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Gastritis Cystica Profunda: A Rare Gastric Tumor Masquerading as a Malignancy

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ABSTRACT

Introduction: Gastritis cystica profunda (GCP) is a rare tumor which occurs more commonly in patients with prior gastric surgery. The nonspecific symptoms and radiographic appearance of this tumor mimic that of other hyperproliferative conditions making diagnosis difficult without definitive surgical resection. This report provides a comprehensive review of GCP and all GCP cases reported to date. **Methods:** A comprehensive literature search (1972-2011) was conducted with all reported GCP cases analyzed. Keywords searched included gastritis cystica profunda, submucosal cysts of the stomach, and heterotopic submucosal gastric glands. **Results:** Thirty-seven GCP cases have been reported since 1972, which includes 29 (78%) men and 8 (21%) women (M:F ratio, 3.6:1). The overall mean age was 60.5 years (range, 39 - 81 years) with 55.6 years (range, 39 - 79) and 62.2 years (range, 39 - 81 years) in women and men, respectively. 65% (N = 24) had prior gastric surgery. 62% (N = 23) of GCP tumors were located in the body; 24% (N = 9) in the fundus; 8% (N = 3) in the antrum; or 6% (N = 2) in the cardia of the stomach. GCP was an incidental finding in 19% of patients. Complete excision was performed most often (73%) followed by endomucosal resection (18%), and polypectomy (4.5%). One patient underwent surveillance (4.5%). **Conclusions:** GCP is a rare gastric tumor, which is difficult to diagnose preoperatively and masquerades as a malignancy. GCP is more common in men and typically presents with nonspecific symptoms. Although a benign lesion, GCP may represent an intermediate histology in the malignant progression to gastric neoplasia. To date, there have been no reports of local recurrence or distant metastasis following definitive surgical excision, which remains the standard of care.

Keywords: Gastritis Cystica Polyposa; GCP; Submucosal Cysts of the Stomach; Heterotopic Submucosal Gastric Glands

1. Introduction

Gastritis cystica profunda (GCP) has been infrequently described in the English literature. The histological findings of cystic glandular inclusions with a connective tissue laden submucosa were first described by Littler and Gleibermann in 1972 [1]. However, it was not until 1981 that Franzin and Novelli coined the term "gastritis cystica profunda," and described fifteen cases of GCP that were initially confused with other gastric pathologies, such as mature erosions and gastric adenomas [2]. Since that time, very few additional cases of GCP have been reported, and in these instances GCP was initially thought to represent Ménétrier's disease, [3-5] gastric adenocarcinoma, [6,7] inverted hyperplastic polyps, [8] and other pathologies. This report describes a rare case of a GCP in the antrum of a surgery-naïve 39 year-old female which endoscopically and sonographically was consistent with a gastrointestinal stromal tumor (GIST). A comprehensive review and discussion of the histogenesis, diagnosis, and management of GCP is also provided.

2. Case Report

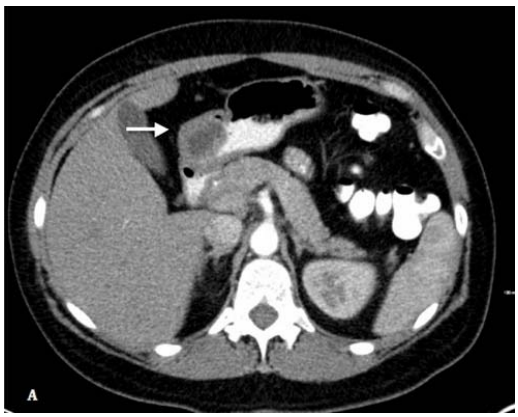
A 39 year-old asymptomatic female, with no history of gastric surgery underwent an abdominal sonogram for surveillance of a known focal nodular hyperplasia of the liver. She had no other significant past medical or surgical history, and took no medications. Sonography revealed a 3 cm submucosal mass in the gastric antrum. Physical examination revealed a non-tender, non-distended abdomen without hepatosplenomegaly or other abdominal masses. Laboratory studies revealed normal hemoglobin and liver function tests (LFTs). A contrast-enhanced abdominal computed tomography (CT) scan revealed a 3 × 2 cm hypodense mass in the gastric an-

trum without evidence of outlet obstruction (**Figures 1(a1)** and **(a2)**). The patient underwent an esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), and mucosal/fine needle aspiration (FNA) biopsy of a 3 cm subepithelial gastric mass located just proximal to the pylorus with normal overlying mucosa (**Figure 1(b)**). Superficial mucosal biopsies revealed benign superficial gastric mucosa with focal chronic inflammation. The well-defined, hypo-echoic antral mass was confined to the submucosa on EUS. There were no perigastric or celiac lymph nodes identified (**Figure 1(c)**). Three 25 gauge and two 22 gauge FNA biopsies of the mass were non-diagnostic, but given the clinical and radiographic findings, a diagnosis of GIST was suspected.

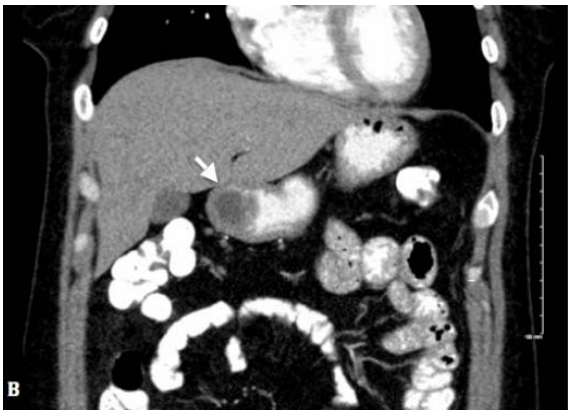
The patient underwent a laparoscopic-assisted antrectomy with Roux-en-Y reconstruction. Gross review revealed a tan-pink, polypoid and rubbery submucosal lesion measuring 3.5 × 3.0 × 1.5 cm with pathologically clear 4.5 cm proximal and 3.7 cm distal margins (**Figure 2(a)**). Intraoperative frozen sections revealed an edematous spindle cell neoplasm with a focus of glandular inclusions suspicious of GIST (**Figures 2(b1)** and **(b2)**). Final microscopic evaluation revealed a submucosal cystic structure lined by benign appearing antral-to-pyloric type gastric mucosa with surrounding hypertrophic muscle tissue consistent with gastritis cystica profunda (**Figures 2(c1)** and **(c2)**). Immunostaining for CD34, c-Kit (CD 117), and S100 were negative, effectively excluding the diagnosis of GIST.

3. Results

Thirty-seven cases of GCP have been documented, including the current case reported here. Clinical and treatment data are detailed in **Table 1**. Among these 37 patients were 29 men and 8 women (M:F ratio, 3.6:1) with



(a1)



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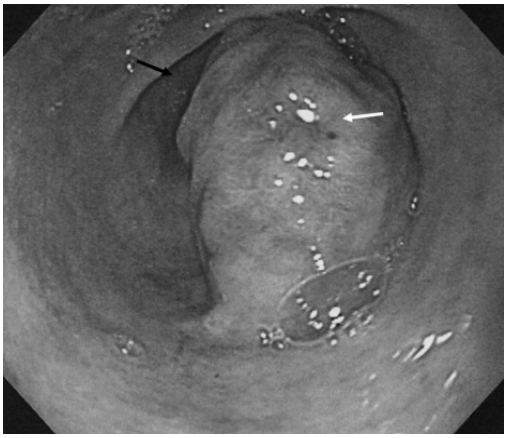
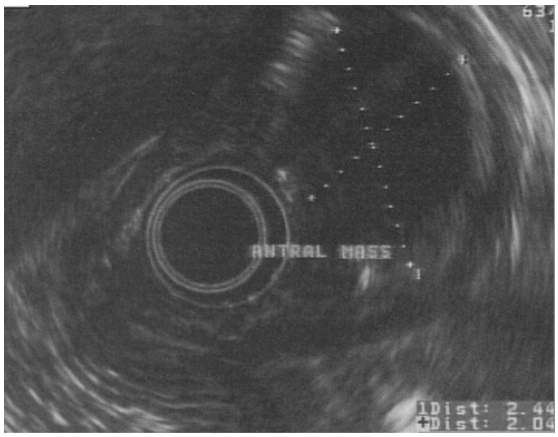
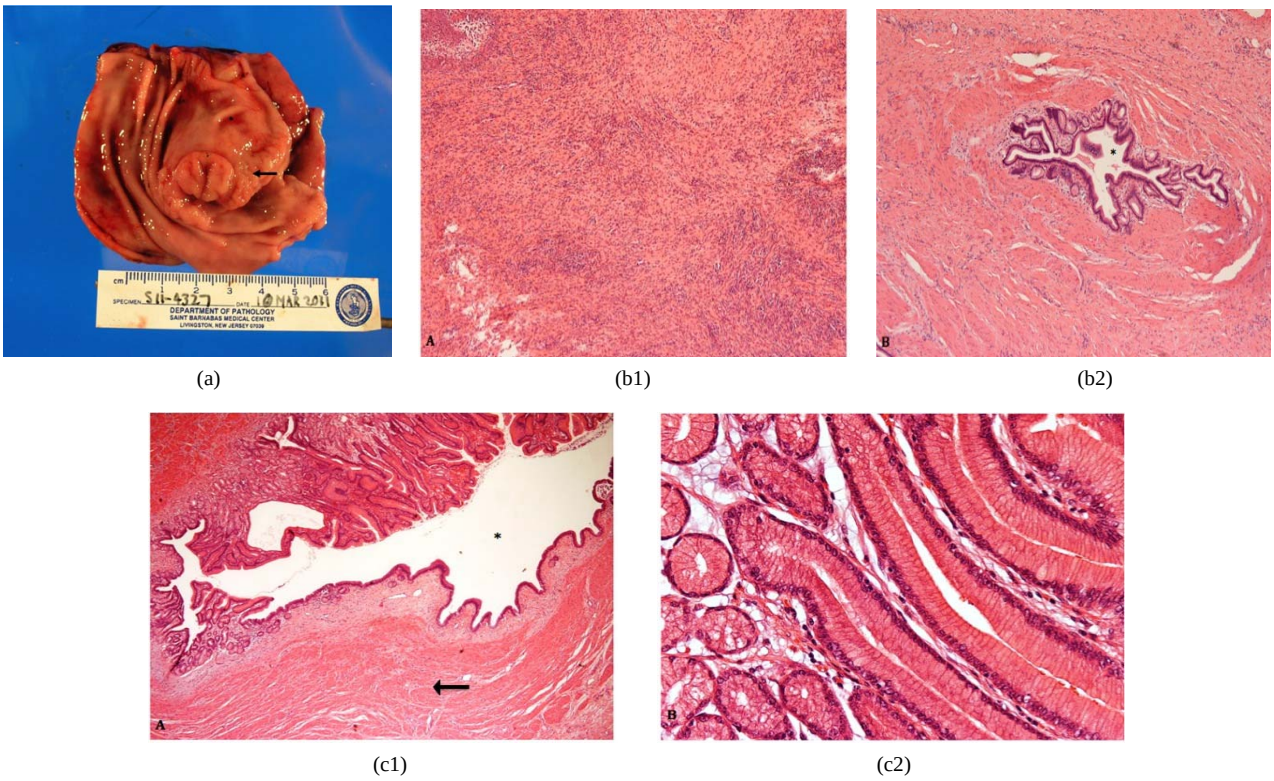


(b)



(c)

Figure 1. (a): Axial (1) and coronal (2) contrast-enhanced computed tomography (CT) images revealing a 3.2 × 2.3 cm non-enhancing, partially necrotic mass (white arrows) in the gastric antrum located just proximal to the pylorus; (b): Esophagogastroduodenoscopy (EGD) image demonstrates a 3 cm subepithelial gastric mass with a lobulated contour located immediately proximal to the pylorus (black arrow) covered by glistening pink mucosa with an erythematous focus (white arrow); (c): Radial endoscopic ultrasound image revealing intact gastric wall layers. The well-demarcated antral lesion (dotted X) represents a 2.4 × 2.0 cm homogeneous, hypocheoic mass that arises completely from within the submucosal layer.



(a) (b1) (b2)

(c1) (c2)

Figure 2. (a): Gross pathologic specimen demonstrates a rubbery, antral lesion confined to the lesser curvature with central ulceration consistent with previous biopsy (black arrow). The remaining mucosa is tan and glistening with focal areas of hemorrhage; (b): Histologic examination of the submitted specimen revealed a submucosal spindle cell proliferation (1) with an isolated glandular inclusion (*) (2) (Hematoxylin-Eosin, 40×); (c): (1) Low power magnification view of the specimen demonstrates dilated, heterotopic gastric glands (*) in the submucosa with surrounding muscular hypertrophy (black arrow). (Hematoxylin-Eosin, 20×) (2) On higher magnification, the irregular cystic dilations are lined by antral-to-pyloric type epithelium in a background of mucoid submucosal stroma (Hematoxylin-Eosin, 40×).

an overall mean age of 60.5 years (range, 39 - 81 years). The mean age among women was 55.6 years (range, 39 - 79 years), and the mean age among men was 62.2 years (range, 39 - 81 years). The most common anatomic GCP location was the gastric body (62%) followed by the fundus (24%), antrum (8%), and cardia (6%); some lesions were at the junction of body and antrum. Abdominal pain was the most common presenting complaint (27%) followed by bleeding/anemia (16%), fullness (8%), and anorexia/weight loss (8%). GCP was an incidental finding in 19% of patients. Prior gastric resection was described in 65% of patients. Of the thirty-seven cases described, treatment plans were provided for only twenty two (59%). Treatments included complete excision (73%), endomucosal resection (18%), polypectomy (4.5%), and surveillance (4.5%). When complete excision was performed, there have been no recurrences reported.

4. Discussion

GCP is a rare gastric lesion characterized by the presence of gastric glands in the submucosa of the stomach with normal overlying mucosa and is often mistaken for other more common gastric pathologies [3-8]. An unspecified mucosal insult or injury is widely accepted as the nidus for GCP genesis, however, the pathophysiology is largely unknown. Whether GCP develops secondary to chronic inflammation, foreign body reaction or ischemic injury is unclear, but some interruption of the muscularis mucosa allows migration of epithelial cells into the submucosal layer and subsequent cystic dilation [6]. The majority of reported cases occurred in patients with a history of gastric surgery (65%), however, as in the current case, GCP has been described in non-operated patients as well [3, 6,9,10]. Mucosal prolapse and duodenal reflux which may occur following gastric surgery are believed to propagate the cystic changes observed within the submucosa [1,11-14]. In animal studies performed on Wistar rats, GCP was observed following both Billroth I and Billroth II partial gastrectomies, although a significantly higher incidence was noted following a Billroth II procedure [11].

Since the initial description of a GCP by Littler and Gleibermann, significant debate has ensued over the malignant potential of these lesions. Historically, the pres-

Table 1. All published cases of Gastritis cystica profunda from 1972-2011.

Study	Location	Age (years)	Sex	Prior Gastric Surgery	Presenting Symptoms	Treatment
Littler *et al.*, 1972 [1]	Fundus	47	M	Y	Epigastric pain, melena, anemia	Partial gastrectomy with gastroenteric anastomosis
Béchade *et al.*, 2007 [3]	Fundus	79	F	N	Epigastric pain	Endomucosal resection (EMR)
Lim *et al.*, 2010 [4]	Antrum	63	F	N	Incidental	Partial gastrectomy
Okada *et al.*, 1994 [5]	Body/Antrum	51	F	N	Abdominal pain	Endomucosal resection (EMR)
Okada *et al.*, 1994 [5]	Body/Antrum	63	M	N	Melena	Endomucosal resection (EMR)
Moon *et al.*, 2010 [6]	Body	77	M	Y	Incidental	Total Gastrectomy
Moon *et al.*, 2010 [6]	Antrum	76	M	N	Anorexia	Endomucosal resection (EMR)
Tsuji *et al.*, 2008 [7]	Body/Antrum	61	M	N	Epigastric pain	Partial gastrectomy with regional lymph node dissection
Yamashita *et al.*, 2002 [8]	Body	69	M	N	Melena	Partial gastrectomy
Yamashita *et al.*, 2002 [8]	Body	81	M	N	Vomiting, fullness	Partial gastrectomy
Koga *et al.* 1979, [12]	Fundus	39	M	Y	Epigastric pain, fullness	Partial gastrectomy
Koga *et al.* 1979, [12]	Fundus	49	M	Y	Epigastric pain	Partial gastrectomy
Koga *et al.* 1979, [12]	Fundus	62	M	Y	Incidental	Partial gastrectomy
Koga *et al.* 1979, [12]	Fundus	63	M	Y	Incidental	Partial gastrectomy
Qizilbash, 1975 [14]	Body	67	M	Y	Incidental	N/A (post-mortem)
Fonde *et al.*, 1986 [9]	Body/Antrum	50	M	N	Epigastric pain, fullness, weight loss, hematemesis	Total gastrectomy with Roux-en-Y esophagojejunostomy
Park *et al.*, 2001 [10]	Fundus	44	F	N	Epigastric pain	Polypectomy
Mitomi *et al.*, 1998 [15]	Body	44	M	N	Abdominal pain	Total gastrectomy
Tomizuka *et al.*, 2008 [19]	Cardia	78	M	Y	Incidental	Partial gastrectomy with Roux-en-Y esophagojejunostomy
Itte *et al.*, 2008 [23]	Fundus	50	M	Y	Epigastric pain, hematemesis, anemia	Surveillance
Kurland *et al.*, 2006 [24]	Cardia	75	M	Y	Anemia, GI bleed	Partial gastrectomy with Roux-en-Y esophagojejunostomy
Wu *et al.*, 1994 [25]	Fundus	58	F	N	Anorexia, weight loss	Total gastrectomy with Roux-en-Y esophagojejunostomy
Franzin *et al.*, 1981 [2]*	Body	42 - 71	12M:2F	Y	NR	NR
Current study, 2011	Antrum	39	F	N	Incidental	Partial gastrectomy with Roux-en-Y esophagojejunostomy

*Franzin *et al.*, 1981 describes 14 cases of GCP based on histological findings alone. The authors do not describe the clinical characteristics or treatment of the patients. The patients were 42 - 71years old: 12 male and 2 female. All lesions were located in body of the stomach. N/A: Not applicable, NR: Not recorded.

ence of submucosal glands in GCP was not thought to represent cancer. Instead they were likened to the histological changes seen in patients with longstanding peptic ulcer disease (PUD) and gastritis [9,12]. More recent reports have described dysplastic changes within the submucosal glands of select GCP cases suggesting an adenocarcinomatous precursor lesion [6,7]. Mitomi *et al.* described increased expression of Ki-67, p53, and p21 in GCP lesions indicative of increased epithelial proliferation and increased DNA repair that could be linked to malignant progression [15]. Furthermore, targeted deletion of a subunit in apical K+ channels in parietal cells in mice (KCNE2) has been noted to result in an increased rate of GCP formation and overt neoplasia suggesting that KCNE2 disruption is a possible risk factor for gastric neoplasia [16].

The differential diagnosis of submucosal lesions within the stomach includes lipoma, leiomyoma, leiomyosarcoma, lymphoma, GIST, and GCP. Although gastric adenocarcinoma begins as a mucosal lesion, gastric cancer can also

present with normal mucosa in 20% - 30% of cases, further obscuring and adding to the difficulty of GCP diagnosis [17]. It has proven nearly impossible to preoperatively distinguish GCP from other gastric lesions based on symptoms alone. A comparison between the demographics, presenting symptoms, and histological appearance of GCP, gastric adenocarcinoma, and GIST is provided in **Table 2**. Clinical manifestations of GCP are typically nonspecific, leading to significant diagnostic uncertainty. Histological examination of biopsy specimen is typically non-diagnostic and a formal surgical excision is usually required. Compared to gastric adenocarcinoma, GCP occurs in younger, male patients and rarely presents with weight loss, anorexia, or abdominal fullness. In regards to distinguishing GCP from GIST, GCP occurs in a similar age range, but is almost four times more common in men, and only rarely associated with anemia or gastrointestinal bleeding (16%) compared to GIST (72%).

Though GCP cannot be diagnosed on endoscopic evaluation alone, GCP generally lacks mucosal erosion, ulceration, marked fibrosis, or firm consistency, which can occur with gastric adenocarcinoma and less commonly with GIST. On EUS, GCP typically appears as a homogeneous, hypoechoic cystic mass with minimal, if any, solid component [10]. Radiographically, GIST and GCP both appear as hypoechoic, intramural polypoid masses with cystic changes [18]. Because the mucosa is spared in GCP, submucosal FNA biopsies are required for a definitive diagnosis, [19] although these too are often non-diagnostic as in the current case described [12]. Histologic examination of a surgically excised specimen is also difficult and may not be possible until the definite surgical excision specimen can be fully evaluated. Immunohistochemical staining of biopsy or surgical specimen is important to make the diagnosis of GCP and exclude other lesions such as GIST, neuroma, and leiomyoma. CD34 is positive in ~60% - 70% of GISTs, while S100 antigen stains positive in only 5% [20]. c-Kit (CD117) expression is the most sensitive marker of GIST and is positive in ~90% - 95% cases [21]. The accuracy of EUS-FNA with immunostaining in preoperative GIST diagnosis has been reported at 91% - 100% [22].

A defined treatment strategy for GCP has not been well described given the rarity of the lesions and the difficulty in diagnosing them preoperatively. To date, all but one case of GCP in which treatment has been detailed were managed with definite surgical resection. In this one case, the patient was operated upon for severe upper gastrointestinal bleeding and ulcer biopsy demonstrated GCP on final histopathology [23]. Given the lack of a pathognomonic endoscopic or radiographic appearance of GCP, surveillance cannot be endorsed. No cases of local recurrence or distant metastasis for GCP follow-

Table 2. A comparison between the common clinical presentations of Gastritis cystica profunda, Gastric cancer, and gastrointestinal Stromal tumor.

	Gastritis Cystica Profunda	Gastric Cancer	Gastrointestinal Stromal Tumor
Incidence	37 reported cases	7.1/100,000 [29]	0.32/100,000 [28]
Male:female ratio	3.6:1	1.7:1 [35]	1:1 [27]
Mean age at diagnosis (range)	60.5 (39 - 81)	69.7 (<19 - 70+) [35]	60 (40 - 80) [31]
Anatomic location	Submucosal	Mucosal	Submucosal
Gross appearance	Soft intramural mass with smooth mucosa	Varied: protruding, non-protruding, or excavated lesion +/– ulcerated mucosa and definite limits [37]	Well-circumscribed, intramural mass with smooth mucosa [26]
Histologic appearance	Cystic gastric glandular inclusions in submucosa	Single or small clusters of cells with marked cytological atypia (pleomorphic nuclei with prominent nucleoli) and architectural atypia (necrosis, cribriforming)[34]	Spindle cells with eosinophilic cytoplasm arranged in whirls [26]
Symptom			
Incidental (%)	19%	20% [38]	30% [32]
Weight loss (%)	8%	62% [35]	32% [33]
GI bleeding or anemia (%)	16%	20% [35]	72% [36]
Pain or fullness (%)	27%	70% [35]	32% [36]
5-year survival rate	100%	27.1% [29]	35% [30]
Curative resection	100%	41.2% [31]	54% [30]

ing surgical resection have been reported.

In summary, GCP is a rare gastric submucosal tumor that is confused with other more common gastric pathologies. It is important to consider GCP in the differential diagnosis of patients presenting with suspicious submucosal gastric lesions, irrespective of nondiagnostic EUS-FNA biopsies. Future studies may help to elucidate the natural history of this disease process, as well as the possibility for malignant potential, thus permitting more evidence-based treatment strategies. Until then, known GCP or suggestive submucosal gastric lesions should be excised using established surgical oncology principles.

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