World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i20.3117

World J Gastroenterol 2013 May 28; 19(20): 3117-3123
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

BRIEF ARTICLE

Synchronous adenocarcinoma and gastrointestinal stromal tumors in the stomach

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Supported by Shanghai Jiaotong University Medical School for Scientific Research, No. 09XJ21013; Shanghai Health Bureau for Scientific Research, No. 2010029; Shanghai Science and Technology Commission for Scientific Research, No. 124119a0300
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Received: January 6, 2013 Revised: April 19, 2013
Accepted: May 9, 2013
Published online: May 28, 2013

Abstract

AIM: To review the clinicopathological characteristics of concurrent gastrointestinal stromal tumors (GISTs) and gastric adenocarcinoma.

METHODS: We retrospectively analyzed eight cases of synchronous adenocarcinoma and GIST in the stomach that had been surgically resected with curative intent between March 2003 and December 2008 in Xinhua hospital and Ruijin hospital. The adenocarcinoma was determined to be the primary tumor based on the histological features. The GIST cells were diffusely and strongly positive for CD34 and CD117.

RESULTS: The patients were six men and two women aged 47-80 years (average, 68.6 years). GIST was preoperatively detected in only one patient. The average sizes of the gastric adenocarcinomas and GISTs were 6.000 ± 2.6186 cm and 1.825 ± 1.4370 cm, respectively. All GISTs were very low- or low-risk lesions that were detected during evaluation, staging, operation or follow-up for gastric adenocarcinoma.

CONCLUSION: We hypothesized that the stomach was influenced by the same unknown carcinogen, resulting in a simultaneous proliferation of different cell lines (epithelial and stromal cell).

Key words: Gastric adenocarcinoma; Gastrointestinal stromal tumor; Synchronous occurrence; Gastrectomy

Core tip: We retrospectively analyzed eight cases of synchronous adenocarcinoma and gastrointestinal stromal tumors (GISTs) in the stomach that had been surgically resected with curative intent between March 2003 and December 2008 in Xinhua hospital and Ruijin hospital. The average sizes of the gastric adenocarcinomas and GISTs were 6.000 ± 2.6186 cm and 1.825 ± 1.4370 cm, respectively. All GISTs were very low- or low-risk lesions that were detected during evaluation, staging, operation or follow-up for gastric adenocarcinoma. We hypothesized that the stomach was influenced by the same unknown carcinogen, resulting in a simultaneous proliferation of different cell lines (epithelial and stromal cell).

Cai R, Ren G, Wang DB. Synchronous adenocarcinoma and gastrointestinal stromal tumors in the stomach. *World J Gastroenterol* 2013; 19(20): 3117-3123 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i20/3117.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i20.3117

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesen-

chymal tumors of the digestive tract and have various clinical and biological characteristics. The expression of c-Kit distinguishes GISTs from true leiomyomas, leiomyosarcomas and other mesenchymal tumors of the gastrointestinal tract[1-3]. The stomach (60%-70%) and small intestine (20%-30%) are the most common sites of GISTs[1,2]. GISTs are composed of spindle (70%) or epithelioid (30%) cells and are positive for c-Kit (CD117), CD34 and occasionally for actin, but almost always negative for desmin and S-100 protein[4], in contrast to other mesenchymal tumors. Benign GISTs are far more common than malignant ones (10%-30%)[1], and all GISTs are often found incidentally at surgery and excised in the same session[5].

Collision tumors of the stomach are uncommon; however, several cases have been reported. Most collision tumors of the stomach are composed of an adenocarcinoma intermixed with a gastric lymphoma[6-9]. Some are composed of an adenocarcinoma intermixed with a carcinoid tumor[8,10,11]. However, gastric collision tumors composed of a GIST and an adenocarcinoma are exceedingly rare. Ruka *et al*[12] found that 10% of their GIST patients had an associated non-GIST neoplasm, usually, a carcinoma. Furthermore, Maiorana *et al*[13] found that of 52 patients with gastric GISTs, six patients (11.5%) had an associated, second gastric tumor (five adenocarcinomas and one carcinoid tumor).

Most of these publications were reports of single cases. Here, we present a series of eight patients with synchronously occurring GISTs and gastric adenocarcinomas. The aim of this study was to evaluate the clinicopathological characteristics of GISTs occurring concomitantly with gastric adenocarcinomas and to provide an English literature review[14,15].

MATERIALS AND METHODS

Patients

We analyzed the clinicopathological findings in eight patients with CD117-immunopositive GISTs (six men and two women) who underwent surgery with a curative intent for a primary, resectable tumor without detectable metastases, between March 2003 and December 2008. Their clinicopathological data were supplemented by a review of all available medical and histopathological records from Xinhua hospital and Ruijin hospital. Selected were the patients with postoperative pathological diagnosis of primary gastric GIST, and patients who didn't received chemotherapy and Imatinib as adjuvant treatment. Excluded were patients who had synchronous gastrointestinal stromal tumors in stomach and extra-stomach neoplasms, patients with initial surgery perfomed in other hospital, and patients with the pathology diagnostic data insufficiency. None of the patients had a family history of gastrointestinal carcinoma or GIST. Prior to the commencement of the present study, our ethics committee deemed that approval of the committee and informed consent were not required for the retrospective analysis of clinical data.

Methods

GISTs were defined as primary spindle cell and/or epithelioid neoplasms of the tubular gastrointestinal tract with CD117 overexpression, with or without CD34 expression according to well-established criteria for the diagnosis of GISTs[16,17]. The risk of aggressive GISTs was assessed using criteria derived from the 2002 Fletcher classification. For each patient with a primary tumor and no metastatic disease at the time of diagnosis, a TGM system[18] was used for staging: T: T1, localized and < 5 cm; T2, localized and ≥ 5 cm; T3, contiguous organ invasion or peritoneal implants; T4, tumor rupture. G: G1, low grade; G2, high grade. M: M0, no metastases; M1, metastases present. The final staging system was determined as follows: Stages Ⅰ (< 5 cm) and Ⅱ (≥ 5 cm) are localized lesions with low histologic grade. Stage Ⅲ lesions are either high-grade tumors of any size or tumors with regional involvement (contiguous organ invasion or peritoneal implants). Stage ⅣA refers to patients with systemic metastases or unresectable tumor. Stage ⅣB is designated when tumor rupture has occurred despite resection of all macroscopic disease. The gastric adenocarcinomas were staged according to the TNM system devised by the International Union Against Cancer[19].

Representative hematoxylin and eosin-stained slides of archival tumor specimens were prepared from formalin-fixed, paraffin-embedded tissue blocks. To confirm the histogenesis of GISTs, immunohistochemistry (IHC) panels were obtained with the following markers: CD117, CD34, smooth muscle actin (SMA) and S-100. The IHC studies were performed using formalin-fixed, paraffin-embedded blocks and primary antibodies to the above markers, on a standard, automated, streptavidin-biotin peroxidase-detection system (EnVision™ Autostainer Visualization System; DakoCytomation, Glostrup, Denmark) equipped with a microwave antigen-retrieval step. Parallel positive controls were run for each antibody. A rabbit or mouse, universal, negative-control monoclonal antibody was used for each specific antibody.

Ethics committee approval

This study was approved by the Bioethics Committees at each hospital.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences, version 11.0 (SPSS Inc., Chicago, IL). Descriptive data are presented as the mean ± SD.

RESULTS

The study consisted of eight patients, including six men (75%) and two women (25%). The median age of the patients at the time of presentation was 68.6 years (range, 47-80 years). The most common presenting features were

Table 1 Size and histological characteristics of gastrointestinal stromal tumors in eight patients

Patient No.	Age (yr)	Sex	Localization	Size (cm)	Growth pattern	Type	Grade	Staging	Surgical resection	Origin
1	47	M	Cardia	2.0	Extraluminal	Spindle	Very low	T1G1M0, Ⅰ	Complete	Subserous
2	80	M	Cardia	1.5	Extraluminal	Spindle	Very low	T1G1M0, Ⅰ	Complete	Subserous
3	60	M	Antrum	0.6	Extraluminal	Spindle	Very low	T1G1M0, Ⅰ	Complete	Subserous
4	67	F	Anterior wall	0.8	Extraluminal	Spindle	Very low	T1G1M0, Ⅰ	Complete	Subserous
5	78	M	Posterior wall	2.5	Extraluminal	Spindle	Low	T1G1M0, Ⅰ	Complete	Submucosal
6	78	M	Body	1.4	Extraluminal	Spindle	Low	T1G1M0, Ⅰ	Complete	Subserous
7	59	F	Anterior wall	0.8	Extraluminal	Spindle	Low	T1G1M0, Ⅰ	Complete	Subserous
8	80	M	Lesser curvature	5.0	Extraluminal	Spindle	Low	T2G1M0, Ⅱ	Complete	Subserous

M: Male; F: Female.

Table 2 Immunohistochemical characteristics of gastrointestinal stromal tumors in eight patients

Patient No.	CD117	CD34	SMA	VIM	S-100	DES
1	+	+	++	+	+	++
2	+	+	+	+	-	+
3	+	+	-	+	-	-
4	+	+	-	+	+	+
5	+	+	-	+	+	-
6	+	+	-	-	±	-
7	+	+	-	-	-	-
8	+	+	-	+	-	-

SMA: Smooth muscle actin; VIM: Vimentin; DES: Desmin.

abdominal discomfort (n = 3), gastrointestinal bleeding (n = 2), difficulty eating (n = 1), nausea and vomiting (n = 1) and weight loss (n = 1). Some patients had more than one of these symptoms. The median duration of disease was 1.5 mo (range, 0.5-6 mo). Total (n = 1) or subtotal gastrectomies (n = 7) were performed in the patients with gastric malignancy.

All patients underwent preoperative gastroscopy, which revealed an ulcerative lesion in four patients, a diffuse infiltrative lesion in two patients and an infiltrative ulcerative lesion in two patients. All lesions were diagnosed as adenocarcinomas on biopsy examination. Body computer tomography (CT) scans and chest images were available for review in all eight patients. In one patient, preoperative CT revealed a soft tissue lesion with a diameter of 5.0 cm in the lesser curvature, this lesion was considered a GIST.

All patients underwent simultaneous, radical resection of the gastric adenocarcinoma and GIST. In most cases, the stromal tumors were an incidental finding during operation. Detailed clinicopathological data for all GISTs are shown in Tables 1 and 2. According to the American Joint Committee on Cancer staging, 87.5% of patients had stage Ⅰ tumors, and 12.5% of patients had stage Ⅱ tumors. The mean GIST size was 1.825 ± 1.4370 cm (range, 0.6-5.0 cm). Seven GISTs were located in the serosal layer, and one was present in the muscular layer. All GISTs were of the spindle type, and were strongly and diffusely positive for CD117 and CD34. Six GISTs were also positive for vimentin (VIM) (75.0%), four for S-100 (50.0%), three for desmin (37.5%) and two for SMA (25.0%).

The synchronous gastric adenocarcinomas were located in different parts of the stomach (Table 3). The mean sizes of the primary adenocarcinomas were 6.000 ± 2.6186 cm (range, 2.0-8.0 cm). No patients had distant metastases at the time of diagnosis. Half of the tumors were poorly differentiated; in the case of the other half, differentiation was not recorded because there is no standard for pathological recording. One of the patients had early gastric cancer, and the other seven had advanced gastric cancers; two patients each had stage Ⅰ and Ⅱ disease, three had stage Ⅲ disease and one had stage Ⅳ disease.

DISCUSSION

The term gastric stromal tumor was originally coined by Mazur *et al*[20]. Most gastric stromal tumors exhibit variable differentiation; these tumors tend to originate from primitive mesenchymal cells[21], rather than from smooth muscle cells. GISTs are rare neoplasms that are most commonly located in the stomach (39%-60%), small bowel (30%-42%), colon-rectum (5%-10%) and esophagus (5%)[22]. The most common symptoms of the patients in the current study were abdominal masses, pain and bleeding[23,24]. The symptoms of these tumors depend on their size and location[24]. GISTs are generally found within the deeper stroma and the submucosa, and therefore, in most of the reported cases of synchronous gastric adenocarcinoma and GIST, the preoperative biopsy specimens have shown only adenocarcinoma. GISTs are often incidentally detected during imaging studies, operation or examination of the resected specimens[25].

In this report, only one case of GIST was detected preoperatively, on a CT scan; the others were found incidentally during or after operation, upon general pathological examination. Owing to the variability and specific characteristics of GISTs, the coexistence of these tumors with other gastric tumors should be considered in the treatment of gastric cancer. To avoid missed diagnosis or misdiagnosis of GISTs, imaging studies such as ultrasonography, CT and magnetic resonance imaging should be performed in patients in whom gastric cancer is detected on gastroscopy. Moreover, surgical exploration in these patients should be careful and comprehensive. If suspi-

Table 3 Clinical characteristics, treatments and outcomes of gastric adenocarcinoma in eight patients

Patient No.	Primary site	Size (cm)	TNM status	Surgical resection	Gross appearance	Histology	Clinical presentation
1	Cardia	8	T3N1M0, ⅢB	Radical operation	Ulcerative infiltrative type	The low differentiation adenocarcinoma	Difficulty in swallowing
2	Antrum	2	T1N0M0, ⅠA	Radical operation	Ulcerative	The low differentiation adenocarcinoma	Haematemesis
3	Antrum	8	T3N0M0, Ⅱ	Radical operation	Ulcerative	Adenocarcinoma	Black stool
4	Antrum	4	T3N1M0, ⅢA	Radical operation	Ulcerative	Adenocarcinoma	Abdominal discomfort
5	Cardia	6	T4N2M0, Ⅳ	Palliative gastrectomy	Ulcerative	Adenocarcinoma	Abdominal discomfort
6	The lesser curvature	10	T3N1M0, ⅢA	Radical operation	Infiltrative type	Tubular adenocarcinoma	Emaciation
7	The posterior wall	4	T2N1M0, Ⅱ	Radical operation	Infiltrative type	The low differentiation adenocarcinoma	Nausea, vomiting
8	Antrum	6	T2N0M0, ⅠB	Radical operation	Uplift ulcer type	The low differentiation adenocarcinoma	Abdominal discomfort

TNM: Tumor, nodes, metastasis-classification.

cious lesions are found, these should not be assumed to be metastases of gastric cancer. Physicians should consider the possibility of other types of tumors, radically resect the suspicious lesion, obtain frozen sections for pathological examination, determine the histological origin of the lesion and apply appropriate surgical techniques. In addition, any nodule on the walls of the digestive tract should be carefully assessed so that no small GIST is overlooked during the postoperative pathological examination.

Liszka *et al*[26] retrospectively analyzed the clinicopathological characteristics of 22 cases of concurrent GISTs and other tumors, including two cases of GISTs accompanied by gastric cancers, and 60 cases of only GISTs. They found that the risk of invasion was much lower and the tumor diameter was smaller in patients with concurrent GISTs and other tumors than in patients with only GISTs ($P < 0.05$), which is consistent with our results. These findings may be attributable to the following factors: the risk of malignant invasion of GISTs is relatively low, and the biological behavior of GISTs might have been inhibited by the gastric cancer. However, definitive evidence for this theory is lacking at present.

The morphology of GIST cells is usually spindle shaped (70%), epithelioid (20%) or mixed. GISTs are immunohistochemically positive for Kit expression (90%-95%) and often for Bcl-2 (80%), CD34 (70%), SMA (35%), S-100 (10%) and desmin (5%) expression. In this study, all the GISTs were strongly and diffusely positive for CD117 and CD34. Six GISTs were also positive for VIM (75.0%), four for S-100 (50.0%), three for desmin (37.5%) and two for SMA (25.0%). Fletcher *et al*[17] proposed a classification for malignancies that was based on tumor size and the number of mitotic divisions. According to this classification, all the tumors in our study were classified as low risk or very low risk; nevertheless, careful follow-up is mandatory.

Collision tumors rarely develop in the stomach. The frequency of secondary malignancies in GIST patients has been reported to be 4.5%-35% in different series[15,27-33]. The most common GIST-associated malignancies were gastrointestinal carcinomas (47%), prostate cancer (9%), lymphoma/leukemia (7%) and breast cancer (7%)[27]. Single case reports have described the occurrence of adenocarcinoma admixed with gastric lymphoma, carcinoid tumor, leiomyosarcoma[13,34-37] or rhabdomyosarcoma[35,36], as well as adenoma admixed with a sarcomatous stromal component[38]. Thus far, only a few case reports of gastric collision tumors consisting of adenocarcinoma and leiomyoma have been documented[39,40]. Rare cases of concurrent presentation of gastric adenocarcinoma and GIST have been reported in the literature[13,15,24,37,41-46]. Maiorana *et al*[13] found that 6 of 52 (11.5%) patients with gastric GISTs had an associated second gastric tumor (five adenocarcinomas and one carcinoid tumor), which considering the restriction of both tumor types to the stomach, indicates a high incidence. In 2000, Maiorana *et al*[13] found that GISTs were the most common non-epithelial tumor that could simultaneously occur with epithelial tumors (carcinomas and carcinoid tumors); they also reported five cases of GIST combined with gastric cancer.

The admixture of gastric epithelial and stromal tumors raises the question of whether such an occurrence is a simple incidental association or whether the two lesions are connected by a causal relationship. Some researchers claim that this simultaneous presentation is coincidental; however, others hypothesize that some unknown carcinogens induce the simultaneous proliferation and oncogenesis of epithelial and stromal cells[13-15,24,41,42,44,45]. Theoretically, genetic mutations could play an important role in the pathogenesis of gastric synchronous tumors; however, no available evidence supports a common genetic mutation underlying gastric adenocarcinoma and GIST[27,47,48]. Another hypothesis suggested in experimental models is that the same unknown carcinogenic agent may interact with two adjacent tissues, causing the simultaneous development of tumors of different histological types[13,41,49-52]. Cohen *et al*[51] reported that exposure to both acetylsalicylic acid and nitrosoguanidine causes synchronous development of both gastric cancer and leiomyosarcoma. An interesting hypothesis is that a single

carcinogenic agent may interact with two neighboring tissues, inducing the development of tumors of different histological types in the same organ[51]. *Helicobacter pylori* has been found to be related to the pathogenesis of gastric carcinoma and mucosa-associated lymphoid tumor[53,54] or GIST[24]. Liu *et al*[42] hypothesized that the stomach was influenced by the same unknown carcinogen, resulting in the simultaneous proliferation of different cell lines (epithelial and stromal cells).

Our study has some limitations: it was retrospective and the number of patients was small. This limited the validity of significant statistical evidence that can be extrapolated from our study. In addition, our study does not answer the question of whether a causal relationship exists between gastric adenocarcinoma and GIST, since we did not perform genetic and molecular ancillary tests. This study, however, highlights an interesting observation of a possible association between gastric adenocarcinoma and GIST that should encourage further statistically validated and genetically based studies.

In conclusion, the synchronous occurrence of GISTs and other gastrointestinal malignancies is more common than it has been considered. The concomitant GIST is usually discovered incidentally during endoscopy, imaging study or operation performed because of the other malignancy. We have reported eight cases of GIST combined with gastric cancer. All the GISTs were positive for CD117 and CD34. The cause of the association between GISTs and adenocarcinoma is difficult to determine. In the majority of cases, this association is most likely coincidental. Surgical excision is the mainstay of therapy, and further research is required for explaining this simultaneous tumor development.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors of the digestive tract and have various clinical and biological characteristics. The expression of c-Kit distinguishes GISTs from true leiomyomas, leiomyosarcomas and other mesenchymal tumors of the gastrointestinal tract.

Research frontiers

GISTs are generally found within the deeper stroma and the submucosa, and therefore, in most of the reported cases of synchronous gastric adenocarcinoma and GIST, the preoperative biopsy specimens have shown only adenocarcinoma. GISTs are often incidentally detected during imaging studies, operation or examination of the resected specimens.

Innovations and breakthroughs

The authors hypothesized that the stomach was influenced by the same unknown carcinogen, resulting in a simultaneous proliferation of different cell lines (epithelial and stromal cell).

Applications

In the majority of cases, this association is most likely coincidental. Surgical excision is the mainstay of therapy, and further research is required for explaining this simultaneous tumor development.

Peer review

Synchronous gastric adenocarcinoma and GIST were not common but can be found sometimes in practice. Usually, intraoperatively serendipitous GISTs are of very low risk and with their max diameters less than 1 cm. Carefully preoperative imaging evaluation might be helpful to find the > 1 cm GIST. This topic is interesting and lack of relevant literatures, especially the data of the epidemiological incidence. If possible, the author should report the data of its proportion in the consecutive series.

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