

CASE REPORT

Endoscopic features of early stage gastric adenocarcinoma of fundic gland type (chief cell predominant type): a case report

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Received: July 1, 2014

Accepted: September 3, 2014

Online Published: September 10, 2014

DOI: 10.5430/crcp.v2n1p17

URL: <http://dx.doi.org/10.5430/crcp.v2n1p17>

Abstract

A 64-year-old *Helicobacter pylori* infection-naïve woman was found to have a small (≤ 10 mm) depression on the anterior wall of the upper gastric body. On white light endoscopy, the lesion appeared to be inconspicuous, whitish with dilated vessels. 0.2% indigo carmine chromoendoscopy enable better visualization of the depression. On narrow band imaging with magnification, the microsurface structure of the surrounding mucosa was absent and a network of tortuous microvessels were observed within the depressed area. Endoscopic ultrasonography indicated that the tumor was confined to the mucosa. The lesion was removed by endoscopic submucosal dissection. Histological finding of the resected specimen revealed that carcinomatous tubules existed in the deep part of the lamina propria with minimal (300 μ m) submucosal invasion which were covered with the atrophic non-neoplastic foveolar epithelium. The tumor was diffusely positive for MUC6 and pepsinogen-I, while it was negative for MUC5AC and H+/K+-ATPase. A diagnosis of early stage gastric adenocarcinoma of fundic gland type (chief cell predominant type) was made.

Key words

Gastric cancer, Fundic gland type, *Helicobacter pylori*, Endoscopic submucosal dissection

1 Introduction

Well differentiated gastric adenocarcinoma ordinary shows morphological phenotype that is similar to foveolar epithelium, pyloric gland or intestinal metaplasia, but gastric adenocarcinoma that shows fundic gland differentiation is uncommon^[1].

There were a few case reports or series of gastric parietal cell carcinoma previously^[2-7] but differentiation of tumor cells to parietal cells were never proven by immunostaining for H+/K+ ATPase, except for a single case of advanced poorly differentiated carcinoma^[4]. A case of gastric adenocarcinoma with chief cell differentiation was first reported by Tsukamoto, *et al.* in 2007^[8]. Ueyama, *et al.* reported ten cases and proposed gastric adenocarcinoma of fundic gland

(chief cell predominant type) as a new entity of gastric adenocarcinoma^[9]. Gastric adenocarcinoma of fundic gland (chief cell predominant type) is defined as a neoplasm that mainly consists of highly differentiated columnar epithelial cells resembling the fundic gland cells, mainly chief cells, with nuclear atypia. Although incidence of this type of cancer seems to be low (1.6% of gastric adenocarcinoma)^[10], recently, several case series have been published in Japan^[11] and other countries^[12-14].

Although the histological characteristic of the gastric adenocarcinoma of fundic gland type is now accepted, endoscopic features of this type of gastric adenocarcinoma have not been fully described. We report a case of gastric adenocarcinoma of fundic gland type that was carefully analyzed with image-enhanced endoscopy before endoscopic submucosal dissection.

2 Case report

A 64-year-old woman was found to have a small (≤ 10 mm) whitish depression with marginal elevation of the surrounding mucosa in the anterior wall of the upper gastric body. Biopsy specimens from this lesion were diagnosed as “indefinite for neoplasia”. She was referred to our endoscopy unit for further evaluation and consideration for endoscopic treatment. She did not receive any medication. She has no family history of gastric cancer. Esophago-gastro-duodenoscopy was carried out to re-evaluate the lesion. The surface of the background gastric mucosa was smooth and gastric folds were preserved circumferentially in the gastric body indicating that the patient did not have chronic atrophic gastritis. A tiny depression was noticed on the gastric fold in the anterior wall of the upper gastric body. The lesion was observed as a whitish area with an indistinctive margin. There were also dilated vessels observed inside (see Figure 1). The depression was contrasted with 0.2% indigo carmine chromoendoscopy (see Figure 2). On narrow band imaging (NBI) with magnification, the microsurface structure of the surrounding mucosa appear to gradually disappear at the boundary of the tumor and a network of tortuous microvessels were observed within the depressed area (see Figure 3). Serum antibody test, histology and culture of biopsy specimens were negative for *Helicobacter pylori* infection. According to the depressed morphology, whitish appearance with dilated vessels, and a negative *Helicobacter pylori* infection, an endoscopic diagnosis of a fundic gland type gastric adenocarcinoma was made. On endoscopic ultrasound examination using a mini-probe (UM-2R, Olympus Medical Systems, Tokyo, Japan), the lesion was observed as arising from the second layer without any evidence of submucosal invasion (see Figure 4). Chest and abdominal computed tomography scan revealed no local or distant metastases. We thus performed an endoscopic submucosal dissection.

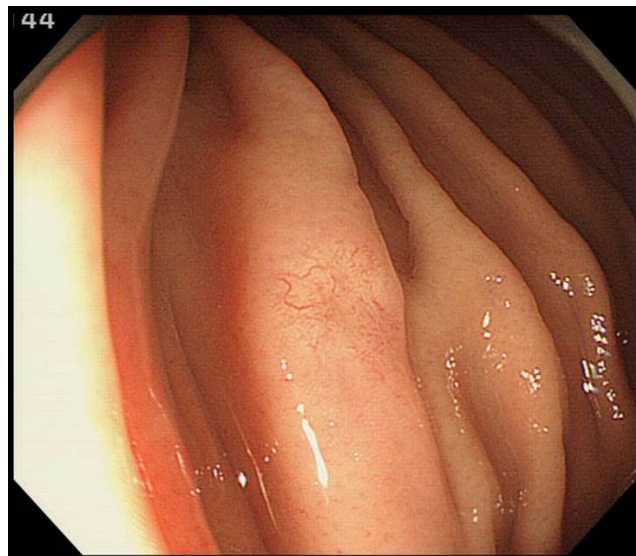


Figure 1. White light image. A small depression was observed at the anterior wall of the upper gastric body. The lesion looked slightly whitish and dilated vessels were noted in the close view.



Figure 2. Chromoendoscopic image. Magnifying chromoendoscopy contrasted the lesion further.

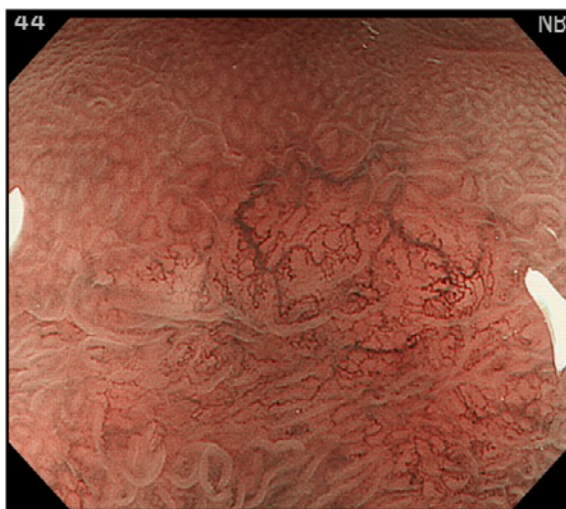


Figure 3. Magnifying narrow band imaging image. Magnifying narrow band imaging showed tortuous subepithelial capillaries in the depressed area.

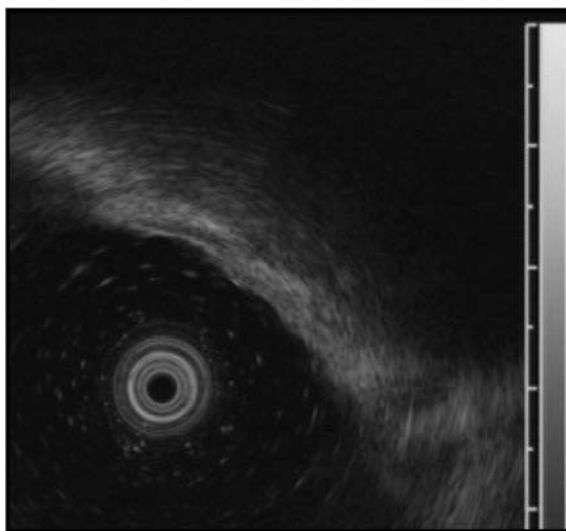


Figure 4. EUS image with mini-probe (20 MHz). The low-echoic tumor was confined to the mucosa.

The lesion was successfully removed *en bloc*. Histological examination of the resected specimen revealed carcinomatous tubules in the deep part of the lamina propria mimicking normal fundic gland (see Figure 5) and invaded minimally into the submucosa (see Figure 6). Immunostaining revealed the carcinomatous glands to be positive for MUC6 and pepsinogen-I, and negative for H+/K+-ATPase and MUC5AC (see Figure 7).

A final diagnosis of gastric adenocarcinoma of fundic gland type (chief cell predominant type) was made. The tumor invaded the submucosa upto 300 µm but had neither lymphatic nor venous permeation; and the horizontal and vertical margins were clear. Therefore, the resection was regarded as curative [4].

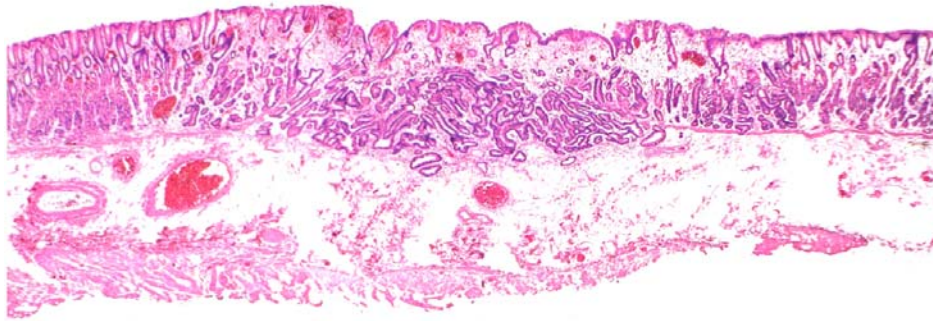


Figure 5. The histological finding. The lesion demonstrated a well differentiated type adenocarcinoma proliferating in the deep part of the lamina propria and invading minimally into the submucosa. The lesion was covered with atrophic non-neoplastic foveolar epithelium (Hematoxylin & Eosin, ×20).

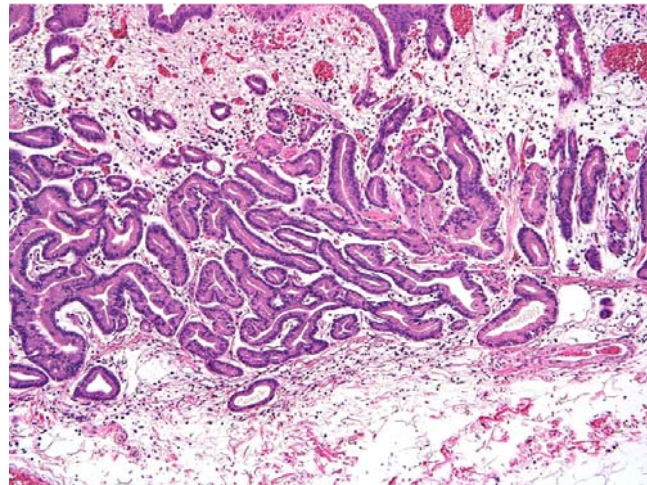


Figure 6. The histological finding. The cancer tubules mimicked fundic glands. (Hematoxylin & Eosin, ×100).

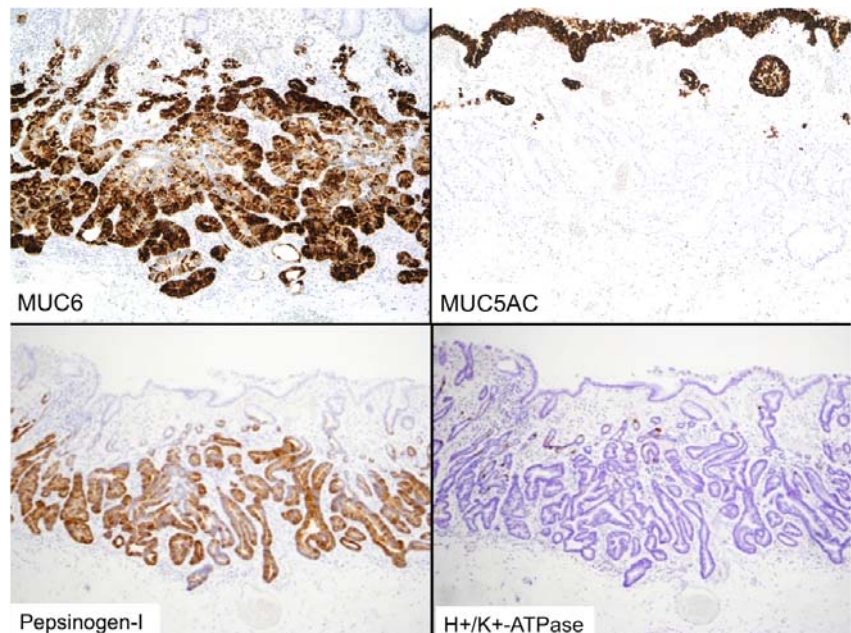


Figure 7. Immunostaining: MUC6, MUC5AC, pepsinogen-I and H+/K+-ATPase, ×100

3 Discussion

In this report, a case of a small gastric adenocarcinoma of fundic gland (chief cell predominant) type which was demonstrated by image-enhanced endoscopy and subsequently treated successfully by ESD was described.

Gastric adenocarcinoma of fundic gland type (chief cell predominant type) frequently develops in the upper part of the stomach in older patients^[9]. Endoscopic finding of gastric adenocarcinoma of fundic gland (chief cell predominant) type may appear to be submucosal tumor-like (60%) or flat or depressed (40%); have a whitish hue (70%); dilated vessels with branching architecture on the surface (50%) with non-atrophic surrounding mucosa (90%)^[15]. The endoscopic appearance of this case had typical features described above. The foveolar epithelium above the cancer tubules became atrophic compared to the surrounding mucosa (see Figure 5) which may appear as whitish on white light endoscopy.

NBI enhances the surface structure and vascular architecture of the superficial mucosa with illumination of two specific short wavelength lights which may improve diagnostic accuracy of superficial neoplasms^[16]. On NBI with magnification, the microsurface structure of the normal mucosa gradually disappeared at the depressed area. Instead dilated subepithelial capillaries that were connected to the thick collecting venules forming a network were visualized. Typical features of presence of a demarcation line and irregular microvessel pattern that is diagnostic of early gastric cancer^[17], was not visualized. Because the cancer tissue was not exposed on the surface according to the histological finding, we speculated that the absent microsurface structure and dilated microvessels were probably “covered” by the atrophic change of the non-neoplastic epithelium on the surface of the cancerous tissue. Accordingly, surface evaluation by magnifying NBI may assist but may not be useful for accurate diagnosis of this type of cancer.

Choi, *et al.* indicated the diagnostic accuracy of conventional endoscopic findings by experienced endoscopists was similar to that of EUS^[18]. Moreover, EUS sometimes overestimates tumor depth^[19], leading to unnecessary surgery in some cases. Histological analysis of resected specimens provides the most accurate assessment of the tumor depth and lymphatic or venous involvement, which define requirement for surgery. Therefore, EUS is not routinely performed before endoscopic resection of early gastric cancer in some centers^[20]. The fundic gland type gastric adenocarcinoma develops in the deep part of the mucosa, and frequently invades the submucosa^[9]. In this case, the cancer tubules proliferated in the deep part of the mucosa which was covered with non-neoplastic atrophic foveolar epithelium. It also invaded the submucosa although only superficially. This suggests that careful pre-treatment assessment with EUS and post-treatment histological evaluation of invasion depth are important for the gastric adenocarcinoma of fundic gland (chief cell predominant) type.

Most of gastric cancers evolve through multiple steps with *Helicobacter pylori* associated superficial gastritis progressing through atrophy with intestinal metaplasia, followed by the development of dysplasia, and finally carcinoma. Ueyama, *et al.* suggested that the gastric adenocarcinoma of fundic gland (chief cell predominant) type was likely to develop in patients with neither *Helicobacter pylori* infection nor atrophic gastritis^[9]. Because *Helicobacter pylori* infection rate has been declining dramatically in recent years in Japan^[21], incidence of this new variant of gastric cancer may increase in the future. Therefore, recognition of typical endoscopic finding of gastric adenocarcinoma of fundic gland (chief cell predominant) type is important for early detection of this type of cancer.

Acknowledgement

Authors are grateful to Professor Takashi Yao for special staining of the ESD specimen and meaningful advice for histological diagnosis.

References

- [1] Yao T, Utsunomiya T, Oya M, *et al.* Extremely well-differentiated adenocarcinoma of stomach: clinicopathological and immunohistochemical features. *World J Gastroenterol.* 2006; 12: 2510-2516. PMID: 16688795.

- [2] Capella C, Frigerio B, Cornaggia M, *et al.* Gastric parietal cell carcinoma--a newly recognized entity: light microscopic and ultrastructural features. *Histopathology*. 1984; 8: 813-24. PMID: 6083970. <http://dx.doi.org/10.1111/j.1365-2559.1984.tb02397.x>
- [3] Hedenbro JL, Hägerstrand I, Rychterova V. Parietal cell carcinoma: a new differential diagnosis for submucosal gastric tumors. *Endoscopy*. 1990; 22: 47-8. PMID: 2307130. <http://dx.doi.org/10.1055/s-2007-1012787>
- [4] Yang GY, Liao J, Cassai ND, *et al.* Parietal cell carcinoma of gastric cardia: immunophenotype and ultrastructure. *Ultrastruct Pathol*. 2003; 27: 87-94. PMID: 12746199. <http://dx.doi.org/10.1080/01913120309923>
- [5] Takubo K, Honma N, Sawabe M, *et al.* Oncocytic adenocarcinoma of the stomach: parietal cell carcinoma. *Am J Surg Pathol*. 2002; 26: 458-65. PMID: 11914623. <http://dx.doi.org/10.1097/0000478-200204000-00007>
- [6] Rychterova V, Hägerstrand I. Parietal cell carcinoma of the stomach. *APMIS*. 1991; 99: 1008-12. PMID: 1958345. <http://dx.doi.org/10.1111/j.1699-0463.1991.tb01293.x>
- [7] Byrne D, Holley MP, Cuschieri A. Parietal cell carcinoma of the stomach: association with long-term survival after curative resection. *Br J Cancer*. 1988; 58: 85-7. PMID: 3166896. <http://dx.doi.org/10.1038/bjc.1988.168>
- [8] Tsukamoto T, Yokoi T, Maruta S, *et al.* Gastric adenocarcinoma with chief cell differentiation. *Pathol. Int*. 2007; 57: 517-22. PMID: 17610477. <http://dx.doi.org/10.1111/j.1440-1827.2007.02134.x>
- [9] Ueyama H, Yao T, Nakashima Y, *et al.* Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. *Am. J. Surg. Pathol*. 2010; 34: 609-19. PMID: 20410811.
- [10] Hidaka Y, Mitomi H, Saito T, *et al.* Alteration in the Wnt/ β -catenin signaling pathway in gastric neoplasias of fundic gland (chief cell predominant) type. *Hum Pathol*. 2013; 44: 2438-48. PMID: 24011952. <http://dx.doi.org/10.1016/j.humpath.2013.06.002>
- [11] Fukatsu H, Miyoshi H, Ishiki K, *et al.* Gastric adenocarcinoma of fundic gland type (chief cell predominant type) treated with endoscopic aspiration mucosectomy. *Dig Endosc*. 2011; 23: 244-6. PMID: 21699569. <http://dx.doi.org/10.1111/j.1443-1661.2011.01125.x>
- [12] Park ES, Kim YE, Park CK, *et al.* Gastric adenocarcinoma of fundic gland type: report of three cases. *Korean J Pathol*. 2012; 46: 287-91. PMID: 23110017. <http://dx.doi.org/10.4132/KoreanJPathol.2012.46.3.287>
- [13] Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. *Am J Surg Pathol*. 2012; 36: 1030-5. PMID: 22472957. <http://dx.doi.org/10.1097/PAS.0b013e31825033e7>
- [14] Chen WC, Rodriguez-Waitkus PM, Barroso A, *et al.* A Rare Case of Gastric Fundic Gland Adenocarcinoma (Chief Cell Predominant Type). *J Gastrointest Cancer*. 2012 Jul 12.
- [15] Ueyama H, Matsumoto K, Nagahara A, *et al.* Endoscopy. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). 2014; 46: 153-7
- [16] Uedo N, Fujishiro M, Goda K, *et al.* Role of narrow band imaging for diagnosis of early-stage esophagogastric cancer: current consensus of experienced endoscopists in Asia-Pacific region. *Dig Endosc*. 2011; 23 Suppl 1: 58-71. PMID: 21535204. <http://dx.doi.org/10.1111/j.1443-1661.2011.01119.x>
- [17] Ezoe Y, Muto M, Uedo N, *et al.* Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. *Gastroenterology*. 2011; 141: 2017-2025. PMID: 21856268. <http://dx.doi.org/10.1053/j.gastro.2011.08.007>
- [18] Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. *Endoscopy*. 2010; 42: 705-713. PMID: 20652857. <http://dx.doi.org/10.1055/s-0030-1255617>
- [19] Yanai H, Noguchi T, Mizumachi S, *et al.* A blind comparison of the effectiveness of endoscopic ultrasonography and endoscopy in staging early gastric cancer. *Gut*. 1999; 44: 361-365. PMID: 10026321. <http://dx.doi.org/10.1136/gut.44.3.361>
- [20] Uedo N, Takeuchi Y, Ishihara R. Endoscopic management of early gastric cancer: endoscopic mucosal resection or endoscopic submucosal dissection: data from a Japanese high-volume center and literature review *Annals of Gastroenterology*. 2012; 25: 281-290.
- [21] Akamatsu T, Ichikawa S, Okudaira S, *et al.* Introduction of an examination and treatment for *Helicobacter pylori* infection in high school health screening. *J Gastroenterol*. 2011; 46: 1353-60. PMID: 21853260. <http://dx.doi.org/10.1007/s00535-011-0450-6>