicopathologic and immunohistochemical features of gastrointestinal stromal tumors: a single-center experience

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Abstract

Introduction: Here we present our 10-year experience regarding gastrointestinal stromal tumors (GISTs) in terms of clinicopathologic features and immunohistochemical staining patterns.
Material and methods: In this single-center retrospective study, during 2008–2018, data of 26 patients with histologically confirmed diagnoses of GISTs were collected. All patients included in the study underwent surgical resection. The Mann-Whitney U test was used for continuous variables.
Results: The mean age of the patients was 60.7 ±10.4 (35–79) years. The most common GIST location was the stomach (88.5%). The mean tumor size was 5.8 cm (1–13 cm) and the most common histologic type of GIST was spindle cell (61.5%). CD 117(c-kit) was positive in 96% of GIST cases, while CD34 was positive in 84.6%, discovered on GIST-1(DOG1) in 46.2%, smooth muscle actin (SMA) in 26.9%, S100 in 19.2%, and desmin in 7.7%. In one CD117 negative patient, DOG1 was positive. Four patients had metastases (15.4%). The mean follow-up time was 56.5 ±36.2 month. The length of hospital stay was significantly longer in patients who had small intestinal GIST (p = 0.010). In immunohistochemical staining, SMA was significantly more common among spindle cell type (p = 0.032).
Conclusions: GISTs are very rare tumors of the gastrointestinal tract, but the accurate diagnosis with immunohistochemical staining is vital for the treatment. So, large scale, prospective and randomized multicenter trials are needed to reduce the misdiagnosis rate of GISTs.

Key words: immunohistochemical staining, gastrointestinal stromal tumors, metastases.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in the digestive tract [1]. They are considered to originate from the interstitial cells of Cajal, but the exact cell(s) of origin for GISTs is unknown [2, 3]. Most GISTs, nearly 85–90%, have c-KIT (CD117) or platelet-derived growth factor receptor α (PDGFRA) mutations. KIT and PDGFRA are tyrosine kinase receptors for stem cell factor and platelet-derived growth factor α respectively. The KIT-negative GISTs are usually positive for DOG1, a calcium activated chloride channel protein also expressed in Cajal cells [4].

The most common organ sites are stomach (50–60%), small intestine (20–30%), colon and rectum (10%) [5]. The liver and the peritoneal cavity are the primary sites of metastasis [6]. GISTs have up to 30% of malignancy potential. They are classified as "very low, low, intermediate or high" to determine the risk of their malignancy [7]. Miettinen demonstrated that the metastatic risk of GISTs increases with the tumor size regardless of the mitotic count [8]. Complete surgical resection with protecting the capsule is the mainstay treatment of GISTs [9].

Histologic features of GISTs are spindled, epithelioid or mixed (spindled and epithelioid) type. The most common histologic type is spindle cell [10]. The histopathologic features of GISTs in resection material are crucial in postoperative management, treatment and determining prognosis of the patients.

This paper provides an overview of the clinicopathologic and immunohistochemical features of GISTs.

Material and methods

All patients diagnosed with GIST in a gastrointestinal surgery clinic, between 2008 and 2018, were retrospectively evaluated. The study protocol was approved by the Ethics Committee of Teaching and Research Hospital (number 2019.4/13-190) and the study was conducted in accordance with the principles of the Declaration of Helsinki (revised in 2013). Demographic data such as age, gender and body mass index (BMI) were recorded. Operating time, length of hospital stay, follow-up time and survival rate were also collected. On the other hand, size and the type of the tumor, metastases rate, predominant cell type, Ki67 proliferation index, number of mitoses/50 high power fields (HPF), the presence of necrosis and hemorrhage were also evaluated.

The risk stratification of patients was evaluated according to the Armed Forces Institute of Pathology (AFIP) classification (Miettinen and Lasota criteria). Accordingly, tumors were classified as very low-risk, low-risk, intermediate risk or high-risk, based on tumor localization (stomach, ileum, rectum), mitotic rate (≤ 5 /50 HPF or > 5/50 HPF) and tumor size (≤ 2 cm, > 2 – ≤ 5 cm, > 5 – ≤ 10 cm and > 10 cm) [11].

Immunohistochemical reactivity to the following antibodies was noted: CD117, CD34, SMA, S-100, Desmin, and DOG1. Unfortunately, we could not investigate PDGFRA mutation. The criteria for the diagnosis of GIST was based on hematoxylin and eosin (H&E) analysis and an immunohistochemistry panel including CD117, CD34, DOG1, SMA, S-100 protein, desmin and Ki67, and was standardized by the pathology department.

Statistical analysis

To summarize the data obtained from the study the results were presented as mean ± standard deviation or median and range. Categorical variables were summarized as number and percentage. Normality checks of the numerical data were performed by the Kolmogorov-Smirnov test. Fisher's exact was used to compare categorical variables. The Mann-Whitney *U* test was used when the continuous variables were not normally distributed. Jamovi and JASP software were used for the statistical analyses and $p < 0.05$ was accepted as statistically significant.

Results

The patient group included 19 (73.1%) male and 7 (26.9%) female patients. The male-to-female ratio was approximately 3 : 1. Age of the patients ranged from 35 to 79 years, mean age of 60.7 ±10.4 years. The mean BMI of the patients was 28.5 ±3.5 kg/m^2 (22–36 kg/m^2). The mean operation time was 168.8 min (60–500 min). Of the 25 patients who underwent curative resection, one patient had severe peritoneal carcinomatosis, so debulking surgery was performed.

The most common GIST location was the stomach (88.5%), followed by the small intestine. The mean tumor size was 5.8 cm (1–13 cm). Moreover, the most common histologic type of GIST was spindle type (61.5%). Table I shows the demographic and pathological characteristics of the patients.

According to the AFIP classification, the majority of the patients were in the low risk category (34.6%). 8 (30.8%) patients were in the high risk, 5 (19.2%) in the very low risk and 4 (15.4%) in the intermediate risk category. The majority of the cases showed mitotic activity of equal to or less than < 5/50 HPF as a whole (mean 3.0). In addition, the mean Ki 67 proliferation index was 3.0.

CD 117 (c-kit) was positive in 96.2% of GIST cases, while CD34 was positive in 84.6%, DOG1 in 46.2%, smooth muscle actin (SMA) in 26.9%, S100 in 19.2 %, and desmin in 7.7%. In two CD117 negative patients, DOG1 was positive. Four (15.4%) patients had metastases. The mean follow-up duration was 56.5 ±36.2 months.

There was no difference in terms of demographic and pathologic features between the gastric and the small intestinal GISTs. Only the length of hospital stay was significantly longer in patients who had small intestinal GIST ($p = 0.010$) (Table II).

The rates of metastasis and survival were comparable in both groups. In general, the two groups did not show a significant difference regarding immunohistochemical staining and expression

Table I. Demographic and pathological characteristics of patients with gastrointestinal stromal tumors

Parameter	Results
Gender:	
Male	19 (73.1)
Female	7 (26.9)
Age	60.7 ±10.4 60.0 (35.0–79.0)
BMI	28.5 ±3.5 30.0 (22.0–36.0)
Tumor site (%):	
Stomach	23 (88.5)
Small intestine	3 (11.5)
Operation time [min]	168.8 (85.8)
Tumor size	5.8 (3.2)
Histologic type:	
Spindle	16 (61.5)
Mixed	8 (30.8)
Epithelioid	2 (7.7)
SMA	7 (26.9)
DOG1	12 (46.2)
S100	5 (19.2)
Desmin	2 (7.7)
Ki67	3.0 (1.0–30.0)
Cd34	22 (84.6)
Cd117	25 (96.2)
Mitotic activity/50HPF	3.0 (1.0–47.0)
Risk:	
Very low risk	5 (19.2)
Low risk	9 (34.6)
Intermediate risk	4 (15.4)
High risk	8 (30.8)
Necrosis	9 (34.6)
Hemorrhage	17 (65.4)
Metastasis	4 (15.4)
Complication	5 (19.2)
Length of hospital stay	7.0 (4.0–15.0)
Survival:	
Alive	23 (88.5)
Mortality	3 (11.5)
Follow-up [months]	56.5 ±36.2

Descriptive statistics are given as mean ± SD and number (%).

patterns except that staining with SMA was significantly more common among spindle cells (p = 0.032) (Table III).

Discussion

GISTs are known as mesenchymal tumors which are reported to be rare because they are generally misdiagnosed.

In this study, in 26 patients treated at the Gastrointestinal Surgery clinic based on positive expression of CD117 antigen, diagnosis of GIST was confirmed in 25 (96.2%) patients. As it showed, the result of KIT expression was not sensitive enough for all patients. A recent study on the GIST genetic cross section illustrates that mutation of the proto-oncogene c-KIT, besides mutation in the tyrosine kinase KIT gene, is also displayed by changes in PDGFRA [12].

Diagnosis of GIST should be based on immunohistochemically positive CD117 or DOG1, as required by standards [13, 14]. Recent studies have shown that CD117 and DOG1 positivity rates are similar (84–95%) [15]. In this study, DOG1 was positively expressed in the one CD117 negative case. On the other hand, Kiśluk *et al.* found a significant difference between DOG1 tumor histological types [16].

In our study, similarly with the literature, the most common location of the GIST was the stomach [17]. GISTs are usually seen in older adults of age greater than 50 years [18]. In this study, the mean age was 60 years. Tumor diameter and mitotic rate are reliable markers accepted by many authors to determine prognosis [19–22]. In the present study, the mean tumor size was 5.8 cm. Miettinen *et al.* reported that tumors larger than 10 cm had increased risk of metastases [8]. For another prognostic factor, Ki67 proliferation index, except for small bowel GISTs, a value more than 10% has been shown to be associated with poor prognosis [23, 24]. Our cases were localized predominantly in the stomach and also had a low proliferation index.

Spindle cell type is the most common histologic type in the literature [25, 26]. As in the literature, the most common histologic type of GIST was spindle cell type (16 cases, 61.5%), followed by mixed type (8, 30.8%) and epithelioid type (2, 7.7%) in our study.

In the light of the literature, GIST may express SMA (30–40%), S-100 (5–10%) and desmin (2–13.4%), with changing degrees in relation with prognosis [24]. In our study, the positive expression rates were 26.9% for SMA, 19.2% for S100 and 7.7% for desmin and our results were similar to the literature. Several studies have shown that desmin and SMA are positively associated with a good prognosis [8, 19, 24, 25].

Table II. Comparison of demographic and pathologic characteristics of GISTs of the stomach and small intestine

Parameter	Location of the tumor		*P*-value
	Stomach (*n* = 23)	Small intestine (*n* = 3)	
Gender:			0.540
Male	16 (69.6)	3 (100.0)	
Female	7 (30.4)	0 (0.0)	
Age, median (range)	60.0 (35.0–79.0)	66.0 (54.0–72.0)	0.469
Operation time, median (range)	150.0 (60.0–500.0)	120.0 (100.0–190.0)	0.313
Tumor size, median (range)	5.0 (1.0–13.0)	9.0 (5.0–13.0)	0.135
Histologic type:			0.415
Spindle	15 (65.2)	1 (33.3)	
Mixed	6 (26.1)	2 (66.7)	
Epithelioid	2 (8.7)	0 (0.0)	
Ki67, median (range)	2.0 (1.0–20.0)	6.0 (5.0–30.0)	0.067
Mitosis rate, median (range)	3.0 (1.0–47.0)	11.0 (3.0–30.0)	0.168
Risk:			0.234
Very low risk	5 (21.7)	0 (0.0)	
Low risk	9 (39.1)	0 (0.0)	
Intermediate risk	3 (13.0)	1 (33.3)	
High risk	6 (26.1)	2 (66.7)	
Necrosis	8 (34.8)	1 (33.3)	1.000
Hemorrhage	14 (60.9)	3 (100.0)	0.529
Metastasis	3 (13.0)	1 (33.3)	0.408
Length of hospital stay, median (range)	7.0 (4.0–10.0)	11.0 (9.0–15.0)	**0.010**
Follow-up time, median (range)	66.0 (8.0–120.0)	36.0 (8.0–40.0)	0.198

Descriptive statistics for variables that did not have normal distribution are given as median (range) and Mann-Whitney U test was used for comparison. Descriptive statistics for categorical variables are given as number (%) and Fisher's exact test was used for comparison. P-values in ***bold*** *were accepted to be statistically significant (p < 0.05).*

A statistically significant finding was seen in SMA positivity among spindle cells (p = 0.032). In contrast, Hashimi *et al.* found that most of the spindle cell variety was negative for SMA (83.3%) and positive for CD34 (73.5%) [27].

There was no difference in terms of demographic and pathologic features between the gastric and the small intestinal GISTs. Only the length of hospital stay was significantly longer in patients who had small intestinal GISTs (p = 0.010). The length of hospital stay was longer because of surgical site infections.

In some Asian studies, the majority of the GISTs generally were low grade tumors [28] and most showed high risk characteristics followed by intermediate and low risk [18, 29, 30]. In this study, the majority of the patients were in the low risk category (34.6%). Eight (30.8%) patients were in the high risk, 5 (19.2%) in the very low risk and 4 (15.4%) in the intermediate risk category.

There are some limitations of this study. First of all, this was a single-center and retrospective study. Secondly, the study had a small sample size. And unfortunately, we could not investigate PDFGRA mutations.

Conclusions

GISTs are quite rare tumors of the gastrointestinal tract, but accurate diagnosis with immunohistochemical staining is vital for the treatment and management of the disease. Moreover, for prevention of misdiagnosis of GISTs, we need to conduct prospective, randomized, multicenter studies with a large sample of patients.

Table III. Immunohistochemical staining patterns of GISTs

Variable	SMA		*P*-value	DOG1		*P*-value	S100		*P*-value
	(–) (*n* = 19)	(+) (*n* = 7)		(–) (*n* = 14)	(+) (*n* = 12)		(–) (*n* = 21)	(+) (*n* = 5)	
Tumor site:			0.999			0.999			0.488
Stomach (*n* = 23)	17 (89.5)	6 (85.7)		12 (85.7)	11 (91.7)		19 (90.5)	4 (80.0)	
Small intestine (*n* = 3)	2 (10.5)	1 (14.3)		2 (14.3)	1 (8.3)		2 (9.5)	1 (20.0)	
Histologic type:			**0.032**			0.685			0.999
Spindle (*n* = 16)	14 (73.7)	2 (28.6)		8 (57.1)	8 (66.7)		13 (61.9)	3 (60.0)	
Mixed (*n* = 8)	5 (26.3)	3 (42.9)		4 (28.6)	4 (33.3)		6 (28.6)	2 (40.0)	
Epithelioid (*n* = 2)	0 (0.0)	2 (28.6)		2 (14.3)	0 (0.0)		2 (9.5)	0 (0.0)	
Risk:			0.470			0.748			0.912
Very low risk (*n* = 5)	3 (15.8)	2 (28.6)		3 (21.4)	2 (16.7)		4 (19.0)	1 (20.0)	
Low risk (*n* = 9)	7 (36.8)	2 (28.6)		5 (35.7)	4 (33.3)		8 (38.1)	1 (20.0)	
Intermediate risk (*n* = 4)	2 (10.5)	2 (28.6)		3 (21.4)	1 (8.3)		3 (14.3)	1 (20.0)	
High risk (*n* = 8)	7 (36.8)	1 (14.3)		3 (21.4)	5 (41.7)		6 (28.6)	2 (40.0)	
Variable	**Desmin**		***P*-value**	**CD34**		***P*-value**	**CD117**		***P*-value**
	(–) (*n* = 24)	**(+) (*n* = 2)**		**(–) (*n* = 4)**	**(+) (*n* = 22)**		**(–) (*n* = 1)**	**(+) (*n* = 25)**	
Tumor site:			0.999			0.408			1.000
Stomach (*n* = 23)	21 (87.5)	2 (100.0)		3 (75.0)	20 (90.9)		1 (100.0)	22 (88.0)	
Small intestine (*n* = 3)	3 (12.5)	0 (0.0)		1 (25.0)	2 (9.1)		0 (0.0)	3 (12.0)	
Histologic type:			0.999			0.476			0.077
Spindle (*n* = 16)	15 (62.5)	1 (50.0)		2 (50.0)	14 (63.6)		0 (0.0)	16 (64.0)	
Mixed (*n* = 8)	7 (29.2)	1 (50.0)		1 (25.0)	7 (31.8)		0 (0.0)	8 (32.0)	
Epithelioid (*n* = 2)	2 (8.3)	0 (0.0)		1 (25.0)	1 (4.5)		1 (100.0)	1 (4.0)	
Risk:			0.517			0.242			0.346
Very low risk (*n* = 5)	5 (20.8)	0 (0.0)		2 (50.0)	3 (13.6)		1 (100.0)	4 (16.0)	
Low risk (*n* = 9)	8 (33.3)	1 (50.0)		1 (25.0)	8 (36.4)		0 (0.0)	9 (36.0)	
Intermediate risk (*n* = 4)	3 (12.5)	1 (50.0)		1 (25.0)	3 (13.6)		0 (0.0)	4 (16.0)	
High risk (*n* = 8)	8 (33.3)	0 (0.0)		0 (0.0)	8 (36.4)		0 (0.0)	8 (32.0)	

Descriptive statistics for categorical variables are given as number (%) and Fisher's exact test was used for comparison. P-values in ***bold*** *were accepted to be statistically significant (p<0.05).*

Conflict of interest

The authors declare no conflict of interest.

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