Histopathological Characteristics of Gastrointestinal Stromal Tumors in a Cohort of Vietnamese Patients

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ABSTRACT

INTRODUCTION: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal system. Histopathological examination takes an important part in confirming the subtypes of GISTs, to choose appropriate therapeutics for patients. This study aims to explore the histopathological characteristics and evaluate the relationship between malignant risk classification (according to Armed Forces Institute of Pathology criteria) and the histopathological features of GISTs in a cohort of Vietnamese patients.

METHODS: We reviewed 89 patients with primary GIST who underwent surgery between 2014 and 2019 at Hue Central Hospital, Vietnam. We investigated histopathological characteristics and immunohistochemical findings of all patients.

RESULTS: The average age was 55.9 ± 11.9 years. A tumor size of 2-5 cm accounted for 64.1%. The most common position was at the stomach which accounted for 48.5%. Among the subtypes of GIST, spindle cells were seen in 85.9% of patients; epithelial form 10.9%; multimorphology (3.2%). 97.4% of the samples were positive for CD117, 61.5% of cases were positive for CD34; and no case was positive for Desmin. The rate of high-risk GIST was dominant (46.9%) as compared to the intermediate-risk (28.1%), low-risk (0.3%-2%), and very low-risk groups (4.7%).

CONCLUSIONS: This study demonstrates the histopathological characteristics of GIST and emphasizes the significant rate of high-risk GIST.

KEYWORDS: Pathology, immunohistochemistry, gastrointestinal stromal tumors (GISTs)

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Introduction

Gastrointestinal stromal tumors (GISTs) are rare, but they are the most common mesenchymal tumors of the digestive system. The incidence of GISTs is reported at 10-15 per million per year.[1] Before the pathogenesis of GISTs was comprehended, most of the cases were diagnosed as gastrointestinal autonomic nerve tumors and leiomyoblastomas. Gastrointestinal stromal tumors belong to a group of cancers labeled as the connective tissue cancer group. The tumors start from the interstitial Cajal cells and can develop in any part of the gastrointestinal system. The most common location is the stomach, which accounts for 55.6%, followed by the small intestine (31.8%), colorectal (6.0%), esophagus (0.7%), and other locations (5.5%).[1] The malignant risk of GISTs is different depending on the primary sites. Malignant GIST of the stomach accounts for 25% of gastric GISTs. In comparison, malignant GIST of the small intestine takes 35%-40% of small intestinal GISTs.[2] The clinical symptoms of GIST are non-specific and varied such as abdominal pain, gastrointestinal bleeding, gastric ulcer, and accidental discovery upon imaging examination.[2] They have diverse histopathological characteristics making it difficult to accurately predict as they can "mimic" the histopathological features of many other mesenchymal and epithelial tumors.[3,4]

There have been some international studies of gastrointestinal tract tumors on histopathology and immunohistochemistry, but few data have been found in Vietnam. This study aims to explore the histopathological characteristics and evaluate the relationship between malignant risk classification (according to Armed Forces Institute of Pathology [AFIP] criteria) and the histopathological features of GISTs in a cohort of Vietnamese patients.

Materials and Methods

Tissue sample collection

Eighty-nine primary GIST samples were collected from patients who underwent surgical resection between 2014 and 2019 at Hue Central Hospital (Hue City, Vietnam). This study was approved by the Board of Ethics in Biomedical Research at Hue Central Hospital, Vietnam (approval number: 01062019/HCH). Informed consent was waived by the Board due to the retrospective study.

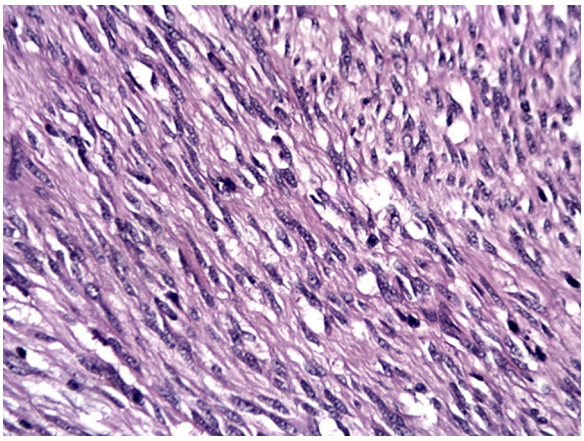

Figure 1. Hematoxylin and eosin stain of gastrointestinal stromal tumors (original magnification 200×).

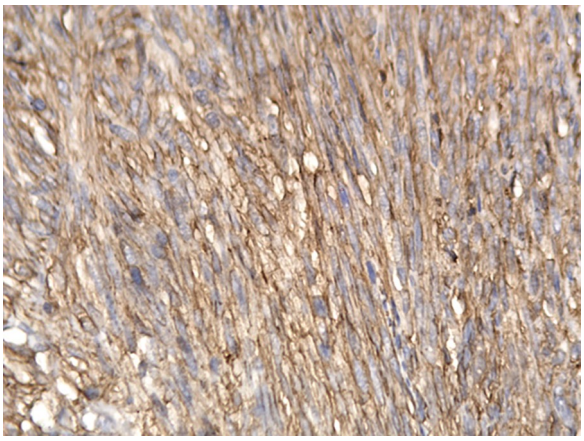

Figure 3. Immunohistochemical staining of gastrointestinal stromal tumors: positive for CD-34 (original magnification 200×).

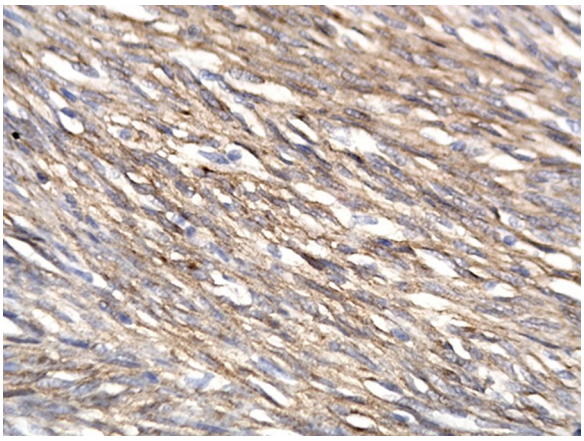

Figure 2. Immunohistochemical staining of gastrointestinal stromal tumors: positive for CD-117 (original magnification 200×).

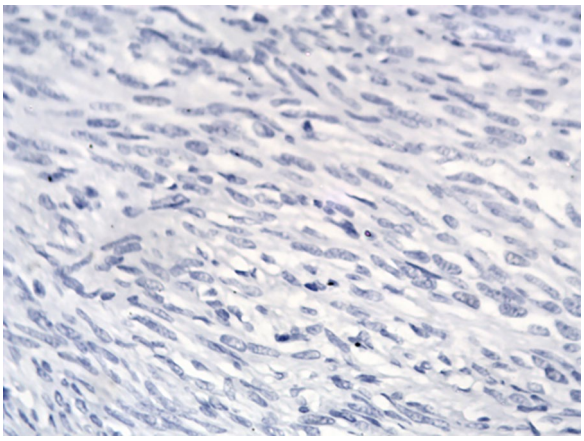

Figure 4. Immunohistochemical staining of gastrointestinal stromal tumors: negative for Desmin (original magnification 200×).

Patients treated with imatinib (Glivec®) before surgery were excluded in the study. The diagnosis of GIST was confirmed based on the histopathological findings and immunoreactivity of CD117.

Clinicopathological data such as age, sex, tumor location, tumor size, tumor stage, clinical manifestations, and surgical treatment were retrospectively reviewed. The location of GISTs was confirmed depending on the primary organ of origin.

Morphological characteristics such as pattern (epithelioid, spindle cell, or mixed) and mitotic activity (per 50 HPFs with 5 mm^2 total area) were evaluated (Figure 1). GISTs were categorized into very low-risk, low-risk, intermediate-risk, and high-risk groups based on the AFIP criteria.[5]

For immunohistochemical studies, we used archival formalin-fixed, paraffin-embedded (FFPE) tissues from those 89 GIST samples and examined them using immunohistochemistry for 1-2 representative tumor blocks from each case.

Immunohistochemistry procedure

We used 3-μm-thick slides for immunohistochemical studies. Primary antibodies for CD-117 (Figure 2), CD-34 (Figure 3), Vimentin, and Desmin (Figure 4) were used to find protein expression. Immunostaining for CD-117 was performed by an automated staining machine under the manufacturer's guide. Immunostaining was defined as positive (labeled [+]) if ⩾10% of tumor cells were stained and as negative (labeled [-]) if <10% of tumor cells were stained. Two senior pathologists blinded to the clinical features of the subjects independently analyzed the immunostaining slides. Cases of inter-observer differences were solved by consensus analysis using a double-headed microscope after independent analysis.

Statistical analysis

All statistical analyses were performed using SPSS software ver. 16.0 (SPSS Inc., IBM, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequency and percentage. The Chi-square test was used to explore the association between the risk level and the rate of mucosal invasion or tumor necrosis. A P value of <.05 was considered as statistically significant.

Table 1. Clinical manifestations of GIST in our series.

CHARACTERISTICS	ALL PATIENTS (N=89)
Age, mean (range)	55.9 ± 11.9 (31-80) years
Sex, n (%)	
Male	65 (73.0%)
Female	24 (27.0%)
Clinical manifestations	
Gastrointestinal bleeding	35 (39.3%)
Abdominal pain	27 (30.3%)
Incidental finding	13 (14.6%)
Abdominal mass	11 (12.4%)
Anemic symptoms	5 (5.6%)
Nausea and vomiting	2 (2.2%)

Abbreviation: GIST, gastrointestinal stromal tumors.

Results

Patient characteristics and clinical manifestations of GIST are shown in Table 1. A predominant frequency is observed in males (73.0%) compared to females (27.0%), with the male/female ratio of 2.7/1. Ages of the patients ranged from 31 to 80 years, mean age of 55.9 ± 11.9 years. The most common signs and symptoms were gastrointestinal bleeding in 35 patients (39.3%), followed by abdominal pain in 27 patients (30.3%), incidental finding in 13 patients (14.6%), abdominal mass in 11 patients (12.4%), anemic symptoms in 5 patients (5.6%), and nausea and vomiting in 2 patients (2.2%).

Tumor sizes ranged from 1.2 to 22.1 cm with a mean size of 9.17 ± 3.2 cm. Median size was 7.1 cm. Most of the tumors were >2-5 cm (57 cases, 64.1%). The GISTs were found in a wide distribution both within and outside the GI system. The most common location was the stomach (49.4%), followed by the colorectal (23.6%) and small intestine (14.6%; Table 2).

As for the treatment performed, the whole of cases underwent surgery (100%). Open surgery was used in 80 cases (89.9%). Laparoscopy was used in 9 selected cases (10.1%). The usual surgical technique was atypical gastrectomy in the case of gastric GIST and segmental resection of the small intestine in more than two-thirds of intestinal GIST cases.

Regarding pathology characteristics of the GIST Series, 97.4% of samples were positive for CD117, 61.5% of cases were positive for CD34, and no case was positive for Desmin. Most cases showed spindle cells (82.0%) or epithelial form (12.4%), and mixed histology form accounted for 5.6% of cases. According to AFIP criteria,[5] 42 cases (47.2%) were classified as high risk, 23 (25.8%) as intermediate risk, 18 (20.2%) as low risk, and 6 (6.7%) as very low risk (as shown in Table 2).

The rate of mucosal invasion or necrosis in the high-risk group seemed to be higher than those in the lower risk groups (intermediary, low, very low) but not statistically significant (Table 3).

Table 2. Pathologic data of GISTs.

CHARACTERISTIC	ALL PATIENTS (N=89)
Tumor size, n (%)	
⩽2 cm	11 (12.4%)
>2-5 cm	57 (64.1%)
>5-10 cm	15 (16.8%)
>10 cm	6 (6.7%)
Tumor location, n (%)	
Stomach	44 (49.4%)
Colorectum	21 (23.6)
Small intestine	13 (14.6%)
Other	11 (12.4%)
Histopathology, n (%)	
Spindle cells	73 (82.0%)
Epithelial form	11 (12.4%)
Polymorphic	5 (5.6%)
Risk level, n (%)	
Very low	6 (6.7%)
Low	18 (20.2%)
Intermediary	23 (25.8%)
High	42 (47.2%)

Abbreviation: GIST, gastrointestinal stromal tumors.

Table 3. Relationship between risk level and mucosal invasion or tumor necrosis.

RISK LEVEL	MUCOSAL INVASION (N=24)	TUMOR NECROSIS (N=33)
Very low (n=6)	0 (0.0%)	0 (0.0%)
Low (n=18)	0 (0.0%)	0 (0.0%)
Intermediate (n=23)	6 (26.1%)	8 (34.8%)
High (n=42)	18 (42.8%)	25 (59.5%)
P value[a]	.2867	.0999

[a]Chi-square test was done within the 2 groups: intermediary-risk and high-risk.

Discussion

This retrospective study, based on 89 Vietnamese patients with GISTs, aimed to explore the histopathological characteristics of this disease. The results were consistent with previous reports in other populations.[6-9] A systematic review of 29 studies on nearly 14 000 GIST patients reported a mean age of 60 years, and the incidence was similar for males and females.[1] Our study showed a higher incidence rate in males and a lower mean age than other studies. However, our average age was

higher than that of the Korean sub-population reported in the systemic review mentioned above.[1]

In our study, the tumor size between 2 and 5 cm accounted for the highest percentage (64.1%) as compared to the other groups of tumor size. According to the study of Miettinen and Lasota[10] or Dematteo et al,[3] the size of the tumor was one of the important prognostic factors to assess the risk of relapse. Patients with a bigger tumor had a higher recurrence risk.

Although many studies have reported the presence of GISTs in the esophagus,[1] no esophageal GISTs were present in our study. Our results showed that GISTs were most predominant in the stomach, followed by the colorectal and small intestine, which was consistent with the findings in most of the literature.

Histopathologically, the patterns of GISTs include several types: spindle cell type, epithelial cells, mixed histology cell type, ring type, mesothelioma, and large cell type.[3] We noted the histological diversity of gastrointestinal stromal tumors, which can "mimic" many histological types of different mesenchymal tumors. In this study, we mainly focused on spindle cells with 55/64 (85.9%). Regarding the other variations of spindle cell GIST, there were 6 cases, including 5 spindle cell cases and 1 epithelial cell case. Mixed histology types included scattered spindle cells and epithelial cells, which were highly proliferative but irregular, with monster nuclei and multiplication. In addition, there were a number of subtypes that should be found in the literature such as ring type, mesenchymal type, and cell type; but we have not seen them before in our hospital.

Due to the lack of DOG1 staining in our hospital, all samples were performed CD117 and the result showed that there were 86 (97.4%) positive samples and 3 (2.6%) negative ones. Thus, we sent 3 paraffin blocs with negative results to another center in Vietnam for staining with DOG1, and all of them were positive. This was considered as the diagnostic criteria of GIST in the CD117-negative cases. In the "Results" section, we only focused on the percentage of the positivity with CD117 immunohistochemical marker in the study.

According to the literature, most GISTs had high-risk features, followed by intermediate- and low-risk ones.[11-14] Our study also had a majority of GISTs classified as high-risk, followed by intermediate-risk, low-risk, and very low-risk groups. In our study, the level of risk seemed to be associated with tumor necrosis and mucosal invasion but not statistically significant. This association was found in some previous studies.[9] The study of De Matteo mentioned other factors that also had the potential to affect the prognosis value such as tumor necrosis and invasion.[3] This further confirmed that 2 factors of tumor infestation and tumor necrosis should be included in the risk factors of GIST.

However, there were still some limitations to our study. Because it was a retrospective study, it lacked clinical outcome information of the patients, which would not enable us to determine overall and disease-free survival. Furthermore, it lacked morphological description of the GISTs as well as molecular analysis to find out the mutations of GISTs in Vietnamese patients.

In conclusion, this study demonstrated the pathological features and immunohistochemical characteristics of 89 Vietnamese GIST patients. The stomach was the most common site of GISTs, followed by the colorectal and small intestine. Further studies are strongly recommended in this field with a larger sample size to investigate the association between the risk levels according to AFIP criteria and the necrosis or mucosal invasion of the tumor.

Author Contributions

PNC and NTX conceived the study and participated in its design; PNC participated in data acquisition; NTX participated in the analyses and interpretation of data; PNC and NTX drafted the manuscript. All authors contributed to the manuscript revision, and read and approved the submitted version.

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