

Clinical presentations of gastric small gastrointestinal stromal tumors mimics functional dyspepsia symptoms

Qing-Xiang Yu, Zhan-Kun He, Jiang Wang, Chao Sun, Wei Zhao, Bang-Mao Wang

Qing-Xiang Yu, Zhan-Kun He, Jiang Wang, Chao Sun, Wei Zhao, Bang-Mao Wang, Department of Gastroenterology, Tianjin Medical University General Hospital, Tianjin 300052, China
Author contributions: Yu QX designed the study and wrote the manuscript; Yu QX, He ZK, Wang J and Sun C collected clinical data and the questionnaire; Yu QX and Zhao W performed data analysis; and Wang BM reviewed and revised the manuscript.
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Correspondence to: Bang-Mao Wang, Professor, Department of Gastroenterology, Tianjin Medical University General Hospital, No 154, Anshan Road, Heping District, Tianjin 300052, China. bmwang0926@gmail.com
Telephone: +86-22-60363800 Fax: +86-22-27813550
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Abstract

AIM: To explore whether clinical presentations of gastric small gastrointestinal tumors (GISTs) mimics gastrointestinal dyspepsia symptoms.

METHODS: The endosonographic data of 167 patients who underwent endoscopic submucosal dissection at the Tianjin Medical University General Hospital, China between 2009 and 2011 were analyzed. GISTs and leiomyomas had a similar intragastric distribution and similar locations within the gastric wall. Therefore, patients with GISTs were chosen as the study group and those with leiomyomas were chosen as the control group. Dyspepsia symptom questionnaires were used to investigate and compare the gastrointestinal symptoms of patients with GISTs and those with gastric leiomyomas before and after endoscopic submucosal dissection (ESD). The questionnaires evaluated symptoms such as epigastric pain, heartburn, regurgitation, epigastric discomfort, nausea and vomiting, abdominal bloating, and eructation. Symptoms were assessed using a four-point scoring scale.

RESULTS: GISTs were the most common gastric submucosal lesion (67 cases, 40.12%), followed by leiomyomas (38 cases, 22.75%). Both groups were similar in terms of gender distribution ($P = 0.49$), intragastric location ($P = 0.525$), and originating layer within the gastric wall ($P = 0.449$), but leiomyomas were more commonly found in the proximal fundus ($P < 0.05$). Overall, 94.2% of the patients with small GISTs and 93.5% of those with gastric leiomyomas experienced some dyspepsia; however, total symptom scores were significantly lower in the GIST group than in the leiomyoma group (1.34 ± 1.27 vs 2.20 ± 1.70 , $P < 0.05$). Each component of the symptom score demonstrated a statistically significant improvement in the GIST patients after ESD ($P < 0.05$), including epigastric pain (0.80 ± 0.90 vs 0.13 ± 0.46), heartburn (0.63 ± 1.08 vs 0.13 ± 0.41), regurgitation (0.55 ± 0.87 vs 0.22 ± 0.57), epigastric discomfort (0.70 ± 0.98 vs 0.32 ± 0.47), nausea and vomiting (0.27 ± 0.62 vs 0.05 ± 0.21), abdominal bloating (0.70 ± 0.90 vs 0.27 ± 0.49), and eructation (0.36 ± 0.61 vs 0.21 ± 0.46). For leiomyoma patients, symptoms such as heartburn, nausea, vomiting, and eructation improved after treatment; however, these improvements were not statistically significant ($P > 0.05$). Thus, the pathophysiology of dyspepsia symptoms may be different between the two groups.

CONCLUSION: Symptoms of gastric small GISTs may mimic those of functional dyspepsia. An alternative diagnosis should be considered in patients with functional dyspepsia and treatment failure.

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Key words: Gastric small gastrointestinal stromal tumor; Gastric leiomyoma; Clinical presentation; Endoscopic ultrasonography

Core tip: We compared the clinical presentations and endosonographic characteristics of gastric small gas-

gastrointestinal stromal tumors (GISTs) and gastric leiomyomas. Specifically, we compared the change in the clinical presentations of these two groups before and after endoscopic submucosal dissection. We found that the symptoms of small GISTs may mimic those of functional dyspepsia, and that small gastric GISTs may produce more severe symptoms than gastric leiomyomas due to the different histological origins. This study is novel as there has been no report regarding the clinical symptoms of dyspepsia caused by small gastric GISTs.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract^[1], with an annual incidence of 12.7-14.5 cases per million^[2,3]. GISTs occur throughout the gastrointestinal tract, but they are preferentially located in the stomach (60%-70%). Recently, micro-GISTs [also called GIST tumorlets and interstitial cell of Cajal (ICC) hyperplasia, ≤ 1 cm in size] have been found in 9.1%-35% of stomachs that are thoroughly examined after surgical removal or at the time of autopsy^[4-7]. Therefore, the incidence of gastric micro-GISTs is higher than that of gastric clinical GISTs.

It is widely accepted that GISTs originate from the ICCs^[8] or mesenchymal stem cells that can differentiate into ICCs^[9]. ICCs are specialized cells in the gastrointestinal tract that generate the rhythmic electrical and contractile activity that exists from the stomach to the rectum, and mediate enteric motor neurotransmission^[10]. ICCs are essential for gut peristalsis.

The symptoms of GISTs are variable and depend on the size, site, relationship with the gastrointestinal wall, and malignancy^[11,12]. When tumors grow to a certain size, gastrointestinal bleeding may result from ulceration of the mucosal surface or abdominal pain may arise from the compression of surrounding tissues or organs. However, small tumors may be asymptomatic or only present with nonspecific gastrointestinal symptoms^[12]. It has been reported that a 62-year-old female patient was diagnosed and unsuccessfully treated for irritable bowel syndrome (IBS) for 11 years and was eventually found to have an obstructing small-bowel GIST. After operation, all of her persistent gastrointestinal symptoms including abdominal pain, nausea, bloating and constipation disappeared^[13]. The case suggested that GISTs that conserve the function of ICCs could alter the motility of the gastrointestinal tract, especially when the tumor is sufficiently small. The symptoms may mimic those of functional gastro-

intestinal disorders. However, there has been no report regarding the clinical symptoms of dyspepsia caused by small gastric GISTs.

This study was designed to assess the change in symptoms before and after endoscopic submucosal dissection (ESD) among gastric small GIST patients using a dyspepsia symptom questionnaire, and to explore whether some dyspepsia symptoms would be associated with gastric small GISTs - the neoplastic transformation of ICCs.

GISTs are one type of submucosal lesions, which arise from tissue under the epithelial layer and include leiomyomas, lipomas, and ectopic pancreas. Various submucosal lesions have different site characteristics, layer of origin, and appearance under endoscopic ultrasound (EUS). Thus, the endosonographic features of gastric submucosal lesions were investigated for choosing the appropriate control group, to explore whether other submucosal lesions would cause some dyspepsia symptoms.

MATERIALS AND METHODS

Diagnosis

A total of 167 patients with a diagnosis of gastric submucosal lesions underwent ESD at the Endoscopy Center of Tianjin Medical University General Hospital between September 2009 and December 2011. Prior to ESD, all the patients underwent EUS to determine tumor location within the gastric wall, size and morphology, sonographic characteristics, and tumor margins. After ESD, all tumor specimens were examined by two experienced pathologists. Immunohistochemical analyses for CD117, CD34, smooth muscle actin, desmin, S-100 and DOG-1 were performed to determine the pathological diagnosis. GIST diagnosis met the criteria of the 2008 Chinese Consensus on the Diagnosis and Treatment of GIST^[14]. The risk stratification of the GIST cases followed the 2008 National Institutes of Health (NIH) Consensus Classification System^[15]. All patients voluntarily gave signed informed consent before ESD, and the study was approved by the Medical Review Ethics Committee of Tianjin Medical University.

The pathological diagnoses of the gastric submucosal lesions and their location in the stomach are shown in Table 1. GISTs were the most common gastric submucosal lesion (67 cases, 40.12%), followed by leiomyomas (38 cases, 22.75%). GISTs and leiomyomas had a similar intragastric distribution and similar locations within the gastric wall, as shown in Table 1. Therefore, patients with GISTs were chosen as the study group, and the patients with leiomyomas were chosen as the control group.

Study of gastrointestinal symptoms

Prior to ESD, a symptom questionnaire was obtained from each patient, who had undergone EUS with a diagnosis of gastric submucosal lesions at our endoscopy center between September 2009 and December 2011. The symptom questionnaire was completed by well-trained physicians in face-to-face interviews. Another symptom questionnaire was obtained from the patients

Table 1 Pathological diagnoses of gastric submucosal lesions and their location

	Gastric fundus			Gastric body			Gastric antrum		
	Muscularis mucosae	Submucosa	Muscularis	Muscularis mucosae	Submucosa	Muscularis	Muscularis mucosae	Submucosa	Muscularis
GIST (<i>n</i> = 67)			46			16	1		4
Leiomyoma (<i>n</i> = 38)			30			6			2
Neurilemmoma (<i>n</i> = 1)									1
Ectopic pancreas (<i>n</i> = 30)					1	2	8	13	6
Lipoma (<i>n</i> = 8)					3			5	
Carcinoid (<i>n</i> = 4)						1	1		2
Inflammatory fibrous polyps (<i>n</i> = 9)							1	8	
Others (<i>n</i> = 10) ¹						1	1	4	
Total	0	2	76	0	4	26	12	30	15

¹Other lesions include vascular malformation, myoepithelial hamartoma, tuberculosis, lymphoma, and gastritis cystic profunda. GIST: Gastrointestinal tumor.

Table 2 Patient baseline features and endosonographic characteristics

	Leiomyoma (<i>n</i> = 38)	GIST (<i>n</i> = 67)	<i>P</i> value
Gender			
Male	15	30	0.597
Female	23	37	
Age (yr, mean ± SD)	51.73 ± 11.16	58.83 ± 8.52	0.001 ^b
Tumor size (cm)			
Median	1.00 ± 0.44	1.22 ± 0.22	0.057
Range	0.6-2.5	0.4-3	
Intra-gastric location			
Gastric antrum	2	5	0.525
Gastric body	6	16	
Gastric fundus	30	46	
Distribution in the gastric fundus			
Proximal to cardia	24	14	< 0.001 ^d
Distal to cardia	6	32	
Site within gastric wall			
Muscularis mucosae	0	1	0.449
Muscularis propria	38	66	
Sonographic characteristics			
Homogenous	36	50	0.010 ^d
Heterogenous with hyperechogenic spots	2	17	
Echogenicity in comparison with the surrounding muscle echo			
Isoechoic	38	54	0.004 ^b
Hyperechoic	0	13	
Margin of the tumor			
Regular	37	61	0.212
Irregular	1	6	

^b*P* < 0.01, ^d*P* < 0.001, leiomyoma group *vs* GIST group. GIST: Gastrointestinal tumor.

by a physician who was blinded to the pathological diagnosis 6-12 mo after ESD. Endoscopy was repeated for each patient to determine whether tumor residue or recurrence could be observed at the same time.

As mentioned above, the symptom questionnaires of the patients with GISTs and leiomyomas were investigated. During follow-up, 10 cases were excluded from the GIST group, and three from the leiomyoma group because of accompanying gastric polyps, peptic ulcers, cholecystitis, and myelocytic leukemia. Five GIST and

four leiomyoma patients were lost to follow-up. After exclusion, 52 patients remained in the GIST group (24 males; age range: 30-78 years; median: 60 years). In the leiomyoma group, 31 patients were included (14 males; age range: 27-70 years; median: 53 years).

Questionnaires

The questionnaires were the Gastrointestinal Symptom Rating Scale^[16] and Dyspepsia Symptom Rating Scale^[17], which evaluate symptoms such as epigastric pain, heartburn, regurgitation, epigastric discomfort, nausea and vomiting, abdominal bloating, and eructation. Symptoms were assessed using a four-point scoring scale, ranging from 0-3 points based on severity with a total score of 0-21 points.

Statistical analysis

The differences in gender and EUS findings between leiomyomas and GISTs were determined. The distribution of gastrointestinal symptoms and the number of patients who recovered completely or remained unchanged were analyzed using the χ^2 test or Fisher's exact test (*n* < 40 or *t* < 1), and the patient age and tumor size were assessed using the independent *t* test. An independent *t* test or Mann-Whitney *U* test was performed to compare the gastrointestinal symptom scores between the GIST and leiomyoma groups. The paired *t* test or Wilcoxon signed-rank test was used to compare the gastrointestinal symptom scores before and after ESD in each group. Statistical analyses were performed using SPSS for Windows version 13.0 (SPSS, Chicago, IL, United States). A *P*-value < 0.05 was considered statistically significant.

RESULTS

EUS characteristics of gastric small GISTs

Patient and EUS characteristics of the two groups are described in Table 2. In this study, the sizes of all GISTs were < 3 cm, classifying them as gastric small GISTs. The average age in the leiomyoma group was lower than that in the GIST group (*P* < 0.05). Both groups were similar in terms of gender distribution (*P* = 0.49),

Table 3 Comparison of total gastrointestinal symptom scores of gastrointestinal tumors and leiomyomas before and after endoscopic submucosal dissection

	<i>n</i>	Pre-ESD	Post-ESD	<i>P</i> value
GIST	52	4.02 ± 2.54	1.34 ± 1.27	< 0.01
Leiomyoma	31	4.40 ± 2.81	2.20 ± 1.70	< 0.01
<i>P</i> value		0.57	0.043	

ESD: Endoscopic submucosal dissection.

intra-gastric location ($P = 0.525$), and originating layer within the gastric wall ($P = 0.449$). The most common site for these two tumors was the muscularis propria in the gastric fundus. As the gastric fundus is divided into proximal fundus to cardia and distal fundus based on the lowest point of the gastric fundus observed through retroflexing the tip of the scope, we found that leiomyomas were more common in the proximal fundus ($P < 0.05$). Leiomyomas tended to be smaller than GISTs ($P = 0.057$). Both groups appeared as spherical, semi-spherical or nodular lesions under gastroscopy. Endosonographic characteristics of leiomyomas showed homogenous hypoechoic masses and appeared as round or oval lesions with well-defined margins. However, GISTs showed heterogeneous hypoechoic masses with defined margins and hyperechoic patches ($P < 0.05$), which had higher echogenicity than the muscularis propria ($P < 0.05$).

Risk stratification of GISTs

The tumor diameters of the 67 GISTs ranged from 0.4 cm to 3 cm with an average of 1.22 ± 0.22 cm: 26 cases were ≤ 1 cm, 30 were 1-2 cm, and 11 were 2-3 cm. Postoperative histopathological results showed that all 67 GISTs were of the spindle cell type, which were occasionally accompanied by fibrosis or hyalinosis. Immunohistochemical analyses revealed that 87% were CD117 positive, 44% were CD34 positive, and 100% DOG-1 positive with mitotic counts ranging from 0 to 3 per 50 high-power fields. Based on the malignancy potential classification of GISTs, 56 cases were at very low risk and 11 were at low risk. None of these patients were given targeted drug therapy. At the end of the follow-up (6-12 mo after ESD), no tumor residue or recurrence was observed.

Comparison of total gastrointestinal symptom scores

As shown in Table 3, both total symptom scores decreased significantly after ESD ($P < 0.01$). The changes suggested that the symptoms of both groups were relieved by the procedure.

Before treatment, total symptom scores were similar in both groups ($P > 0.05$). After treatment, total symptom scores were significantly lower in the GIST group than in the leiomyoma group ($P < 0.05$), indicating that symptomatic relief by ESD was significantly greater for the GIST patients.

Gastrointestinal symptom distribution of both groups before and after ESD

Before treatment, the most common symptom of GIST patients was epigastric pain, followed by bloating and discomfort, regurgitation, heartburn, eructation, nausea, and vomiting. The duration of symptoms ranged from 1 mo to 6 years. Three (5.8%) patients were incidentally found during routine physical examinations and one was admitted for upper gastrointestinal bleeding. The most common symptom of leiomyoma patients was discomfort, followed by bloating, epigastric pain, eructation, regurgitation, heartburn, nausea, and vomiting. The duration was from 2 wk to 20 years. Two (6.5%) patients were incidentally found during routine physical examinations. Before treatment, leiomyoma patients more often had epigastric discomfort ($P = 0.021$).

After treatment, symptoms of 13 (25%) GIST patients disappeared completely. However, two (3.8%) of 52 patients with no change in total symptom scores presented with discomfort, bloating, and eructation. Five (16.1%) leiomyoma patients had complete relief of their symptoms, but there were five (16.1%) patients with unchanged total symptom scores who had discomfort and regurgitation. There were no significant differences in symptom distribution between the groups ($P > 0.05$) (Tables 4 and 5).

Comparison of symptom scores between GIST and leiomyoma patients before and after ESD

Comparison of each component of the symptom scores between GISTs and leiomyomas before and after ESD revealed no difference ($P > 0.05$) (Table 6). Each component of the symptom score demonstrated a statistically significant improvement in the GIST patients after ESD ($P < 0.05$). For leiomyoma patients, symptoms such as heartburn, nausea, vomiting, and eructation improved after treatment; however, these improvements were not statistically significant ($P > 0.05$), while other symptoms were significantly improved ($P < 0.05$).

DISCUSSION

The clinical presentations of GISTs are variable, ranging from asymptomatic to abdominal discomfort, early satiety, bloating, abdominal pain, gastrointestinal bleeding, and abdominal masses^[18]. The symptoms of GISTs correlated with tumor size, site, relationship with the gastrointestinal wall, and malignancy^[11,12]. Previous reports have revealed that 70% of the GIST patients presented with different levels of clinical symptoms; 20% were asymptomatic and were found incidentally during routine physical examinations or other surgeries; and 10% were found during autopsy^[3]. However, small tumors are usually asymptomatic or only present with nonspecific digestive symptoms^[12]. Huang *et al*^[19] reported that 55.7% (59/106 cases) of the symptomatic gastric GIST patients presented with dyspepsia. Besides the case mentioned above, a female patient with refractory gastroesophageal

Table 4 Symptom distribution of gastrointestinal tumor and leiomyoma patients before and after endoscopic submucosal dissection

		Epigastric pain	Heartburn	Regurgitation	Discomfort	Nausea and vomiting	Bloating	Eructation
GIST <i>n</i> = 52	Pre- ESD	50% (26/52)	28.8% (15/52)	34.6% (18/52)	38.5% (20/52)	19.2% (10/52)	44.2% (23/52)	28.8% (15/52)
	Post- ESD	9.6% ^a (5/52)	11.5% ^a (6/52)	17.3% ^a (9/52)	26.9% (14/52)	3.8% ^a (2/52)	19.2% ^a (10/52)	17.3% (9/52)
Leiomyoma <i>n</i> = 31	Pre- ESD	38.7% (12/31)	32.2% (10/31)	32.2% (10/31)	64.5% ^c (20/31)	16.1% (5/31)	45.1% (17/31)	35.5% (11/31)
	Post- ESD	16.1% (5/31)	25.8% (8/31)	25.8% (8/31)	41.9% (13/31)	6.4% (2/31)	19.4% ^a (6/31)	16.1% (5/31)

^a*P* < 0.05 vs the same group before treatment; ^c*P* < 0.05 vs GIST group. GIST: Gastrointestinal tumor; ESD: Endoscopic submucosal dissection.

Table 5 Comparison between complete symptom resolution and unchanged health status after endoscopic submucosal dissection

	<i>n</i>	Resolved completely	Unchanged
GIST	52	13	2
Leiomyoma	31	5	5
<i>P</i> value		0.5	0.124

GIST: Gastrointestinal tumor.

reflux disease (GERD) was reported to have a small GIST (1.4 cm × 1 cm) in the gastric fundus 6 years after GERD diagnosis. Her symptoms of regurgitation and heartburn resolved after laparoscopic surgery. O’Riain *et al*^[20] described a familial GIST patient with recurrent small intestinal diverticulosis with perforation, and the authors assumed that diffuse and nodular ICC hyperplasia led to abnormal small intestinal motility, which caused decreased small intestinal peristalsis associated with small intestinal diverticulosis and perforation. These cases suggest that small GISTs may alter normal gut motility, resulting in gastrointestinal symptoms. However, there are no reports regarding the clinical symptoms of dyspepsia caused by small gastric GISTs.

Currently, it is believed that submucosal lesions are asymptomatic or produce nonspecific symptoms^[21]. However, based on the data from our gastrointestinal center, most patients with submucosal lesions underwent gastroscopic examinations due to epigastric bloating, epigastric pain, regurgitation, and heartburn. Most of them were not found to have any associated gastrointestinal diseases or other diseases; therefore, the correlation between submucosal lesions and symptoms still needs to be clarified. The mechanisms underlying the symptoms are complex. The common mechanism for the symptoms of submucosal lesions may involve abnormal gastric wall distention because of the space-occupying lesion and compression of the superficial mucosa. However, different submucosal lesions may have different mechanisms for the vague and nonspecific symptoms due to their different histological origins. For example, patients with ectopic pancreatic tissue complain of abdominal pain, bloating, nausea, and vomiting. The mechanism underlying these symptoms is thought to be related to the digestive enzymes and vasoactive substances produced by the ectopic pancreas, or epigastric pain or gastrointestinal spasms resulting from

the inflammation associated with gland duct obstruction of the ectopic pancreas^[22].

According to the results of our study, GISTs are the most common gastric submucosal lesion, followed by leiomyomas. They are similar in size, morphology and site of origin, and are found in similar locations within the gastric wall. However, heterogeneous hypoechoic masses with hyperechoic patches, and higher echogenicity than muscularis propria are helpful for identifying gastric small GISTs. In the gastric fundus, leiomyomas are closer to the cardia, while GISTs are mainly located in the greater curvature of the fundus. The reason for this distribution is unclear. It may be related to the density of ICCs reported in the prior study^[23].

Recently, the endoscopic removal of small GISTs by ESD has become technically feasible^[24-26]. ESD is the most minimally invasive treatment for tumors arising from the muscularis propria; therefore, it has also the smallest effect on symptoms.

In this study, the fact that only 5.8% of GIST patients and 6.5% of leiomyoma patients were found incidentally during routine physical examinations suggests that most of these patients presented with gastrointestinal symptoms. Total symptom scores of both groups decreased significantly after ESD, suggesting that the symptoms were probably caused by the submucosal lesions. After ESD, total symptom scores were significantly lower in the GIST group than in the leiomyoma group, and each component of the symptom score demonstrated a statistically significant improvement in the GIST patients after ESD (*P* < 0.05), including epigastric pain, heartburn, regurgitation, epigastric discomfort, nausea and vomiting, abdominal bloating, and eructation. For leiomyoma patients, symptoms such as heartburn, nausea, vomiting, and eructation improved after treatment; however, these improvements were not statistically significant (*P* > 0.05). These data suggest that GISTs may have more impact on the symptoms.

GISTs are thought to originate from ICCs or their precursors because they share similarities such as cellular ultrastructure^[27]. High levels of CD117, CD34, protein kinase C θ , and nestin are expressed in both GISTs and ICC cells^[8,28-30]. Diffuse ICC hyperplasia has been described with c-kit mutation, and is associated with the development of multiple GISTs^[31,32]. In addition, some expressed genes of GISTs are related to the electrophysiological activity of ICCs, such as the potassium ion channel gene *KCNK3*, *KCNK2*^[33], and the calcium-activated

Table 6 Comparison of symptom scores between gastrointestinal tumors and leiomyomas before and after endoscopic submucosal dissection

		Epigastric pain	Heartburn	Regurgitation	Discomfort	Nausea and vomiting	Bloating	Eructation
GIST <i>n</i> = 52	Pre ESD	0.80 ± 0.90	0.63 ± 1.08	0.55 ± 0.87	0.70 ± 0.98	0.27 ± 0.62	0.70 ± 0.90	0.36 ± 0.61
	Post ESD	0.13 ± 0.46 ^a	0.13 ± 0.41 ^a	0.22 ± 0.57 ^a	0.32 ± 0.47 ^a	0.05 ± 0.21 ^a	0.27 ± 0.49 ^a	0.21 ± 0.46 ^a
Leiomyoma <i>n</i> = 31	Pre ESD	0.64 ± 0.86	0.60 ± 0.82	0.60 ± 0.82	1.00 ± 0.82	0.20 ± 0.50	1.00 ± 0.82	0.56 ± 0.92
	Post ESD	0.24 ± 0.52 ^a	0.32 ± 0.56	0.32 ± 0.56 ^a	0.52 ± 0.65 ^a	0.08 ± 0.28	0.40 ± 0.64 ^a	0.32 ± 0.69

^a*P* < 0.05 vs before treatment. ESD: Endoscopic submucosal dissection.

chloride channel gene *DOG-1*^[34-36]. Furuzono *et al*^[37] have found that malignant GIST cells preserve several, but not all, ionic mechanisms underlying pacemaker activity in ICCs. However, leiomyomas originate from smooth muscle cells. Based on these data, we suggest that GISTs, especially small GISTs, likely retain partial biological features of ICCs and somehow induce or aggravate abnormal gastrointestinal electric activity, resulting in gastrointestinal dyspepsia symptoms. This mechanism differs from that of leiomyomas.

In addition, the symptoms of only 25% of GIST patients and 16% of leiomyoma patients completely resolved after ESD. The incomplete resolution of symptoms for the other patients suggests that the mechanism for the gastrointestinal symptoms is complicated and may relate to the formation of postoperative scar, visceral hypersensitivity, and psychological factors.

The symptoms of small gastric GISTs may mimic those of functional dyspepsia. Small gastric GISTs may have more impact on symptoms than gastric leiomyomas, due to their different histological origins. The incidence of gastric micro-GISTs is higher than that of gastric clinical GISTs. We suggest that some symptoms in patients with functional dyspepsia are the result of functional alteration of gut peristalsis due to the increased number of ICCs in a slow-growing GIST, even when the tumor is small and difficult to detect by routine investigations. Thus, an alternative diagnosis should be considered when treating patients with functional dyspepsia who fail to respond for a prolonged period. However, multicenter studies with a larger cohort of patients, and more research about gastric myoelectrical activity and the physiology of gut motility related to GISTs are needed.

COMMENTS

Background

Gastrointestinal stromal tumors (GISTs) are among the most common mesenchymal tumors of the gastrointestinal tract, and are thought to originate from the interstitial cells of Cajal (ICCs). These cells are involved in the regulation of gastrointestinal motility, and the ionic mechanism underlying their pacemaker activity is preserved by GISTs. Therefore, these tumors, particularly when small, may preserve the biological functions of these cells, thereby disturbing the normal gastric myoelectrical activity and resulting in dyspepsia symptoms. The aim of the present study was to explore whether gastric small GISTs - the neoplastic transformation of the ICCs - result in gastrointestinal dyspepsia symptoms.

Research frontiers

GISTs are thought to originate from ICCs or their precursors because they share similarities such as cellular ultrastructure. Some expressed genes of

GISTs are related to the electrophysiological activity of ICCs. Furuzono *et al* have found that malignant GIST cells preserve several, but not all, ionic mechanisms underlying pacemaker activity in ICC.

Innovations and breakthroughs

Several case reports have suggested that GISTs which may conserve the function of ICCs could alter the motility of the gastrointestinal tract, especially when the tumor is sufficiently small. The symptoms may mimic those of functional gastrointestinal disorders. However, there are no reports regarding the clinical symptoms of dyspepsia caused by small gastric GISTs.

Applications

The symptoms of some small gastric GISTs may mimic those of functional dyspepsia. The incidence of gastric micro-GISTs is higher than that of gastric clinical GISTs. The authors suggested that some functional dyspepsia symptoms result from functional alteration of gut peristalsis due to the increased number of ICCs in a slow-growing GIST, even when the tumor is significantly small and thus difficult to detect by routine investigation. Therefore, an alternative diagnosis should be considered when treating patients with functional dyspepsia who fail to respond for a prolonged period.

Terminology

GISTs are mesenchymal tumors derived from the ICCs. The incidence of GISTs is 10-20 cases per million and the stomach is the most common location (60%-70%). ICCs are specialized cells in the gastrointestinal tract that generate the rhythmic electrical and contractile activity that exists from the stomach to the rectum, and mediate enteric motor neurotransmission.

Peer review

The manuscript submitted by Yu *et al* addresses an important topic related to GISTs and the symptom severity following removal of the tumor. In general, the manuscript is well written. There are some minor sentence structure issues that should be resolved by the authors when reading through the manuscript. The statistics are sound and the overall methods section is well written.

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