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CASE REPORT

Risk Factors for Mucosal Ulceration in Gastric Gastrointestinal Stromal Tumors (GIST)

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Abstract

Background: Gastrointestinal stromal tumors (GIST) are the most common subepithelial tumors in the gastrointestinal (GI) tract and they are usually located in the stomach. To date, only a few studies have investigated the risk factors for GIST ulceration and bleeding and there have been no prior publications focused on role of *Helicobacter pylori* in GIST ulceration. The aim of current study was to investigate the risk factors of mucosal ulceration in gastric GISTs.

Methods: A retrospective study was conducted of 130 patients with a histological diagnosis of gastric GIST, recruited from four medical centers in Israel. The following details were extracted fom each patient: patient's age and gender; tumor location, size, mitotic rate and Ki-67 index; whether or not metastases were present, the patients' international normalization ratio (INR) and the use of antiplatelets, anticoagulants or proton pump inhibitors (PPI).

Results: The median age of the patients was 69 years. Approximately one third of lesions demonstrated a mucosal ulceration. Upper GI bleeding or iron deficiency anemia (77.5%) were the most common indication for endoscopy in patients found to have an ulcerated GIST at endoscopy. On univariate analysis, mucosal ulceration in gastric GIST was associated with older age, increased number of mitoses, high Ki-67 index, location in the cardia and fundus and an elevated INR. Multivariate analysis showed significant differences only for number of mitoses (OR = 1.287, 95% CI 1.054-1.57, p = 0.013).

Conclusion: In this large retrospective study, the only risk factor associated with tumor ulceration in gastric GISTs was increased mitotic rate.

Keywords

Gastrointestinal stromal tumor, *Helicobacter pylori*, Gastric ulcer, GI bleeding

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal (GI) tract [1]. The most common site of a GIST is the stomach (50-60% of cases) followed by the small intestine (30-35%), the large intestine and rectum (5%) and, most rarely, the esophagus (< 1%). Extra-intesti-

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nal sites may include the omentum, mesentery and retroperitoneum [2-3]. One third of GISTs are found incidentally, by endoscopic examination [4]. While other cases may present with GI bleeding, anemia or other symptoms such as dyspepsia. GISTs originating from the small intestine may present as an acute abdomen and/or with intestinal obstruction [5]. Tumors that involve the submucosal layer have a higher risk of ulceration and a substantial risk of bleeding [6]. Indeed, GI bleeding (usually as with melena and/or hematemesis) is the most common presenting symptom in GISTs, occurring in 22-35% of cases [7-9]. The severity of the GI bleeding varies from occult bleeding and iron deficiency anemia to life-threatening bleeding and hemorrhagic shock [10-13]. GIST ulceration and GI bleeding have great impact on patient's prognosis, usually being correlated with worse prognosis [8,14-20], though there is one report of better prognosis in GISTs that bleed [14].

Gastric GISTs tend to grow toward the serosa but as they enlarge they can also expand into and ulcerate through the gastric mucosa, though this occurs only in a minority of the cases [3,7]. Only a few studies, all from South-East Asia, have addressed why some GISTs penetrate the gastrointestinal mucosa, producing an ulcer and eventually cause GI bleeding [14,19-21].

We hypothesized that certain changes in the gastric mucosa overlying a gastric GIST, for example the presence of *Helicobacter pylori* (*H. pylori*) gastritis, may explain why certain gastric GISTs ulcerate. We therefore examined retrospectively the correlates of gastric GIST ulceration, including mucosal factors, tumor factors (such as location, size and proliferative indices) and other clinic-pathological variables in a large series of gastric GISTs.

Methods

We performed a retrospective analysis of patients diagnosed with a gastric GIST in four Medical Centers in Israel; Shamir (Assaf Harofeh) Medical Center, Sheba Medical Center, Rabin Medical Center and Sourasky Medical Center, between 2007 and 2017 years. This study was approved by the local institutional review board of each medical center in 9 April 2017. Israel legislation on studies of anonymized retrospective data does not require informed consent. All clinical investigations were conducted according to the ethical guidelines of the Declaration of Helsinki.

The diagnosis of GIST was established by pathological examination of a biopsy sample or surgical resection. Exclusion criteria were age < 18-years-old, patients with a GIST found at a site other than the stomach and patients without a definite GIST diagnosis.

Patients' demographics, (gender, age), tumor site, *H. pylori* status, medications, International normalized ratio (INR) were all extracted from the medical records. Also recorded were the indication for the first endoscopy that resulted in the tumor being identified. For example: GI bleeding, iron deficiency anemia, dyspepsia or dysphagia, or whether the tumor was found incidentally during follow up for another upper GI indication such as surveillance of a gastroduodenal or esophageal ulcer, or Barret's esophagus or for investigation of a tumor found incidentally on an imaging study such as a CT scan done for other reasons.

Tumor ulceration was identified by the following means: (1) During endoscopy (2) On gross pathological examination, or (3) Identification by the surgeon during surgical resection of the tumor. Information on tumor characteristics such as size, number of mitoses, Ki-67 index, presence of metastases, and pathological diagnosis and grading were also collected. *H. pylori* status was recorded from either biopsy results or histological examination of the resected tumors. In patients lacking information about *H. pylori* status a second revision of their pathologic slides for *H. pylori* evaluation, including immunohistochemistry was performed. We also used the Israeli community medical data system "Ofek" in order to search for any missing patient data. Any cases missing any of these variables listed above were excluded from the final analysis.

Statistical Analysis

Categorical variables were reported as numbers and percentage. Continuous variables were evaluated for normal distribution using histogram and reported as medians and interquartile range (IQR). Categorical variables were compared between groups using chi-square test or fisher's exact test. Continuous variables were compared using the Mann-Whitney test.

Multivariate logistic regression was used to study the association between each of the statistically significant predictors in the univariate analysis with findings of ulceration, while controlling for other significant predictors in the univariate analysis. All statistical tests were two sided and $p < 0.05$ was considered statistically significant. SPSS software was used for all statistical analysis (IBM SPSS statistics version 25, IBM corp. Armonk, NY, USA, 2017).

Results

A total of 130 patients with gastric GIST diagnosed between 2007-2017 were identified. Forty of them presented with an ulcer, 90 of them had no ulcer. The median age was 69 years (IQR 59-76). 51% of the cases were males.

Dyspepsia/dysphagia were the most common indications for gastroscopy (37% of the cases), followed by upper GI bleeding (34% of the cases). In the group of patients with an ulcerated gastric GIST, the most common indication for the diagnostic index gastroscopy was upper GI bleeding or iron deficiency ane-

Table 1: Indication for the first gastroscopy in which a gastric GIST was found.

Symptom	Total (n = 130)	With ulcer (40)	Without ulcer (90)	P value (95%)
IDA and/or UGIB	34.1%	77.5%	14.6%	< 0.001
Dyspepsia ordysphagia	37.2%	22.5%	43.8%	
Incidental finding	28.7%	0%	41.5%	

GIST: gastrointestinal stromal tumor; IDA: iron deficiency anemia; UGIB: upper gastrointestinal bleeding.

Table 2: Univariate regression analysis of risk factor for gastric GIST ulceration.

Variable	Valid data	Total	With ulceration (n = 40)	Without ulceration (n = 90)	P value (95%)
Age (years)	130	69 (59-76)	71	68	0.49
Gender	130				
Males		66 (50.8%)	23 (57.5%)	43 (47.8%)	0.306
Females		64 (49.2%)	17 (42.5%)	47 (52.2%)	
H. pylori infection	109	23 (21.1%)	10 (27.8%)	13 (17.8%)	0.230
Positive					
Antiplatelets drugs	130	39 (30%)	13 (32.5%)	26 (28.9%)	0.678
PPI	129	35 (27.1%)	12 (30%)	23 (25.8%)	0.623
Metastasis	128	10 (7.8%)	4 (10.5%)	6 (6.7%)	0.482
Size (cm)	129	4.5 (3-7)	5 (3.2-7)	4.25 (2.87-7)	0.217
Ki-67 (%)	107	3.4% (1-7%)	5% (2.7-10%)	3% (1-5.5%)	0.016
Mitotic count (#/50 HPF)	114	2.75 (1-5)	3 (2-6.5)	2 (1-4.5)	0.015
INR	120	1.01 (0.98-1.12)	1.07 (0.99-1.18)	1.01 (0.97-1.09)	0.021
Lesion Location	130	Upper stomach (cardiafundus)			0.006
		40 (30.8%)	19 (47.5%)	21 (23.3%)	
		Lower stomach (bodyantrum)			
		90 (69.2%)	21 (52.5%)	69 (76.7%)	

GIST: gastrointestinal stromal tumor; PPI: proton pump inhibitors; HPF: high power field; INR: international normalized ratio.

Table 3: Multivariate regression analysis of risk factor for gastric GIST ulceration.

Variable	p-value	Odds ratio	Lower limit (95% CI)	Upper limit (95% CI)
Age	0.125	1.038	0.99	1.088
Lesion site-cardia fundus	0.063	2.76	0.946	8.107
INR	0.94	1.076	0.14	8.26
KI-67 (%)	0.708	0.989	0.935	1.046
Mitotic count (# per 50 HPF)	0.013	1.287	1.054	1.57

INR: international normalized ratio; HPF: high power field.

mia (77.5%), compared with the group with no ulcer (14.6% of these cases were diagnosed during an endoscopy performed for upper GI bleeding or iron deficiency anemia, p < 0.0001). In no patients with an ulcer was their tumor diagnosed incidentally (Table 1).

On univariate analysis of mucosal ulceration in gastric GISTs, statistical significance was observed for older age, increased mitotic rate, high Ki-67 index, location of the tumor in the cardia or fundus and elevated INR (Table 2). No significant difference was noted in the prevalence of *H. pylori* between GIST with or without ulcer. The multivariate analysis showed statistical significance only for the number of mitoses (OR = 1.287, 95% CI 1.05-1.57 p = 0.013 (Table 3).

Discussion

Several studies have investigated the relationship between mucosal ulceration and GI bleeding in patients with GISTs. Park, et al. reported a significant association between mucosal ulceration visualized by CT scans ("dimpling") and GI bleeding [21]. Our results are consistent with these previous reports showing that most of the patients with ulcerated gastric GIST, unlike those without ulcer, developed occult or overt GI bleeding (77.5% vs. 14.6% , p < 0.0001). To date, for GISTs location in small intestine, positive immunohistochemical stains

for s-100 and CD-34, high Ki-67, prolonged prothrombin time, male gender and the presence of metastases are the only significant risk factors that have been associated with bleeding. There have been no consistent relationships reported tumor size and GI bleeding in prior reports [14,19-21]. By contrast, our study showed, that the only risk factor associated with ulceration of gastric GISTs was increased mitotic rate.

The origin of gastric GISTs is usually from the fourth layer of the stomach (muscularis propria) or, more rarely, from the third layer (submucosa). It is diagnosed most commonly in the sixth generation [22] and has equal distribution between males and females, [23] as also noted in our study. Gastric GISTs usually grows toward the serosa with no involvement of the gastric mucosa, but they can also protrude through the gastric mucosa, leading to ulceration and subsequently a GI bleed [23-27]. A study from Thailand calculated that mucosal ulceration caused by a GISTs represents about 1.4% of idiopathic peptic ulcer disease [27].

Why do only subsets of gastric GISTs develop mucosal ulceration?: One possible explanation relates to characteristics of the overlying gastric mucosa. It is well known that the most common causes for gastric ulceration unrelated to GISTs, are *H. pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs) [24]. Therefore, it was of interest to determine whether *H. pylori* may be a significant risk factor for gastric GIST ulceration. However, no such association was noted in univariate analysis. Consistent with our results, Nonaka, et al. also reported, in 46 patients with gastric GISTs, that the most common mucosal characteristics are non-atrophic, *H. pylori* negative or mild-atrophic *H. pylori* positive gastritis [28]. This study demonstrated that the gastric mucosa lying above the GISTs is usually relatively healthy. Because of low report on people taking NSAIDs we could not evaluate their connection with GIST ulceration. The second group of possible risk factors predisposing to ulceration and bleeding is patient related parameters, such as males, older age, overweight and the use of antiplatelets or anti coagulants [25,26]. All these factors including medications such as aspirin and PPIs had no significance in the multivariate analysis as risk factors for gastric GIST ulceration.

Finally, tumor-related factors may play a role in the development of ulcer over a gastric GIST. A previous study reported that GISTs located in the cardia are more vascular and may have a higher tendency to bleed [29], even though in the general population most gastric ulcers are located in the incisura and antrum [24]. In our study the univariate analysis identified a significant association between tumors located in the cardia and fundus and the risk of ulceration, but this association did not remain statistically significant in the multivariate analysis. Our results demonstrate that it is the tumor's increased growth rate, represented by the mitotic index that appears to have the highest contribution to the tendency for ulcer development.

Though our study is the largest yet to focus on ulceration specifically in gastric GISTs in the Western population, the sample size is relatively small owing to the rarity of these tumors (130 cases identified from 4 centers over 10 years). Another limitation is the retrospective nature of this study.

In conclusion, this is the first study to describe the risk factors for mucosal ulceration of gastric GISTs. Based on our data, increased mitotic rate is the only factor correlated with mucosal ulceration and bleeding; *H. pylori* gastritis and medication usage do not play a significant role, arguing against the efficacy of *H. pylori* eradication and the use of PPIs in preventing gastric GIST bleeding. However, prospective randomized controlled studies of *H. pylori* eradication and PPI administration are needed to confirm the validity of this approach to preventing further bleeding in patients with gastric GISTs.

Conflict of Interest Statement

The authors declares that there is no conflict of interest.

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