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Original Article

Gastritis cystica profunda: clinical and pathologic study of seven cases and review of literature

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Abstract: Gastritis cystica profunda (GCP) is a rare lesion characterized by hyperplasia and cystic dilatation of the gastric glands in the submucosal layer. Here we report seven cases of GCP. The patients are 5 women and 2 men with a mean age of 62 (range, 42-82) years at the time of diagnosis. The patients presented with abdominal distension, sour regurgitation, and heartburn. One case had the previous gastric surgery and the other six cases had no special history. The lesions were located in the fundus (4/7), corpus (1/7), cardia (1/7), and antrum (1/7). Endoscopic analysis revealed pedunculated polyps, or a dome-shaped polyp. Histologically, all cases showed dilated tubular glands, mainly located in the submucosa, among the muscularis mucosa, and occasionally in the lamina propria. The glands were lined by bland single columnar epithelium with infolding features in some areas. Mitotic activity and marked cellular atypia were not present. The stroma in some cases was mildly edematous with infiltrated lymphocytes and plasma cells. There was no epithelial dysplasia in the overlying mucosa. Immunohistochemically, the Ki-67 index was < 1%. P53 immunostaining was generally characterized as wild type in all cases. Based on the morphology of the glands and the cells and the possible mechanism of hyperplasia and cystic dilatation of the gastric glands, it is easy to differentiate GCP from a well-differentiated adenocarcinoma.

Keywords: Gastritis cystica profunda, gastritis, ectopic gland, stomach

Introduction

The presence of the cystic dilatation of the gastric glands in the submucosa is a benign tumor-like lesion. This phenomenon was first described by Scott and Payne in 1947 [1]. The term "gastritis cystica polyposa" was first used by Littler, et al in 1972 [2]. They found the lesion occurred at gasteoenteric anastomosis, which produced clinical symptoms of obstruction by its large size and prolapse through the anastomosis. They first compared the gastritis cystica polyposa with the similarities of the colitis cystica profunda. Thus, "gastritis cystica profunda (GCP)" was used in the literature [2]. It has also been suggested that GCP represents a manifestation of hyperplastic and metaplastic responses to mucosal injury caused by several factors, such as chronic inflammation, ischemia, and the presence of foreign materials [3]. GCP is a rare lesion, which usually occurs in the fundus of the stomach [3]. However, it also presents in the cardia, corpus, and antrum [4]. It is characterized by polyp-like or elevated lesion and cystic dilatation of the gastric glands, which extend into the submucosa of the stomach [2].

GCP may present clinically as abdominal pain, bloating, gastric obstruction, bleeding, and mucosal ulceration [5]. GCP is generally benign, although there are reports of GCP associated with cancer [6]. GCP and carcinoma have different treatment methods and prognoses, so it is very important to differentiate the GCP from adenocarcinoma.

Here we report seven cases of GCP, which presented in the fundus, corpus, cardia, and antrum. We mainly focus on the pathologic and clinic features, the possible mechanism of the presence of gastric glands in the submucosa, and the cystic dilation change. We also discuss the difference between GCP and well-differentiated adenocarcinoma.

Table 1. Summary of clinicopathologic features

No.	Age	Sex	Symptoms	Past medical history	Location	Surgical Procedure	Followup
1	82	F	Swallow not free	No special	Cardia	ESD	No recurrence
2	51	F	Abdominal distension	Hypothyroidism	Corpus	ESD	No recurrence
3	68	M	Abdominal distension and Heartburn	No special	Fundus	ESD	No recurrence
4	65	F	Heartburn and sour regurgitation	hypertension	Fundus	ESD	No recurrence
5	65	M	Abdominal pain	distal gastrectomy	Fundus	B	No recurrence
6	42	F	Abdominal pain and sour regurgitation	No special	Fundus	ESD	No recurrence
7	67	F	Abdominal distension and Heartburn	No special	Antrum	ESD	No recurrence

F, female; M, male; ESD, endoscopy submucosal dissection; B, biopsy.

Materials and methods

Endoscopic examination

All cases were first examined under white light using an EVIS LUCERA ELITE CV-290Video System Centre (Olympus Corp., Tokyo, Japan).

Patients and tissue specimens

We retrospectively reviewed clinical data from the medical records of seven patients diagnosed with a polypoid or elevated GCP who were treated at the Department of Pathology of the Peoples' Liberation Army 989 Hospital. Hematoxylin and eosin-stained slides were available for all cases. The surgical specimens were fixed in 10% neutral buffered formalin, dehydrated in graded alcohol solutions, embedded in paraffin, and cut into 4-μm-thick sections for hematoxylin and eosin staining and visualization using light microscopy.

Immunohistochemical studies

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections. Immunohistochemical analysis was performed using the BOND-MAX Automated IHC/ISH Stainer (Leica Biosystems GmbH, Wetzlar, Germany). The primary antibodies used included Ki-67 (C3G4) and P53 (DO7). All antibodies were purchased from Henan Celnovte Biotechnology Co. Ltd (Zhengzhou, China).

Results

Clinical findings

The patient cohort included two males and five females with a mean age of 62 (range, 42-82) years at the time of diagnosis. The most common clinical symptoms included abdominal distension, sour regurgitation, and heartburn (**Table 1**).

Endoscopic examination results

The lesions were located in the fundus (4/7) (**Figure 1A-C**), corpus (1/7) (**Figure 1D-F**), cardia (1/7) (**Figure 1G-I**), and antrum (1/7) (**Figure 1J-L**). Endoscopic analysis under white light revealed pedunculated polyps, or a dome-shaped polyp (**Figure 1A**, **1D**, **1G**, **1J**).

Macroscopic features

All cases showed a well-demarcated lesion. The lesions had a polyp-like or elevated lesion (**Figure 1C**, **1F**, **1I** and **1L**). The average diameter of lesion was 1.3 cm (range, 0.4 to 2.2 cm). There was cystic degeneration in the cut in case 6.

Microscopic features and immunohistochemistry results

All cases showed dilated tubular glands, mainly located in the submucosa, along the muscularis mucosa, and occasionally in the lamina propria. The glands were lined by bland single columnar epithelium with the infolding features in some area. The cells had no cellular dysplasia and no mitosis. The stroma was mildly edematous with infiltrated lymphocytes and plasma cells. There was no epithelial dysplasia in the overlying mucosa. There were dilated lymphatic vessels and blood vessels in the lamina propria and submucosa (**Figure 2**).

Immunohistochemically, the Ki-67 index was < 1%. The dilated glands showed no excessive expression of Ki-67 compared with the sur-

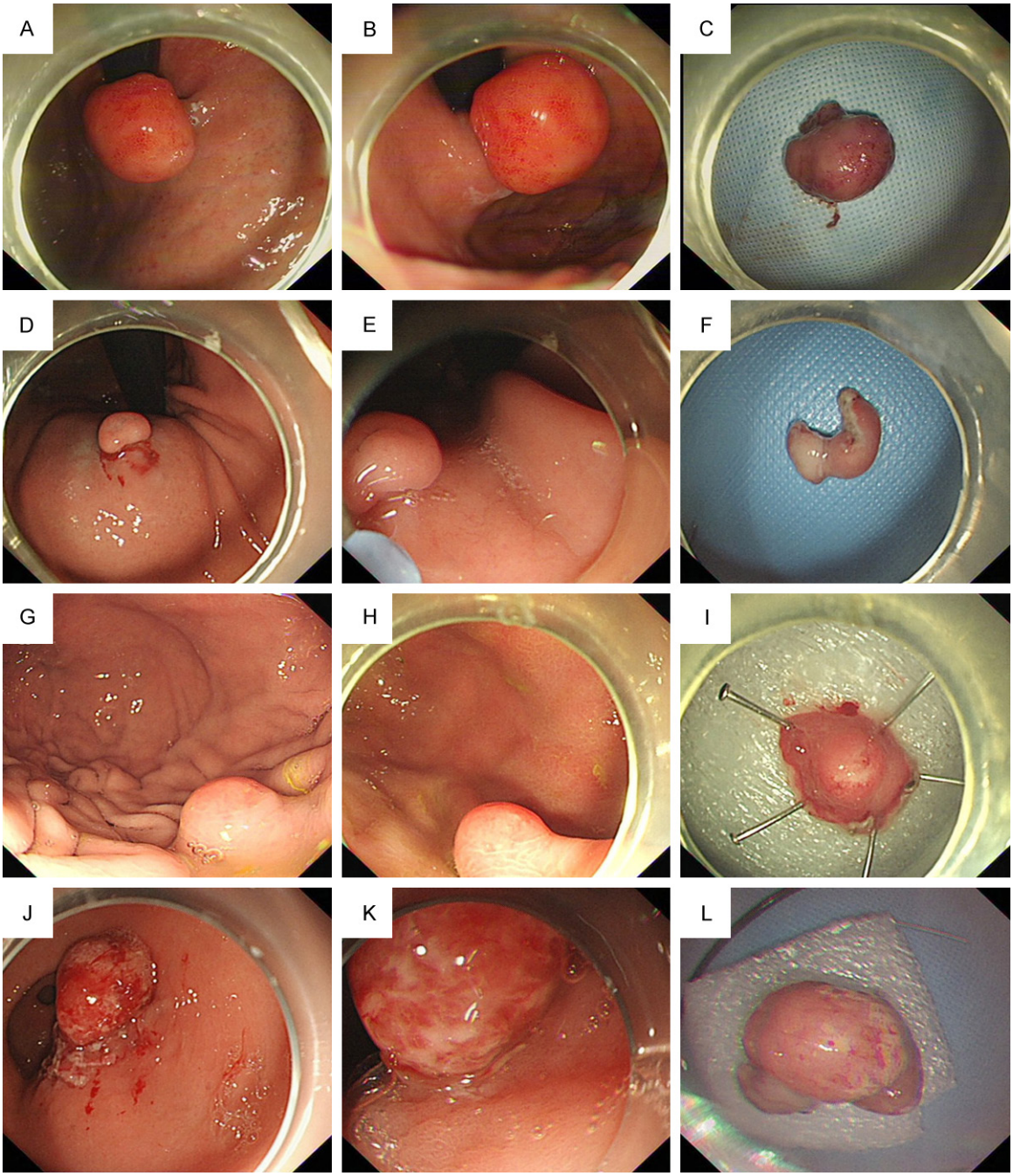

Figure 1. A-C. (Case 1 in **Table 1**). A and B. A protruded lesion located in the greater curvature of fundus. The lesion was well defined. C. A protruded lesion from an ESD specimen. D-F. (Case 2 in **Table 1**). D and E. A polyp-like well demarcated lesion located in the greater curvature of fundus. F. An ESD specimen showed a polyp-like lesion. G-I. (Case 3 in **Table 1**). G and H. A polyp-like with well demarcated lesion located in the greater curvature of cardia. I. An ESD specimen showed a polypoid lesion. J-L. (Case 7 in **Table 1**). J and K. An elevated well demarcated lesion located in the greater curvature of antrum. There was congestion and erosion in the surface. L. An ESD specimen showed a dome-shaped lesion.

rounding normal gastric tissues. The Ki-67 expression had no difference between the superficial and deeper dilated glands. P53 immunostaining was generally characterized as wild type in all cases.

Discussion

GCP is an uncommon lesion, which usually occurs in the fundus of the stomach [1, 2]. It can occur in the cardia, corpus, and antrum [3].

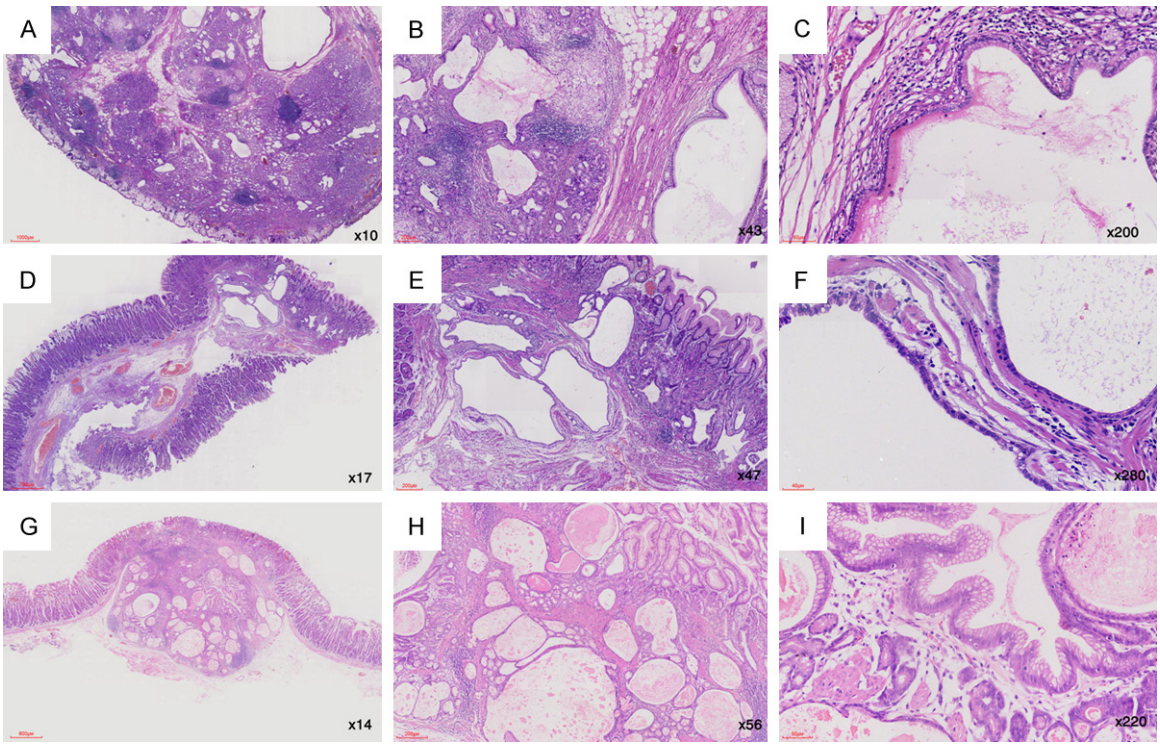

Figure 2. A-C. (Case 1 in **Table 1**). A. Lower power shows the dilated glands located in the muscularis mucosae. B and C. Medium and higher power shows dilated glands filled with eosinophilic secretion and debris. The glands were round but the columnar epithelium was infolded with wavy appearance in some areas. The stroma was edematous and there were some inflammatory cells around the glands. D-F. (Case 2 in **Table 1**). D and E. Lower power showed the dilated tubules located in the lamina propria, muscularis mucosae, and the submucosa. F. Higher power showed the dilated tubules filled with eosinophilic secretion and debris. G-I. (Case 3 in **Table 1**). G. Medium power showed the dilated tubules located in the muscularis mucosae. H and I. Medium and higher power showed dilated tubules filled with eosinophilic secretion. In some areas, the columnar epithelium was infolded with wavy appearance.

Xu, et al reported 34 cases of GCP, and the most location in their paper was the cardia (15/34), and then antrum (12/34), and some other cases occurred in the corpus (4/34), argularis (2/34), and fundus (1/34) [4]. In our cases, the lesions mainly located in the fundus (4/7), and the other cases present in the corpus (1/7), cardia (1/7), and antrum (1/7).

The mechanism of gastric gland presence in the submucosa is still unclear. Some studies found that GCP usually occurred several years after previous gastric surgery [2, 6-8]. The current study revealed that only one case of GCP had a history of previous surgery (case 5). However, the other six cases had no history of surgery. These results indicated that past surgery is only a small part of the reason for development of GCP. Our results are concurrent with previous reports [9-11]. Mongolian gerbil model animals infected with Helicobacter pylori could develop GCP. Additionally, the H. pylori cag-pathogenicity island-dependent immunological response may trigger GCP [11]. In our cases, there was no active inflammation in the background, or Helicobacter pylori infection.

It also has been postulated that the development of GCP may be related to gastrojejunostomy with subsequent reflux of bile and small intestinal contents may cause atrophic gastritis and intestinal metaplasia [12]. Deng et al reported a 50-year-old man presented with intermittent abdominal fullness for 2 years, along with nausea, which often occurred after consuming food that could cause gastric irritation, and the condition improved without intervention after 10 minutes. He had no history of gastrointestinal surgery. After the lesion was removed by ESD, they found tiny cysts lined by flattened epithelium within the submucosa, consistent with gastritis cystica profunda, and gland hyperplasia, with a yellow-brown substance deposit. There were dilated cystic

glands in the submucosa and bile deposits [13]. In our seven cases, there was no atrophic gastritis and intestinal metaplasia in the background. We also did not find bile deposits in the gastric mucosa.

Two main theories have been proposed to explain occurrence of ectopic pancreas: misplacement theory and metaplasia theory. The most widely held misplacement theory claims that during the period of embryonic rotation of the dorsal and ventral buds, deposits of pancreatic tissue migrate from the main body of pancreas and are implanted at various ectopic sites [14, 15]. On the other hand, the metaplasia theory implicates that during embryogenesis endodermal tissues migrate to the submucosa and then turn into pancreatic tissue [16]. We postulate that the development of GCP in part may be related to the stomach dynamic obstacles and food accumulated in the stomach, which results in a gap in the local muscularis mucosae, and the stomach glands or stem cells migrate into the submucosa or the muscularis mucosae.

We also address how the cystic dilatation of glands occurs. This phenomenon may be the related to muscularis mucosae. An interruption in the muscularis mucosae may be caused by erosion of the gastric mucosa in chronic gastritis or ischemia [17]. After the disruption of the muscularis mucosae the mucosal epithelial cells migration into the submucosa, the mucosal epithelial cells and muscularis mucosae begin to proliferate. With the hyperplasia of muscularis mucosae, the secretion of the glands in the submucosa can not be excreted to the gastric cavity and then the glands are passively dilated [3, 18]. In our case 5, there was a previous gastric surgery, and the muscularis mucosae showed haphazard arrangement.

Nabothian cysts of the uterine cervix are mucus-filled cysts usually 2-10 mm in size located on the surface of the endocervix and occasionally are found deep in the wall of the uterine cervix or paracervical soft tissue [19]. The cysts form when the duct in the gland neck becomes obstructed, leading to entrapped mucus secretions [19]. Gastric glands belong to exocrine glands, which empty into the base of the foveolae. In our cases, the dilated glands were mostly located in the submucosa, within the muscularis mucosae, and occasionally in the lamina propria. These findings suggest that the glands were dilated resulting from the gland neck being obstructed. With the pressure of the foods, the stomach glands get extended into the muscularis mucosae and even migrate to the submucosal layer.

There are differences between GCP and adenocarcinoma in treatment methods and progression, so it is very important to differentiate GCP from adenocarcinoma. First, the GCP is a passive process. The glands in the GCP show concordant with the surrounding interstitium. There are no desmoplastic reactions. However, carcinoma is an active process. The glands in the carcinoma show infiltrative features. There are desmoplastic reactions in the carcinoma. Secondly, adenocarcinoma has a precancerous lesion in the surrounding or the remnant glands. However, the surrounding or the remnant glands show normal features in the cells and architecture in our cases. Thirdly, glands differ in shapebetween GCP and adenocarcinoma. The cystically dilated glands have no cellular and nuclear dysplasia. There are no mitoses in these glands. Ki-67 immunostaining results indicate that these glands have no activity. P53 immunostaining shows a wild type of these glands. However, the glands in the adenocarcinoma have obvious cellular and nuclear dysplasia. There are obvious mitoses and even pathologic mitoses in these glands. Ki-67 immunostaining may show a high index. The P53 immunostaining may show a sense mutation or nonsense mutation. Finally, adenocarcinoma has neoplastic necrosis in the lumen of the glands. However, the luminal materials in the GCP glands are only secretions. There is some debris in some cases, which results from the long-term obstruction and then disintegration of the secretions.

GCP can cause severe upper gastrointestinal bleeding and gastric outlet obstruction and can mimic cancer in some cases [5, 8, 18, 20]. In some reports, the patients were at high risk for gastric cancer and some patients had a relationship to adenocarcinoma [20, 21]. Butt, et al reported a case of GCP presenting as gastric outlet obstruction and mimicking adenocarcinoma [22]. Some authors prefer a more proactive approach to remove GCP endoscopically, once diagnosed [23]. In our cases, the patients

showed no special features with abdominal distension, sour regurgitation, and heartburn. Most patients (6/7) received an ESD.

Disclosure of conflict of interest

None.

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