Gastric gastrointestinal stromal tumor (GIST): incidence, diagnosis and histopathological aspects

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Abstract

Introduction: Gastrointestinal stromal tumors (GISTs) are malignant mesenchymal tumors. Most of GISTs are located in the stomach whereby tumors can be scattered in the whole region and are typically presented as submucosal tumors (SMT). Regarding macroscopic examination, it is indistinguishable between GISTs with other benign submucosal tumors such as leiomyoma, heterotopic pancreatic tissue, neurofibromatosis, lipoma, Schwann cell tumor or leiomyosarcoma. However, some researches showed that it is possible to determine GISTs and other types of submucosal tumors based on the layers of the stomach wall, and the position relative to the anatomical part of the stomach.

Patients and methods: A descriptive cross-sectional case series included 152 patients who were diagnosed with SMT and treated in Nhan Dan Gia Dinh hospital and University of Medicine and Pharmacy at HCM city from 2016 to 2021. Objectives: evaluate the frequency of gastric GISTs in the stomach based on the ratio of gastric GISTs compares to other SMT, the incidence of these tumors in each corresponding anatomical location of the stomach (cardia, fundus, body, and pyloric antrum regions) and the histopathological results (pathology and immunohistochemistry) between GISTs and the types of SMTs.

Results: In 152 cases, female/male ratio was 0,58/1. Mean age was 54 years old. The ratio of gastric GISTs was 71.71%. The most frequent locations were in the body, fundus and less often in the cardia and pyloric antrum (48.6%, 22%, 15.6%, 10.1%) and 4 other cases (3,7%) with more than 2 tumors in the stomach. The most common clinical manifestations epigastric pain (47.7%), hemorrhage (19.7%), without symptoms (25.7%) and discomfort: gas, bloating, and belching accounted for 7.9%.

Conclusion: Gastric GISTs covered 71.71% of all the SMTs and the most frequent locations were in the body 48.6%, fundus 22%, cardia 15.6% and pyloric antrum 10.1%.

Keywords: Gastric gastrointestinal stromal tumor, gastric submucosal tumor, immunohistochemistry.

Introduction

Submucosal tumors (SMT) are protuberant lesions located in gastrointestinal tract and covered by intact gastrointestinal mucosa. The majority of SMT locate in the stomach and is commonly classified into 2 main groups. The most common group is Gastro Intestinal Stromal Tumor (GIST) accounts for 50% [8]. The less common one is termed sarcoma which can be seen in the soft tissues, including lipomas, myo-lipomas, leiomyomas, sebaceous cysts, neurofibromatosis, leiomyosarcoma. Our aim of study is to identify the incidence of SMT in a relevant location in the stomach and the brief characteristics and histopathological examination result, the ratio of GISTs and other tumors.

Materials and methodology

Subjects: All gastric SMTs were diagnosed and treated at Nhan Dan Gia Dinh Hospital and University of Medicine and Pharmacy in HCM city from 2016-2021

Methodology: A descriptive cross-sectional case series study

Statistical Analysis

Nominal variables are presented as absolute or percentage values, quantitative variables standardly distributed are presented as mean ± standard deviation, whereas nonstandard distribution are presented as median with the values of 25% and 75%. To compare 2 groups of quantitative variables that have standardized distribution, we used t-test or Mann-Whitney test. Compare 2 groups of variables using the normal Chi test or Fisher. The chosen error threshold is $\alpha = 0{,}05$.

The clinical variables include: Data was gathered from medical reports and analyzed by SPSS 20.0 software.

Medical ethics: The Ethics Committee in Biomedical Science of University of Medicine and Pharmacy at HCM city approved on April 12, 2019, code 387/DHYD-HDDD

Results

There were 152 cases during research period with 56 male patients and 96 female patients (36,8% and 63,2%) respectively. With the mean age of $54{,}48 \pm 14{,}77$ years old (19 – 86 years old). 71 cases were detected due to epigastric pain, 30 cases had gastrointestinal hemorrhage, 39 cases without symptoms, incidentally found by endoscopy or through initial screening CT scan or abdominal ultrasound, the other groups were found due to symptoms related to digestive disorders: bloating, indigestion, belching … There were 109 cases confirmed with gastric GISTs, 16 cases of leiomyoma, 14 cases of ectopic pancreatic tumor, 3 cases of schawann cell tumor and the other tumors were neurofibromatosis, lipoma, benign mesothelioma … The rate of GISTs appeared in the stomach parts: cardia, fundus, body, and pyloric antrum, consecutively, 15,6%, 22%, 48,6%, 10,1%, and there were 4 cases (3,7%) with more than 2 tumors in the stomach.

Tumor size and symptoms:

The average tumor size was $4{,}47 \pm 3{,}31$ cm (1 – 20 cm) with the distribution in size as following:

Table 1: Per-operative classification of tumor size

Size	N	%
≤ 2 cm	31	20,4
2 cm < tumor ≤ 5 cm	91	59,9
5 cm < tumor ≤ 10 cm	22	14,5
> 10 cm	8	5,3
Total	152	100

Gastroendoscopy:

Among 146 gastro endoscopies, 132 cases were detected (92%), 10 cases were not detected during the procedure (6%), 4 cases (2%) had gastric lumen that was smooth, with a diagnostic image indicating a tumor suppresses from the outside into the gastric lumen

Biopsies:

Only performed 15% and mostly detected inflammatory tissues, there was 1 case using the deep biopsy technique twice but did not successfully find tumors. 2 cases were suspected to be GISTs, 1 case was suspected the mesenchymal malignancy.

Abdomen CT scan with contrast is an essential means to assess the location, size, and contrast enhancement characteristic of a tumor to evaluate the malignant degree. GIST often poorly absorbed contrast agents, inconsistent density, ulcerative lesions through the mucosa or deeper such as ulceration into the tumor tissue which creates gas cluster inside the tumor lumen, are the factors related to high risk of malignancy, intraluminal necrosis is the characteristic of GIST associated with a high and average degree of malignancy.

Macroscopic aspect:

The macroscopic aspect of GISTs usually has light yellow, or ivory white, the tissue density is quite consistent, scattered hemorrhage inside the tumor around the central or peripheral area,

the majority of mucosa is smooth and normal, it may appear ulceration, mild ulceration, or inflammatory edema. The image of stromal tumor with intermediate-grade tends to have larger size, mostly develop multi-lobe, might have mucosal ulceration, but rarely has a deep ulcer, sometimes fluid in the lumen. The image of high-grade GIST tends to be huge, develops multi-lobe and may have a subcapsular hemorrhage, tumor tissue has many hemorrhage areas due to excessive development, may have central necrosis, mucosa often has deep ulceration or continuously lose a long part, many cases ruptures into the lumen with necrosis that created an image of a lumpy tumor in the lumen, it can be easily confused with adenocarcinoma while identifying through endoscopy.

Figure 1: GISTs with 3 levels of malignant possibilities: low, average, high

Smooth muscle tumors are usually white, may have many small lobes, mostly consistent in density, and rarely has central necrosis like stromal. Microscopic examination shows many smooth muscle cells arranged in interlacing bundles. In terms of macro and micro examinations, it is nearly identical to complete GISTs.

Heterotopic pancreatic tumor on macro examination shows light yellow or white to brown, lobulated glandular structure with interstitial ducts within the tumor tissue. Microscopic examination shows the exocrine glandular structures are lobular, clear ducts, drain into the main ducts.

Histopathology and immunohistochemistry

Despite clinical symptoms, endoscopic images and CT scan that suggested images of gastro GISTs

identified with other tumors have same image of macroscopic aspect. However, to confirm the final diagnosis, it still requires histopathological examination and the result of immunohistochemistry. In addition to GISTs diagnosis based on positive expression of CD117, DOG-1, and tumor size, the mitotic rate 50 high power field (HPF) and Ki67 index is extremely important.

Histopathological results: 115 cases (75,66%) suggested GISTs. 9 cases (5,92%) suspected GIST and needed to be identified with other mesothelioma, 7 cases (4,61%) are leiomyoma, 2 cases (1,32%) suspected adenocarcinoma and 19 remaining cases (12,5%) are benign tumors (heterotopic pancreatic tumor, lipomas, gastric cysts, etc ...)

Immunohistochemistry result: There were 136 cases required immunohistochemistry test with 109 cases of gastric GIST confirmed by CD117, DOG-1. 27 remaining cases resulted in 16 cases of leiomyoma, 3 cases of schawann cell tumor, 1 neurofibroma and 1 benign mesenchymal tumor, 1 neuroendocrine tumor, 1 involuntary muscle sarcoma, 1 inflammatory fibrous polyp, 1 choroidal tumor, 1 benign fibroma, 1 calcified fibroma.

Discussions

Age

The mean age was 54,48 ± 14,77 (19 – 86 years old), the disease scatterly distributed through all age groups. This age is comparable to other authors reports [7],[4],[3]. Gastric SMT group was more common within 50 – 70 age (68% of total gastric GISTs patients) with average age was 59,06 ± 12,34 years old which was higher than the remaining groups 42,86 ± 14,16 (p < 0.001 t test).

Gender

The overall ratio male/female was 0,58/1. This ratio was consistent with Le Huu Luus study [5], whereas different with European author groups which slightly increased in male [10] or equivalent [9], and when solely counting patient groups with tumors > 5cm, our ratio male/female was 0,94/1 that was similar to European authors.

Tumor size

The most common GISTs group with an average size was 5,14 ± 3,61 cm. Meanwhile, the size of tumour ranging from 2cm to 5cm occured the most. Our result is similar with Kim [15]. Gastric SMT group with size ≤ 2 cm accounts for 42% of adenocarcinomas types. Kataoca[14] gastric SMT tumors with size ≤ 2 cm, 53% were GISTs.

GISTs rate: tumor ≤ 5 cm (53,3%), tumor > 5 (93,3%), and especially tumor ≥ 8,3 cm in our series had 17/17 cases (100%). Therefore, the tumor size was considered to be proportional to the incidence rate of GISTs and with the tumor ≥ 8,3 cm, our GISTs rate accounted for 100%.

Comparing with leiomyoma: the 2nd most common after GISTs. With average size, the median is 2.7± 1.44 cm (p = 0.003 < 0.05 t test) the size difference was statistically significant. Chois research [12] also showed the difference in size between gastric stromal tumor with schwannoma tumor but not with leiomyoma.

Comparing with heterotopic pancreas tissue group: the 3rd most common after 2 above groups, the average size was 2.29 ± 0.94 (p < 0.001 t test) the difference was statistically significant.

Parts location in stomach

Evaluating in order from top to bottom along stomach body, we found:

Cardiac: 17 cases of GISTs (60,7%), 9 cases of leiomyoma (32,14%), one neurofibroma, and one glomus tumor.

Fundus: 23 cases of GISTs (92%), one leiomyoma, one mesenchymal tumor , one lipoma.

Body: 51 GISTs (76,12%), 4 heterotopic pancreas tissue, 3 leiomyoma, one lipoma, one neuroendocrine, 2 schwann cells tumor, one sarcom, one benign mesenchymal neuroma, one benign fibroma, one calcified fibroma

Table 2. Locations of GISTs with stomach parts

Authors	Cardiac	Fundus	1/3 upper	1/3 middle	1/3 lower	Antrum - pyloric	Many locations
Kim[15]	13,7%		41,7%	18,2%	22,6%		3,8%
Choi[12]	13,1%		44,4%	28,3%	14,1%		
Ceccarelli[11]	2,7%		Lesser curvature 11,1%, Body 75%			11,1%	
Us	11,2%	20,6%	26,2%	24,3%	4,7%	9,3%	3,7%

Pyloric antrum: 11 cases of GISTs (44%), 9 cases of heterotopic pancreas (36%), 2 leiomyoma, 2 schawann cells tumor, one neurofibroma, one benign fibroma

Our result was similar with Choi [12], Kim [15] that GISTs occured the most in 1/3 upper of stomach, then 1/3 middle and lower, cardiac and antrum – pyloric areas are less common than the remaining locations. This means, there is a connection between tumor location and tumor characteristics in the stomach.
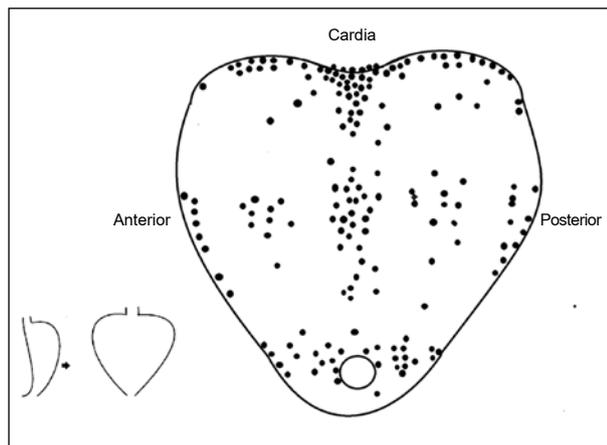

Figure 2: Tumors location recorded during surgery

Mitotic degree and Ki67

Mitotic index assessment, there were 72 cases of GISTs following the mitotic counting results.

Table 3: Malignant risk and mitotic index

Malignancy possibility	Low and really low	Average	High
Mitotic ≤ 5/QT50	50	10	2
Mitotic > 5/QT50	1	1	8

We divided malignancy possibility levels based on NIH standards or preferably termed Fletcher's criteria revised by Joensuu [13]. We classified group of mitotic index ≤ 5/QT50 & > 5/QT50 to assess malignant risk to converge with national and international research.

Ki67 is an antigen-specific monoclonal antibody-related to cell division and it is a signal of mitotic activity. In Viet Nam, Ki67 was evaluated in gastrointestinal cancer and was used in GISTs to assess the malignant possibility. [2],[6],[1]

In the group of 107 GISTs, we have analyzed 51 cases with Ki67, the data focused on Ki67 ≤ 5% related to the low possibility of malignancy, and around Ki67 ≥ 10% related to high possibility. In our opinion, malignancy possibility can be classified based on Ki67 indication, such as Ki67 ≤ 5% – low, 5% < Ki67 < 10% – average, Ki67 ≥ 10% – high.

Table 4. Malignant possibility of Ki67 index in different reports

Authors	Low NCAT	Average NCAT	High NCAT
Zhao[17]	Ki67 < 5%	5% ≤ Ki67 ≤ 8%	Ki67 > 8%
Yang[16]	Ki67 < 10%		Ki67 ≥ 10%
Our	Ki67 ≤ 5%	5% < Ki67 < 10%	Ki67 ≥ 10%

We found that in the study, the Ki67 index for low-risk malignancy was similar to the report of author Zhao [17] and the high risk of malignancy was equivalent to that of author Yang [16]

Conclusions

The rate of SMTs concluded as GISTs was 71,71% in which the majority of SMTs were proved to require surgical treatment. Even in the situation of GISTs not being detected, these group still needed precise interventions (neuroendocrine tumor, sarcom ...)

Moreover, tumor siz of SMT is a standard to evaluate the high risk of GISTs as it is proportional to the high incidence of malignancy.

Conflict of interest: The authors declare that they have no conflict of interest.

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