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Original Article

The value and misdiagnosis analysis of endoscopic ultrasonography in diagnosing subepithelial lesions of the upper digestive tract

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Abstract: Aim: To evaluate the value of endoscopic ultrasonography (EUS) in diagnosing subepithelial lesions of the upper digestive tract and to investigate reasons for misdiagnosis. Methods: A total of 1364 cases with subepithelial lesions of the upper digestive tract examined by EUS were included in this retrospective study. Diagnoses by EUS were compared with those by pathological examination through endoscopic biopsy, endoscopic resection, or surgery. We further selected misdiagnosed cases and investigated the reasons for the misdiagnosis. Results: Diagnoses of 106 cases by EUS were consistent with those by pathological examination. Otherwise, 35 cases did not agree with the pathology. The diagnostic accuracy using EUS for subepithelial lesions in the upper digestive tract was up to 75.18% (106/141), which was far superior to that of gastroscopy (33.33%, 47/141, $P < 0.01$). A tumor originating from the muscular layer with a heterogeneous echo pattern is seen more frequently in stromal tumors than in leiomyomas ($P < 0.01$). Besides excluding a malignant gastric stromal tumor, the possibility of gastric heterotopic pancreas should be considered if a protuberant lesion originating from the muscular layer is detected in the gastric antrum, especially in the greater curvature, with a heterogeneous echo pattern, irregular shape, and unclear border. Conclusion: EUS is a valuable tool for the diagnosis of upper gastrointestinal subepithelial lesions. However, it is still limited for the differential diagnosis among leiomyomas, stromal tumors, and schwannomas. In addition, it can be difficult to differentiate gastric stromal tumors from atypical gastric heterotopic pancreas.

Keywords: Endoscopic ultrasonography, gastric heterotopic pancreas, leiomyoma, misdiagnosis, stromal tumor

Introduction

The term subepithelial lesion is applied to a mass or bulge covered by normal-appearing mucosa identified during a standard endoscopy and is usually found incidentally during gastrointestinal (GI) endoscopy. It is inappropriate that some authors call these subepithelial lesions submucosal tumors (SMTs), because many of them do not originate from the submucosa and are not tumors [1-4]. Thus, subepithelial is a more appropriate term than submucosal even though submucosal tumor is still recognized and used widely.

GI endoscopy is an important diagnostic and therapeutic tool for patients with mucosal diseases in the digestive tract. Some protuberant lesions, such as polyps, can be precisely diagnosed by endoscopy with superficial mucosal biopsies. However, endoscopic biopsy cannot always ascertain the diagnosis because the lesion can be out of the reach of standard biopsy forceps [5, 6]. The etiology of most subepithelial lesions of the GI tract cannot be determined by endoscopy [7]. In recent years, great progress has been made in diagnosing subepithelial lesions of the upper digestive tract using endoscopic ultrasound (EUS). EUS has distinct advantages for examining subepithelial lesions of the upper digestive tract which include reliably characterizing the nature, size, and layer of origin of lesions, and accurately differentiating extramural from intramural, leading to a diagnosis [8]. EUS is useful in the evaluation of extraluminal organs that compress the GI tract lumen and is 100% accurate for the differential diagnosis, proving superior to transabdominal

Table 1. Disease spectrum of 1364 subepithelial lesions in the upper digestive tract

EUS diagnosis	Esophagus (n)	Gastric (n)	Duodenum (n)	Total (n)
Leiomyoma	486	32	7	525
Stromal tumor	82	358	41	481
Extrinsic compression	37	79	8	124
Heterotopic pancreas	0	67	4	71
Cyst	16	10	31	57
Varix	25	12	3	40
Lipoma	6	19	5	30
Lymphoma	0	19	1	20
Leiomyosarcoma	7	0	0	7
Fibroma	0	6	1	7
Hamartoma	1	1	0	2

ultrasound or CT scans [9]. Though EUS is the most sensitive imaging procedure for the characterization and diagnosis of subepithelial tumors, especially small ones [8, 10-13], it is limited in qualitative diagnosis. For example, some subepithelial lesions were misdiagnosed with EUS including some patients with an esophageal stromal tumor that was misdiagnosed as an esophageal leiomyoma, and some patients with a gastric leiomyoma that was misdiagnosed as a gastric stromal tumor.

Therefore, the present retrospective study aims to investigate the causes of misdiagnosis and to share our experiences with other endosonographers to help improve diagnostic accuracy. Beyond that, we also evaluate the value of EUS in diagnosing subepithelial lesions of the upper digestive tract.

Patients and methods

Patients

A Total of 1364 cases of subepithelial lesions in the upper digestive tract were examined by EUS in the First Affiliated Hospital of Wenzhou Medical College from May 2005 to February 2017. There were 756 men and 608 women, with a mean age of 54.8 years (range, 6-93 years). Of all cases, 106 cases with a pathological examination were obtained.

Methods

EUS was performed by 2 experienced endosonographers who were blinded to the final diagnosis. A two-channel endoscope (GF-UM2000; Olympus, Tokyo, Japan) and a 12 MHz probe (GF-UM 2R, Olympus, Tokyo, Japan) were used for the ultrasonographic study. The patients were placed in the left lateral position and sedation (mostly with a benzodiazepine) was usually administered. Scanning of the subepithelial lesion was performed after filling the upper digestive tract with 100-500 ml of de-aerated water. A diagnosis was made according to the layer of origin, nature, internal echo pattern, and border of the lesion.

Diagnoses by EUS were compared with those by pathological examination through endoscopic biopsy, endoscopic resection, or surgery. Furthermore, we retrospectively analyzed the EUS image features of the majority of misdiagnosed cases and investigated the reasons for the misdiagnosis.

Statistical analyses

The difference in the accuracy of diagnosis between gastroscopy and EUS was assessed using the χ^2 test or Fisher's exact test, and the difference in the EUS findings between leiomyomas and stromal tumors was assessed using the χ^2 test or Fisher's exact test. $P < 0.05$ was considered to be statistically significant.

Results

Disease spectrum of subepithelial lesions in the upper digestive tract

Of the 1364 patients recruited in this study who were examined by EUS, 525 (38.49%) patients had leiomyomas, 481 (35.26%) had stromal tumors, 124 (9.09%) had extrinsic compressions, 71 (5.21%) had heterotopic pancreas, 57 (4.18%) had cysts, 40 (2.93%) had varices, 30 (2.20%) had lipomas, 20 (1.47%) had lymphomas, 7 (0.51%) had sarcomas, 7 (0.51%) had fibromas, and 2 (0.15%) had hamartomas. The disease spectrum of protuberant lesions in the upper digestive tract is shown in **Table 1**.

Misdiagnosed cases

Diagnoses of 106 cases by EUS were consistent with those by pathological examination.

Table 2. EUS image features of 106 cases of EUS diagnosis agree with the pathology

Pathological Results	Esophagus (n)	Gastric (n)	Duodenum (n)	EUS findings
Leiomyoma	31	1	0	Within muscularis, hypoechoic, homogeneous, well-demarcated
Stromal tumor	2	41	2	Within muscularis, hypoechoic, 14 patients of inhomogeneous, 3 patients of unclear border
Lipoma	2	0	0	Within submucosa, hyperechoic, homogeneous, well-demarcated
Leiomyosarcoma	1	0	0	Within muscularis, hypoechoic, inhomogeneous, unclear border
Heterotopic pancreas	0	12	0	Within submucosa, hypoechoic or mix echo, 9 patients of inhomogeneous, 5 patients of unclear border
Lymphoma	0	13	0	Thicken the wall, disruption of layer, hypoechoic, inhomogeneous, unclear border
Cyst	0	0	1	Within submucosa, anechoic, well-demarcated

Table 3. EUS image features of 35 cases of EUS diagnosis that do not agree with the pathology

Pathological results	EUS diagnosis	N	EUS findings
Esophageal	Esophageal	7	Within muscularis, hypoechoic, 2 patients of inhomogeneous, 1 patient with unclear border
Leiomyoma	Stromal tumor		
Gastric	Gastric	5	Within muscularis
Leiomyoma	Stromal tumor		Hypoechoic, homogeneous, well-demarcated
Esophageal	Esophageal	4	Within muscularis
Stromal tumor	Leiomyoma		Hypoechoic, homogeneous, well-demarcated
Gastric	Gastric	1	Within muscularis
Stromal tumor	Leiomyoma		Hypoechoic, homogeneous, well-demarcated
Gastric	Gastric	1	Within muscularis, hypoechoic, inhomogeneous, well-demarcated
Leiomyosarcoma	Stromal tumor		Within muscularis
Esophageal	Esophageal	1	Within muscularis, hypoechoic, inhomogeneous, unclear border
Schwannoma	Stromal tumor		Within muscularis, hypoechoic, inhomogeneous, well-demarcated
Gastric	Gastric	3	Within muscularis, hypoechoic, 1 patient of inhomogeneous, 1 patient of unclear border
Schwannoma	Stromal tumor		Within muscularis, hypoechoic, 1 patient of inhomogeneous, 1 patient of unclear border
Gastric heterotopic pancreas	Gastric	9	Within muscularis, hypoechoic, 6 patients of inhomogeneous, 4 patients of unclear border
	Stromal tumor		
Gastric heterotopic pancreas	Gastric	1	Within submucosa
	Fibroma		Hypoechoic, homogeneous, well-demarcated
Duodenal heterotopic pancreas	Duodenal	1	Within muscularis
	Stromal tumor		Hypoechoic, homogeneous, well-demarcated
Gastric	Gastric	1	Within muscularis
Carcinoid	Stromal tumor		Hypoechoic, homogeneous, well-demarcated
Gastric lymphoma	Gastric cancer	1	Disruption of layer, hypoechoic, inhomogeneous, unclear border

Otherwise, 35 cases did not agree with the pathology. The diagnostic accuracy of gastric lymphomas was 92.86% (13/14) with 1 gastric lymphoma patient misdiagnosed as gastric cancer. The diagnostic accuracy of gastric stromal tumors was 97.62% (41/42) with 1 gastric stromal tumor patient misdiagnosed as gastric leiomyoma. In contrast, the diagnostic accuracy of esophageal stromal tumors was very low. Of the 6 cases with esophageal stromal tumors, only 2 patients had the correct diagnosis with the remaining 4 patients misdiagnosed as esophageal leiomyoma. The diagnostic accuracy of esophageal leiomyomas was 81.58% (31/38) with the other 7 patients all misdiagnosed as esophageal stromal tumor. The diagnostic accuracy of gastric leiomyomas was even lower than esophageal leiomyomas. Of the 6 gastric leiomyoma patients, only 1 patient had the correct diagnosis with the remaining 5 patients misdiagnosed as gastric stromal tumor. Of the 22 patients with gastric heterotopic pancreas, 9 patients were misdiagnosed as gastric stromal tumor and 1 patient misdiagnosed as gastric fibroma. All 4 patients with schwannoma were misdiagnosed as stromal tumor. One patient with gastric leiomyosarcoma was misdiagnosed as gastric stromal

Table 4. The difference between EUS and gastroscopy in the accuracy of diagnosis

Pathological results	Patients with pathologically confirmed (N)	Agree with pathology (EUS)	Agree with pathology (gastroscope)	*P-value*
Leiomyoma	44	32	19	0.005
Stromal tumor	50	45	15	0.000
Heterotopic pancreas	23	12	8	0.234
Lymphoma	14	13	4	0.001
Sarcoma	2	1	0	/
Lipoma	2	2	1	/
Cyst	1	1	0	/
Schwannoma	4	0	0	/
Carcinoid	1	0	0	/
Total	141	106	47	0.000

The difference in the diagnostic accuracy of subepithelial lesions in the upper digestive tract between EUS and gastroscopy was considered statistically significant ($P < 0.01$).

tumor. One patient with gastric carcinoid tumor was misdiagnosed as gastric stromal tumor. One patient with duodenal heterotopic pancreas was misdiagnosed as duodenal stromal tumor. The misdiagnosed cases are shown in **Table 2**.

EUS image features

Of the 44 patients with pathologically confirmed leiomyoma, the EUS images of 2 patients showed a heterogeneous echo pattern, and the EUS image of 1 patient showed an unclear border. Of the 50 patients with pathologically confirmed stromal tumor, the EUS images of 14 patients showed a heterogeneous echo pattern, and the EUS images of 3 patients showed an unclear border. The leiomyoma and stromal tumor mentioned above originated in the muscularis. All 9 misdiagnosed patients of gastric heterotopic pancreas had lesions that originated in the muscularis with 6 patients having lesions located in the gastric antrum (including 5 patients in the greater curvature), 2 patients having lesions located in the gastric body, and 1 patient having lesions located in the junction of the gastric antrum and gastric body. All 9 of these patients showed an echo-poor pattern under ultrasound with 5 patients shaped like fusiformis and the other 4 shaped irregularly. Six patients' internal echo was heterogeneous, and 4 patients' outlines of one or two cross-sections were not so clear. The other EUS subepithelial lesion findings are shown in **Tables 2** and **3**.

The difference in the diagnostic accuracy of subepithelial lesions in the upper digestive tract between EUS and gastroscopy

The diagnostic accuracy using EUS for subepithelial lesions in the upper digestive tract was up to 75.18% (106/141), which was far superior to that of gastroscopy (33.33%, 47/141, $P < 0.01$) (**Table 4**).

Discussion

Subepithelial lesions are the most common protuberant lesions of the upper digestive tract, and many of them are leiomyomas and stromal tumors. There is common agreement that EUS is the best choice for diagnosing and differentiating subepithelial lesions in the GI tract due to its higher sensitivity and specificity than other imaging modalities [9]. EUS can characterize lesions by providing information on echogenic origin, size, borders, homogeneity, and the presence of echogenic or anechoic foci [9]. Endosonographically, the wall of the GI tract consists of 5 layers of alternating echogenicity. The first layer is hyperechoic and represents the superficial layer of the mucosa. The second layer is hypoechoic and consists of the deep layer of the mucosa including the muscularis mucosa. The third layer is hyperechoic and is the submucosa. The fourth layer is hypoechoic and is the muscularis propria. The fifth layer is hyperechoic and is the serosa or adventitia [14].

In our study, the diagnostic accuracy using EUS for subepithelial lesions in the upper digestive tract was up to 75.18%, which was far superior to that of gastroscopy at 33.33% ($P < 0.01$). Compared with gastroscopy (**Table 4**), EUS has obvious advantages when examining leiomyomas, stromal tumors, and gastric lymphomas ($P < 0.01$), whereas it does not have clear superiority when examining some atypical gastric heterotopic pancreases compared with gastroscopy ($P > 0.05$).

Leiomyomas and stromal tumors are the most common gastrointestinal tract mesenchymal

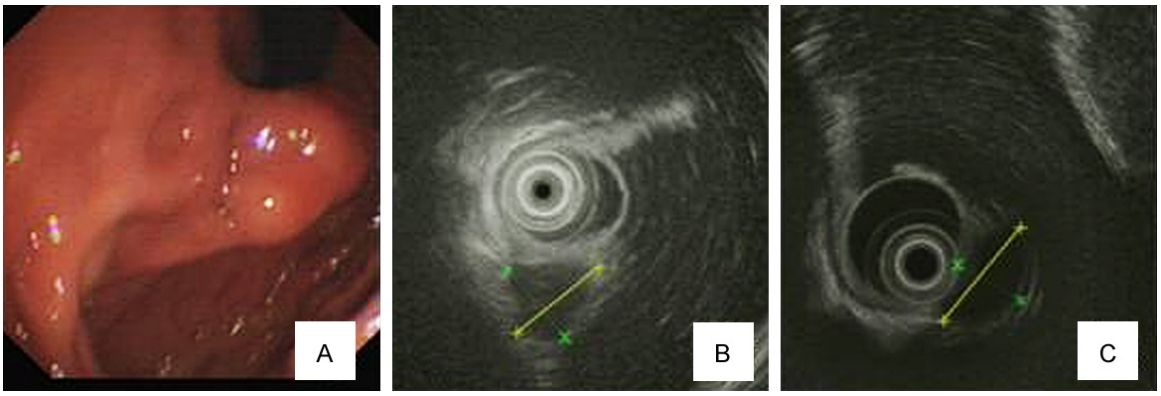

Figure 1. Endoscopic and EUS finding of a gastric leiomyoma which was misdiagnosed as a gastric stromal tumor. (A) The lesion located in the gastric fundus. EUS findings (B, C): within muscularis, hypoechoic, homogeneous, well-demarcated.

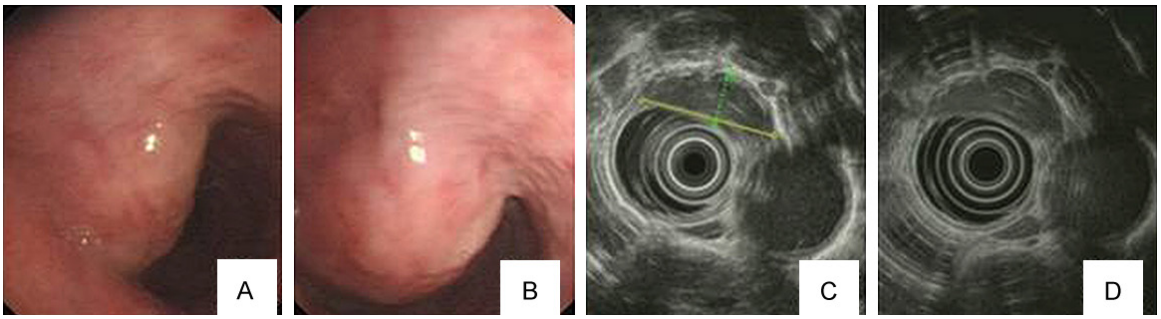

Figure 2. Endoscopic and EUS finding of a esophageal stromal tumor which was misdiagnosed as a esophageal leiomyoma. Endoscopy findingds (A, B): The lesion located in the mid-esophagus; EUS findings (C, D): Within muscularis, hypoechoic, homogeneous, well-demarcatedIt was difficult to differentiate an esophageal stromal tumor from an esophageal leiomyoma by these pictures.

tumors (GIMTs). In clinical practice, preoperative differentiation between leiomyomas and stromal tumors is usually difficult even if EUS-guided fine-needle aspiration (EUS-FNA) or a tru-cut biopsy is performed [15-17]. Very little is known about differentiating stromal tumors and leiomyomas by EUS [18]. As we know, features of leiomyomas and stromal tumors seen with EUS include both a round shape and a homogeneous, hypoechoic mass with regular borders [19]. Both of them originate in the muscular layer and, therefore, the misdiagnosis of leiomyomas as stromal tumors and vice versa is commonly seen with EUS. In this study, 12 cases of leiomyomas were misdiagnosed as stromal tumors. Likewise, 5 cases of stromal tumors were misdiagnosed as leiomyomas. Because the clinical morbidity of gastric stromal tumors is considerably greater than that of gastric leiomyomas (the number of pathologically confirmed gastric stromal tumors in our study was 42, while the number of gastric leiomyomas was only 6), we usually diagnose a subepithelial lesion as a gastric stromal tumor when we see the lesion originating in the muscular layer with a homogeneous echo pattern and clear border under ultrasound. Therefore, this could inevitably result in some gastric leiomyomas misdiagnosed as gastric stromal tumors (**Figure 1**). Similarly, due to the greater morbidity of esophageal leiomyomas than that of esophageal stromal tumors (the number of esophageal leiomyomas in this study was 38, while the number of esophageal stromal tumors was only 6), we often diagnose a subepithelial lesion as an esophageal leiomyoma when we see the lesion originating in the muscular layer with a homogeneous echo pattern and clear border with EUS. This can also lead to the misdiagnosis of esophageal leiomyomas as esophageal stromal tumors (**Figure 2**). It seems impossible to differentiate leiomyomas from stromal tumors by EUS. Of the 44 patients in our study with pathologically confirmed leiomy-

Table 5. The difference in the EUS findings between leiomyomas and stromal tumors

Variables	Leiomyomas (N = 44)	Stromal tumors (N = 50)	*P*-value
Internal echo pattern			0.003
Homogenous	42	36	
Inhomogeneous	2	14	
Border			0.620
Clear	43	47	-
Unclear	1	3	

A tumor originating from muscular layer with heterogeneous echopattern is seen more frequently in stromal tumor than in the leiomyoma of upper digestive tract ($P = 0.003 < 0.01$).

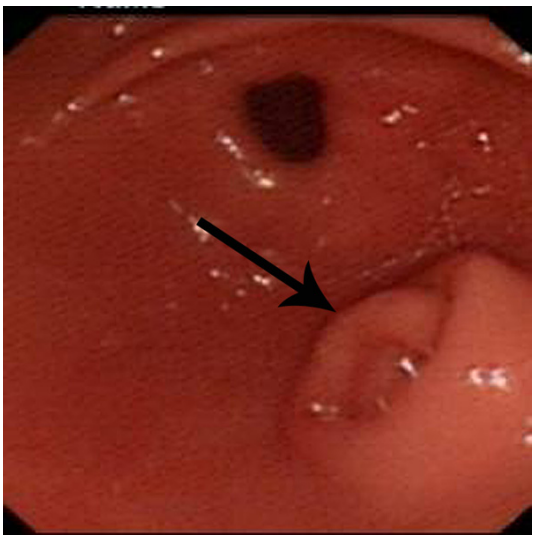

Figure 3. Endoscopic finding of a typical gastric heterotopic pancreas. The lesion occurred in the greater curvature and had an umbilicate pit with an opening on the top of the lesion that was characteristic (arrows).

oma, the EUS appearance of 2 patients showed a heterogeneous echo pattern, and the EUS appearance of 1 patient showed an unclear border. Of the 50 patients with pathologically confirmed stromal tumor, 14 patients showed a heterogeneous echo pattern, and 3 patients showed an unclear border (**Table 5**). Thus, a tumor originating from the muscular layer with a heterogeneous echo pattern is seen more frequently in stromal tumors than in leiomyomas of the upper digestive tract ($P < 0.01$). This means that we can basically exclude the possibility of gastric leiomyoma if a subepithelial lesion originates from the muscular layer with a heterogeneous echo pattern. Whether the border is clear or not does not play a role in distinguishing between stromal tumors and leiomyomas under EUS ($P > 0.05$). Stromal tumors and leiomyomas could be precisely distinguished by immunohistochemistry methods.

Of the misdiagnosed cases, another finding was that 9 patients with gastric heterotopic pancreas were misdiagnosed as gastric stromal tumor. The typical gastric heterotopic pancreas has umbilicate pits with openings on the top of the lesions under the gastroscope (**Figure 3**), and the lesions often occur in the gastric antrum, particularly in the greater curvature. Usually, the characteristics of gastric heterotopic pancreas under EUS demonstrate an indistinct margin, mixed or hypoechoic echogenicity, a heterogeneous lesion, and originate in the third layer, although a few originate in the 2nd or 4th layers [2, 3, 20]. Some typical gastric heterotopic pancreases under EUS present with anechoic structures that correspond to ductal formations. Therefore, the typical gastric heterotopic pancreas is not as easily misdiagnosed as other diseases with the gastroscope and EUS. Gastric GI stromal tumors with EUS are characteristically located in the muscular layer, generally appear with an echo-poor pattern, are more or less homogeneous, and more or less well-demarcated. In a previous study [21], signs of a suspected malignant gastric stromal tumor included a size greater than 4 cm, irregular borders, lobulations, anechoic spaces, or echogenic foci. In our study, 9 gastric heterotopic pancreases originated in the muscularis, and all of these presented without umbilicate pits with openings on the top of the lesions. As a result, they were all misdiagnosed as gastric stromal tumors (**Figure 4**). Gastric stromal tumors are the most common tumors of gastric subepithelial lesions, and the clinical incidence of gastric heterotopic pancreas is much lower. Therefore, we might consider the primary diagnosis to be a gastric stromal tumor when we encounter an atypical gastric heterotopic pancreas originating in the muscular layer, because its appearance on EUS is similar to that of a gastric stromal tumor. The 9 misdiagnosed cases remind us that it is sometimes difficult to distinguish an atypical-shaped gastric heterotopic pancreas in the muscularis from a gastric stromal tumor by EUS. We should observe more cross-sections carefully under

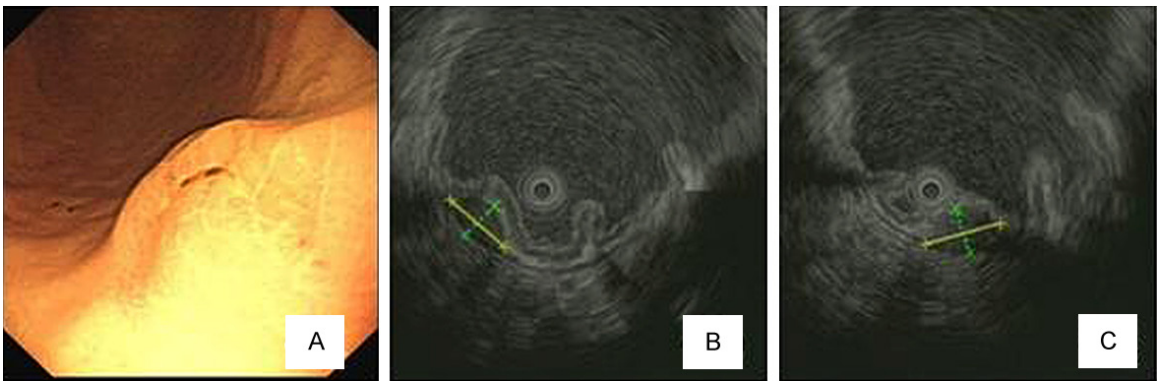

Figure 4. Endoscopic and EUS finding of gastric heterotopic pancreas that was misdiagnosed as a gastric stromal tumor. (A) The lesion was located in the gastric body and did not have an umbilicate pit with an opening on the surface. EUS findings (B) within muscularis, hypoechoic, homogeneous, well-demarcated. EUS findings (C) within muscularis, hypoechoic, inhomogeneous, unclear border. It reminded us that we should observe more cross-sections carefully under ultrasound.

ultrasound when a subepithelial lesion originating from the muscular layer is detected in the gastric antrum, especially in the greater curvature, with a heterogeneous echo pattern, irregular shape, and unclear outline. We should also see if there is a possibility of gastric heterotopic pancreas besides excluding a malignant gastric stromal tumor, using EUS-FNA if necessary.

Differentiation between leiomyomas, schwannomas, and GI stromal tumors is also extremely difficult by EUS imaging modalities. Since GI schwannomas are rare and the schwannoma appearance is similar to that of leiomyoma or GI stromal tumors [22-24], 4 cases of schwannomas were misdiagnosed as gastric stromal tumors in our group. In addition, studies have shown interobserver agreement to be poor, and the diagnostic accuracy depends most importantly on the experience of the endosonographer [25].

In conclusion, EUS is a valuable tool in diagnosing subepithelial lesions in the upper digestive tract, but it is still common to see some subepithelial lesions misdiagnosed with EUS. Therefore, we should appreciate the importance of a misdiagnosis of upper digestive tract subepithelial lesions. Due to the small number of misdiagnosed cases, analyzing the reasons for misdiagnosis could not be possible in this study. A larger number of study cases and prospective multicenter studies are needed.

Disclosure of conflict of interest

None.

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