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Gastritis Cystica Profunda Accompanied by Multiple Early Gastric Cancers

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Gastritis cystica profunda (GCP) is a rare disease which shows multiple cystic gastric glands within the submucosa of the stomach. GCP lesions mainly develop at the site of gastroenterostomy and exhibit benign behavior. However, there have been a number of debates over its malignant potential. Several reports have documented GCP accompanied by gastric carcinomas, but the relationship between the two conditions remains uncertain. Here we report two cases of GCP with dysplasia accompanied by synchronous multiple early gastric cancers without previous gastric surgery. **(Korean J Gastroenterol 2010;55:325-330)**

Key Words: Gastritis cystica profunda; Gastric cancer; Dysplasia

Introduction

Multiple small cysts are rarely found in the submucosa of the stomach. Gastritis cystica profunda (GCP) is a uncommon disease characterized by gastric foveolae elongation along with the hyperplastic and cystic dilatation of the gastric glands extending through the tissue beneath the submucosa.[1] It occurs not only at the site of gastroenterostomy, but also in the stomach without previous gastric surgery.[2-5] GCP may present as a subepithelial tumor or a polyp, but rarely as a giant gastric mucosal fold.[6,7] GCP is usually regarded as a benign lesion,[3,4,8] but there are some controversies about its malignant potential. There have been some reports of cases about GCP accompanied by gastric carcinoma or adenoma with high grade dysplasia. However, the relationship between GCP and gastric carcinoma does not seem to have been fully explained in those reports. Herein, we report two cases of GCP with dysplasia accompanied by synchronous multiple early gastric cancers occurred in patients without previous gastric surgery.

Case reports

Case 1

A 77-year-old man was admitted to our hospital for evaluation and treatment of gastric cancer. Two weeks ago, he visited

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to a private clinic because of abdominal discomfort, and finally was diagnosed as gastric cancer. Physical examination revealed epigastric tenderness but no palpable abdominal mass. His hemoglobin level was 12.1 g/dL, and stool occult blood test was negative. Blood chemistry panel was unremarkable. Abdominal computed tomography (CT) showed focal eccentric mural thickening with mucosal enhancement at the anterior wall of pylorus. Esophagogastroduodenoscopy performed at our hospital revealed two depressed nodular lesions at prepyloric antrum (Fig. 1) and several small smoothly elevated mucosal lesions at anterior and posterior wall of the lower body (Figures are not shown). Biopsy specimens of prepyloric antrum showed well-differentiated adenocarcinoma. Endoscopic submucosal dissection (ESD) of the antral lesion was performed. Histologically, two foci of well-differentiated adenocarcinomas (1.5×1.2×0.3 cm and 1.0×0.5×0.1 cm, respectively) were seen on the resected tissue. The tumor cells were found to infiltrate to the submucosa without lymphovascular invasion. Further surgical procedure was not required because both lateral and deep resection margins were free of tumor cells. Four months later, previous multiple small smooth elevated lesions at anterior (Fig. 2A) and posterior (Fig. 2B) walls of the lower body became somewhat enlarged on the subsequent esophagogastroduodenoscopy, which seemed to be subepithelial tumors. Endoscopic ultrasound (Fig. 2C) of the lesions revealed small hypoechoic cysts in the submucosa of the anterior and posterior walls of the lower body. ESD of these two lesions was performed due to increased size. Histologically, numerous tiny cysts were present within the submucosa, and the cysts were lined by flattened epithelium and contained mucinous collections, which was con-

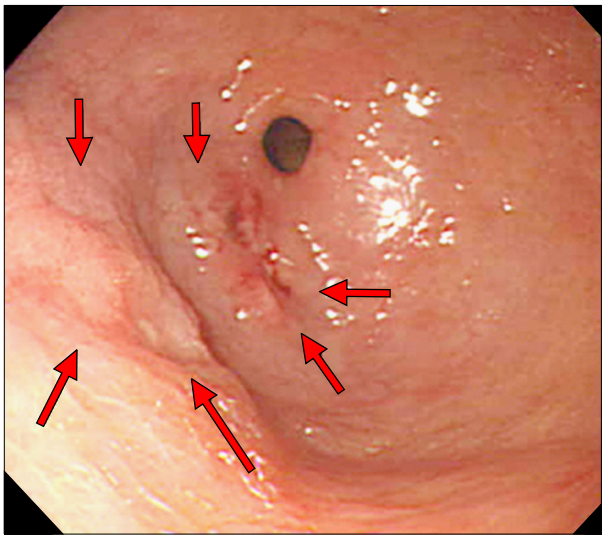

Fig. 1. The gastroscopy images showed two depressed nodular lesions (arrows) at the prepyloric antrum and several small smoothly elevated mucosal lesions at anterior wall of the lower body.

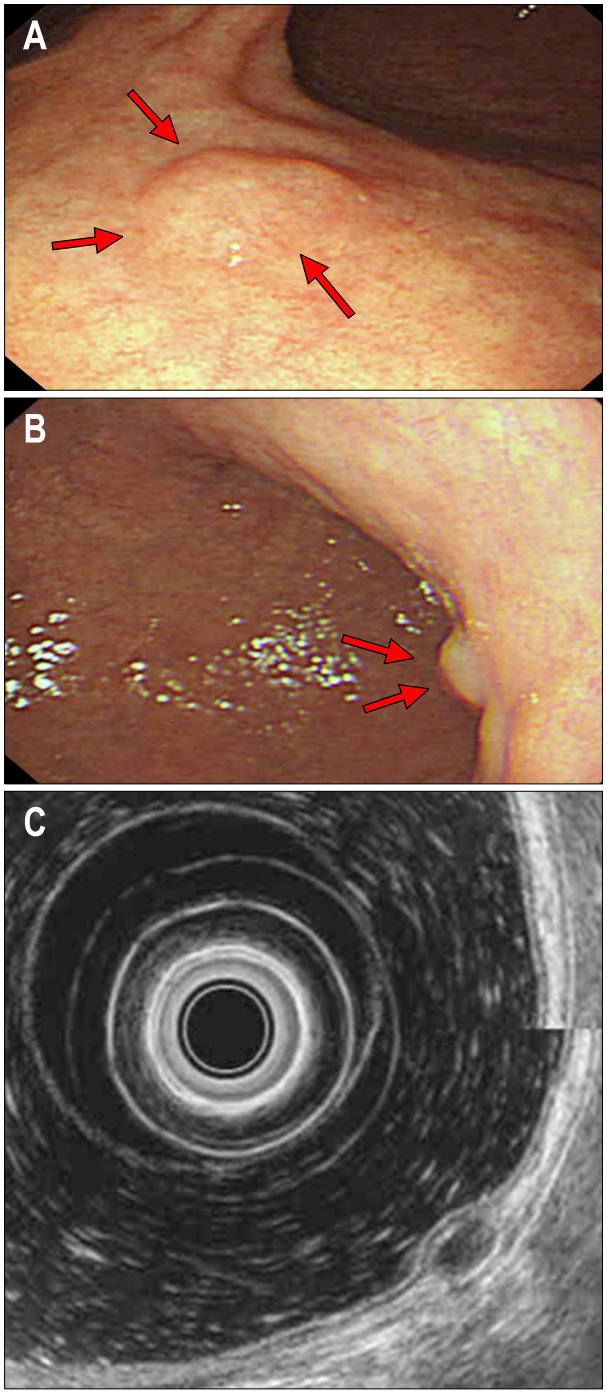

Fig. 2. The small smoothly elevated lesions (arrows) at anterior (A) and posterior (B) walls of the lower body were slightly enlarged compared with previous examination. (C) The EUS image of the elevated lesion at posterior wall of the lower body showed a hypoechoic mass originating from the third layer, suggesting a submucosal cyst.

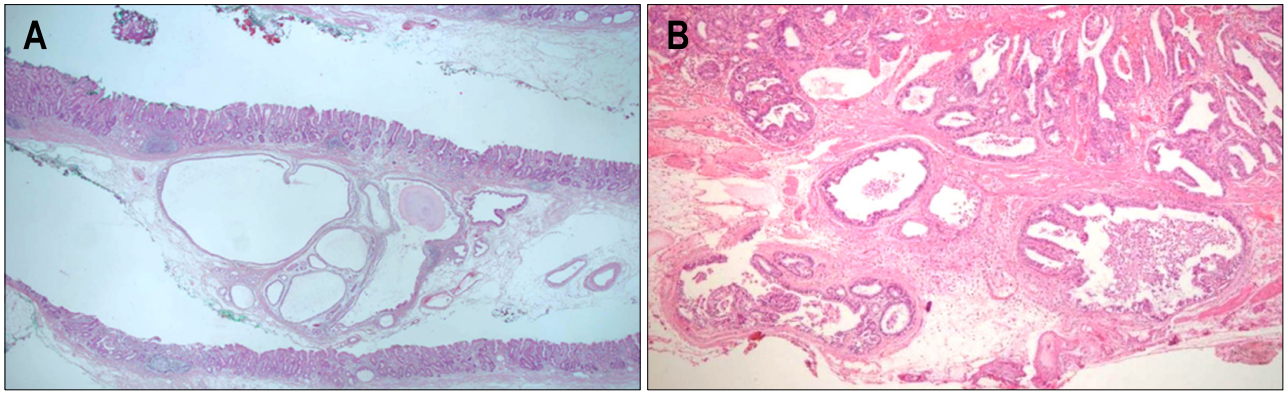

Fig. 3. (A) The EMR specimen of posterior wall of lower body showed numerous tiny cysts lined by flattened epithelium within the submucosa, consistent with gastritis cystica profunda (H&E, ×40). (B) EMR specemien of anterior wall of lower body. The cancer cells focally infiltrated to the superficial submucosal layer, and multiple cysts lined by flattened epithelium were present within the submucosa, consistent with gastritis cystica profunda (H&E, ×100).

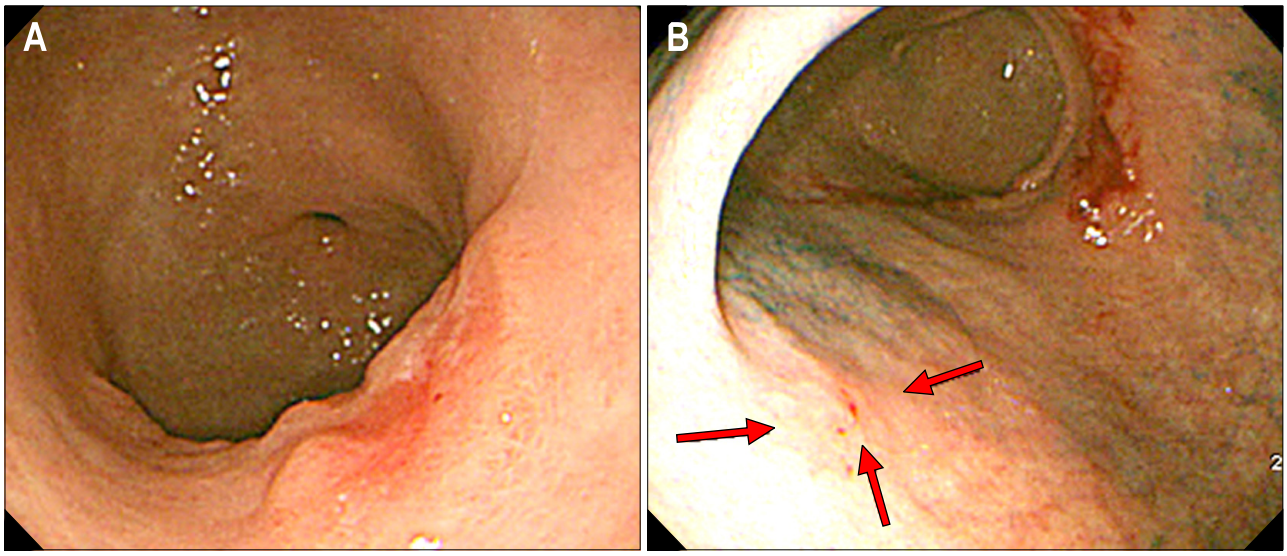

Fig. 4. Esophagogastroduodenoscopy showed (A) a central irregular depressed reddish mucosal lesion with slighltly elevated nodular margin at greater curvature of the antrum and (B) a focal flat elevated lesion at anterior wall of the lower body.

sistent with GCP (Fig. 3A). However, a tiny focus of well-differentiated adenocarcinoma (0.6×0.4×0.1 cm) was seen on the ESD tissue at the anterior wall of the lower body. The cancer cells focally infiltrated to the superficial submucosa (Fig. 3B). The relationship between adenocarcinoma and GCP could not be identified. After all, the patient underwent total gastrectomy. Post ESD scar and other multifocal GCP were found with no residual malignancy. After operation, the patient has been in good condition without any evidence of recurrence or disseminated disease for 24 months.

Case 2

A 76-year-old man visited our hospital because of anorexia and tenesmus. Blood tests and physical examination showed no abnormalities. Esophagogastroduodenoscopy revealed central irregular depressed reddish mucosal lesion with slighltly elevated nodular margin at greater curvature of the antrum (Fig. 4A) and focal flat elevated lesion at anterior wall of the lower body (Fig 4B). Biopsy result of the antral lesion (Fig. 4A) was moderately differentiated adenocarcinoma and the lesion of the lower body (Fig. 4B) showed some atypical glands. Colonoscopy revealed a huge mass nearly obstructing the lumen of the rectum

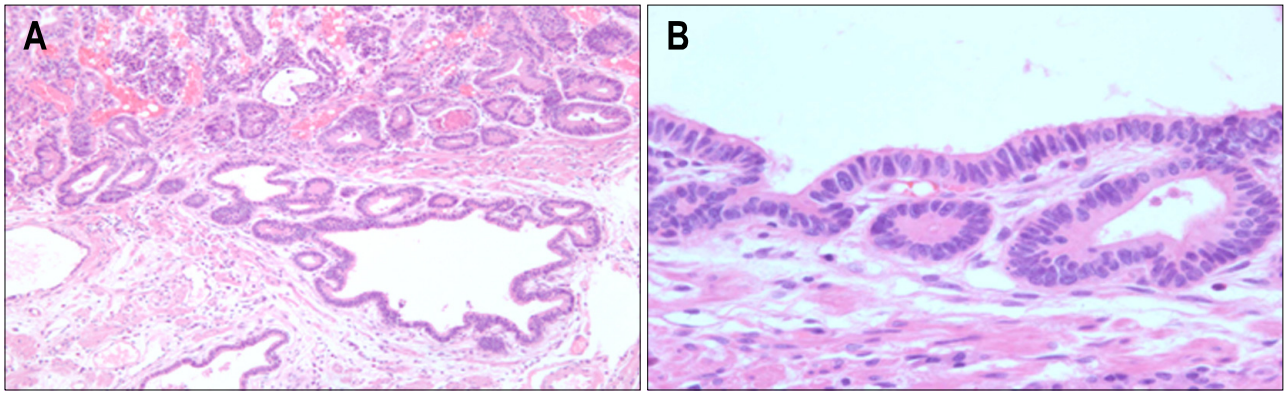

Fig. 5. (A) Some cysts of gastritis cystica profunda showed stratifications of proliferating epithelial cells (H&E, ×100) with (B) mild cytologic atypia (H&E, ×200). No mitosis was seen. In the mucosa above the GCP, adenocarcinomatous glandular cells were seen.

located 8 cm above the anal verge. The biopsy specimen of the rectal mass revealed an adenocarcinoma originating from villotubular adenoma. Abdominal CT showed no significant gastric or perigastric lesion of the stomach and the 6 cm sized circumferentially enhancing segmental mass of the rectum. ESD of the gastric lesion was planned before receiving rectal cancer operation. ESD of the lesions at greater curvature of the antrum and anterior wall of lower body were performed. The ESD specimen of the antrum measured to be 7.5×4.3×0.4 cm which contains moderately differentiated adenocarcinoma (up to 2.1×1.5×0.1 cm) within mucosa and GCP with mild dysplasia. The ESD specimen of the lower body measured to be 4.5×3.3× 0.3 cm which contains well differentiated adenocarcinoma (0.8×0.7×0.1 cm) within mucosa. All adenocarcinomas were confined within the mucosa and lymphovascular tumor invasion was not seen. Characteristically, numerous dilated tiny cysts were found within the submucosa beneath the moderately differentiated antral adenocarcinoma. The cysts were also lined by flattened epithelial cells, consistent with GCP (Fig. 5A). However, there were focal stratifications of proliferating epithelial cells of the cysts with mild cytologic atypia, suggestive of favoring feature for low grade dysplasia (Fig. 5B).

Discussion

Since the first report by Littler and Glebermann in 1972, several cases on GCP have been reported in the literature.[1-5] Various terminology for GCP have been used such as diffuse submucosal cysts of the stomach,[3] submucosal heterotopic gastric glands,[8] gastritis cystica polyposa[2] or diffuse heterotopic cystic malformation of the stomach.

The pathophysiologic mechanisms of GCP have been considered to include chronic inflammation, ischemia and the presence of a foreign body.[1-5] There is an interruption of the muscularis mucosa caused by erosion of the gastric mucosa in chronic gastritis and ischemia, or by the effects of surgery and presence of suture material which causes epithelial cells to migrate into the submucosal layer. The result is cystic dilatation of glands in the basal mucosa and submucosa with superficial inflammation in the lamina propria. Although chronic gastritis is frequently associated with persistent *H. pylori* infection, it remains uncertain whether the organism is associated with the early stage of its inflammatory process. *H. pylori* infection was found on histopathologic examination of our two cases with chronic gastritis. In our case, all patients were treated for *H. pylori* eradication with standard regimen comprising amoxicillin 1 g, clarithromycin 500 mg, and omeprazole 20 mg, all *b.d.*

GCP has been often reported in the setting of prior gastric surgery, presumably because of mucosal prolapse or reflux of intestinal contents.[2-4] However, it was found not only at the site of the gastroenterostomy but also in the stomach of patients without any previous surgery. In our cases, the patients had no previous history of surgery. Macroscopically, GCP may present as a subepithelial tumor or solitary, diffuse polyps or a giant gastric mucosal fold.[6,7] Particularly, hypertrophic folds of the stomach should be differentiated from Menetrier's disease, malignant lymphoma and gastric carcinoma of the linitis plastica type as well as gastritis cystica profunda.[9,10]

GCP are found mainly in the posterior and anterior wall of the gastric body and in the intermediate zone between the fundic and pyloric glands, where gastric ulcer and erosion often arise. GCP seldom may give rise to clinical symptoms, but may

present clinically as abdominal pain, bloating, gastric obstruction, bleeding, and mucosal ulceration.[1,11,12]

GCP can be diagnosed by esophagogastroduodenoscopy, abdominal CT and EUS. EUS provides a clear picture of theses disorders. The EUS appearance of GCP consists of multiple cysts within a thickened submucosal layer.[13] As endoscopic forcep biopsy specimen is usually limited to the mucosa, information regarding the state of the submucosa is seldom available, thereby obtaining only a small fragment of the lesion. Therefore, in some cases endoscopic differential diagnosis of GCP can be difficult, for which wide resection through ESD is required. The combination of EUS and ESD appears to be very effective for the diagnosis of GCP, because as many unnecessary surgical procedure as possible could be avoided in cases of GCP. Our cases were diagnosed by combination of EUS and EMR.

GCP is generally benign, although there have been some reports of GCP associated with cancer.[4,14-16] Also, GCP may represent a paracancerous lesion. According to Korean report, GCP accompanied other disease in 28 cases (71.8%), of which 16 cases of EGC, 9 cases of adenoma and 3 cases of advanced adenocarcinoma.[17] According to Iwanaga et al,[3] GCP accompanied 3.0% of gastric carcinoma and 1.4% of benign gastric disease. Since the first report of a case of adenocarcinoma arising in association with GCP occurring at the gastroenterostomy site by Qizilbash,[11] several cases on the relationship with cancer have been reported.[6,16,17] There was a report on histological feature stating that GCP had some characteristics of malignancy such as metastatic and dysplastic alteration. Expression of Ki-67, p53, and p21 in GCP were as high as in cancer tissue.[13]

Our patients had multiple GCP accompanied by synchronous multiple early gastric cancers. In the case of the first case, adenocarcinonoma focally infiltrated to the superficial submucosa. In the second case, there was GCP with mild cytologic atypia, favoring low grade dysplasia in submucosa. Although relationship between adenocarcinoma and GCP was uncertain, but we considered that GCP could be caused to dysplasia and cancer. Both of the cases accompanied multiple early gastric cancers (EGC). Although there have been no definite evidences that GCP is precancerous lesion, dysplastic change in submucosal cystic dilated gland of GCP suggest that it may have a malignant potential. However, it is very difficult to make an early diagnosis of the cancer developed within submucosal gland of GCP using endoscopy or tissue biopsy. Therefore, in case of multiple GCP lesions, we should consider a possibility of another cancerous lesion that may harbor in these GCPs. We report two cases of GCP accompanied by synchronous multiple early gastric cancers occurred in patients without previous gastric surgery.

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