

Ectopic gastric mucosa in the submucosa of the stomach: A case report

JIAN-HUA XI¹, NAI-YING SUN², WEN-JUN GUO² and XING-JIE YANG²

Departments of ¹Geriatrics and ²Pathology, Sunshine Union Hospital, Weifang, Shandong 261000, P.R. China

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Abstract. Under normal circumstances, gastric mucosa only exists within the stomach. However, in certain situations, gastric mucosal tissue may undergo ectopia, commonly occurring in the esophagus and intestine, with rare occurrences within the stomach itself. A comprehensive literature review was performed to understand the distinct characteristics of ectopic gastric mucosa (EGM) in the stomach and investigate a rare incident of this disease, providing an in-depth analysis of the clinical, histopathologic, and differential diagnostic findings. The case was a 47-year-old man with acid reflux, heartburn, abdominal distension, and diarrhea (5-10 times daily) for >10 years. A gastroscope indicated a submucosal protuberance lesion in the gastric body that felt hard with biopsy forceps. A well-defined nodule under the mucosal muscle was revealed microscopically, composed of epithelial elements and no atypia. Immunohistochemical staining demonstrated similar EGM expression patterns compared with normal gastric mucosa. The present case report highlights the importance of accurate EGM diagnosis and understanding.

Introduction

Ectopic gastric mucosa (EGM) is typically discovered incidentally and may be asymptomatic or present with nonspecific gastrointestinal symptoms (1). Several reports describe the canceration of EGM (2-4). Thus, active treatment of EGM is necessary to prevent further complications and deterioration.

EGM can occur in several locations, such as the esophagus and colon, or in rarer instances in the anus (5) and umbilicus (6). To the best of our knowledge, there are no incidences of EGM of the stomach that have been reported in the literature. The present report describes a case of EGM, and the

clinicopathological characteristics and immunohistochemical (IHC) findings are described.

Case report

Case presentation. A 47-year-old man was admitted to the Sunshine Union Hospital (Weifang, China) in June 2023 due to acid reflux, heartburn with abdominal distension, and diarrhea (5-10 times a day) for >10 years. The patient had not received systematic medication during this period or experienced abdominal pain, belching, nausea, vomiting, fever, or noticeable weight change. However, chronic atrophic gastritis was found in the patient during a gastroscopy in 2022. Routine blood tests and the laboratory examination were normal. A ¹³C-urea breath test showed no *Helicobacter pylori* infection.

Endoscopic examination revealed a submucosal eminence, and the biopsy forceps felt slightly hard when touched (Fig. 1). Based on the endoscopy results, leiomyoma, ectopic pancreas, gastrointestinal stromal tumor, and early gastric cancer were considered. The tumor was excised entirely with endoscopic submucosal dissection (ESD). The final diagnosis awaited pathological examination.

Pathological findings

Macro-examination. A piece of mucosal tissue with a 2x2x0.3 cm volume was obtained. The tissue specimens were fixed in 4% neutral formalin at room temperature for 48 h, followed by dehydration with alcohol and treatment with xylene. Subsequently, the specimens were embedded in paraffin at 62°C and cooled. Serial sections (4 µm) were prepared and stained at room temperature with hematoxylin (~5% for 5 min), followed by eosin (~1% for 2 min (H&E)) staining. Additionally, IHC staining was performed using the paraffin-embedded tissues.

Microscopic observation. H&E and IHC staining were examined using an Olympus BX53 light microscope (Olympus Corporation). H&E staining (Fig. 2) showed normal gastric pits, gastric fundus glands, and mucosal muscles in the gastric body. EGM components were located below the mucosal muscles between the muscularis propria. The components demonstrated a well-defined nodular shape without connecting with the glands of the lamina propria. EGM composed of surface mucous, main, and parietal cells that formed a structure similar to gastric pits and gastric fundus glands, exhibited no prominent structural atypia, cell atypia, or glandular expansion.

Correspondence to: Mr. Xing-jie Yang, Department of Pathology, Sunshine Union Hospital, 9000 Yingqian Road, Weifang, Shandong 261000, P.R. China
E-mail: atcom163@163.com

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IHC staining (Fig. 3) was performed overnight at 4°C using the following primary antibodies (prediluted by the manufacturer; Guangzhou ABP Medicine Science & Technology Co., Ltd.): anti-mucin-5AC (MUC-5AC, cat. no. IM109), anti-mucin-6 (MUC-6, cat. no. IM398), anti-mucin-2 (MUC-2, cat. no. IM108), anti-synaptin (Syn, cat. no. IM136), anti-smooth muscle actin (SMA, cat. no. IM005), and anti-Ki-67 (cat. no. IR098). For IHC, tissue sections (3 μ m) were fixed in 4% formalin at room temperature for 48 h before paraffin embedding. The sections were rehydrated in a descending alcohol series (xylene, 100% ethanol, 95% ethanol, 85% ethanol, and ethanol-free water) and underwent antigen retrieval with EDTA antigen retrieval treatment (EnVision FLEX Target Retrieval Solution, High pH; cat. no. K8000; Agilent Technologies, Inc.) in a microwave for 3 min at high heat (wattage, 700 W), followed by incubation at room temperature for 8 min. Endogenous peroxidase activity was quenched using 3% hydrogen peroxide in methanol before incubation with the primary antibodies. The secondary antibody from EnVision FLEX/HRP (prediluted by the manufacturer; cat. no. K8000; Agilent Technologies, Inc.) was used to treat the sections at room temperature for 25 min. Subsequently, a chromogen detection reagent was used according to the manufacturer's protocol (EnVision FLEX DAB+ Chromogen; cat. no. K8000; Agilent Technologies, Inc.). IHC revealed that MUC-5AC was positively expressed in the EGM surface mucus cells and MUC-6 in the EGM mucous neck cells. SMA was expressed in the mucosal muscle and was used to determine the integrity of the mucosal muscle. The Ki-67 proliferating index was <1% of EGM. Additionally, Syn was positive in scattered neuroendocrine cells near the basal region of the gland, consistent with the positive pattern of neuroendocrine cells in the glands of the lamina propria. Finally, MUC-2 was negatively expressed in EGM and normal gastric mucosa.

Pathological diagnosis. The patient was diagnosed with (gastric body) EGM in the submucosa.

Follow-up. ESD removed the tumor completely, and post-operative recovery was good. No recurrence was observed during the 5 week follow-up.

Discussion

Two theories currently explain the mechanism of EGM in the stomach. The most widely accepted theory is that the EGM is an embryological remnant. The second theory is that EGM is the product of abnormal inflammation-related proliferation (7). In the present report, the 47-year-old patient was hospitalized due to several atypical symptoms, including chronic atrophic gastritis, for ~10 years. For the 'congenital malformation' theory to apply to this patient, EGM could not have caused the symptoms. According to the second theory, the symptoms were potentially caused by EGM. Alternatively, the symptoms could have been the result of chronic colitis. There is no direct evidence to support whether EGM caused these symptoms.

To the best of our understanding, few reports exist about EGM in the stomach, and EGM before pathological examination has not been considered. The collected literature (Table I) was reviewed (7-10), and found that all the patients were males aged 23-72 years old with primary complaints of nonspecific

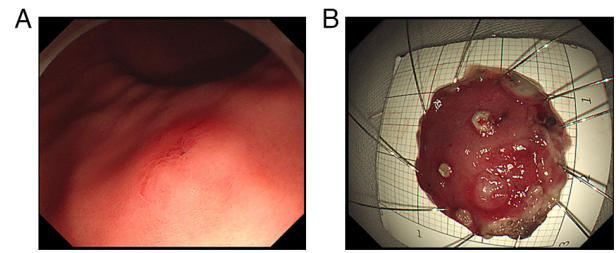


Figure 1. Endoscopic image of the tumor. (A) A protuberant tumor under the mucosa. (B) The tumor was removed by endoscopic submucosal dissection.

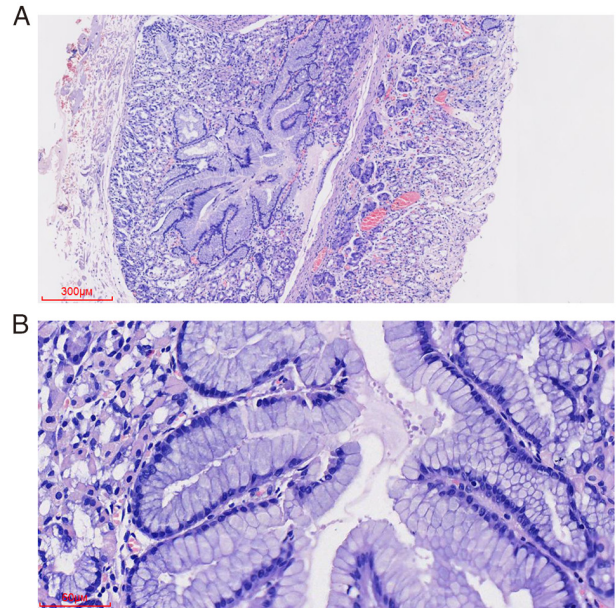


Figure 2. Histopathological appearance of ectopic gastric mucosa in the submucosa. (A) Low magnification: The ectopic gastric mucosa was located below the mucosal muscle with clear boundaries. Magnification, x40; H&E staining; scale bar, 300 μ m. (B) A partially enlarged view of the tissue section in panel (A). The ectopic gastric mucosa was composed of mucus cells, main cells, and parietal cells; no cell atypia was present. Magnification, x200; scale bar, 60 μ m. H&E, hematoxylin and eosin.

abdominal symptoms. The diseased sites in the stomach varied (for example the pylorus, gastric fundus, lesser curvature, and gastric body). There were no records of death in the cases with the follow-up data. Notably, all patients were Eastern Asians (for example Chinese and Japanese). Eastern Asian countries have the highest incidence of gastritis and gastric cancer in the world (11,12). With the results of the present study, it is suggested that regardless of severity, gastric diseases in Eastern Asians should be treated cautiously to prevent the disease from progressing. Additionally, regular physical examinations are recommended for the early detection and timely management of any gastric diseases.

EGM is distinct from other diseases, including gastric adenocarcinoma of the fundic gland, neuroendocrine tumor grade G1, ectopic pancreas, gastritis cystica profunda, and inverted hyperplastic polyp (IHP). First, in gastric adenocarcinoma of the fundic gland type, the gland is similar to a normal gastric fundus gland, with several cell types such as main and parietal cells. Typically, under the microscope, the cell

Table I. Overview of the literature on ectopic gastric mucosa in the stomach.

First author, year	Language	Age, years	Chief complaint	Race	Examination	Diagnosis before pathological examination	Ectopic site	Cancerous	Operation	Follow-up	(Refs.)
Wang <i>et al</i> , 2019	English	30	Abdominal distension of a six- month duration	Chinese	Gastroscopy	-	The cardia of the gastric fundus, located between the muscularis mucosae and submucosa	No	ESD	Alive after 1 year	(7)
Zhou <i>et al</i> , 2002	Chinese	48	Paroxysmal upper abdominal pain for more than 2 years	Chinese	Barium meal examination	Leiomyoma, GC	Pylorus, muscular layer	No	Subtotal gastrectomy	-	(8)
Gu <i>et al</i> , 2002	Chinese	23	Pain in stomach a month ago	Chinese	Gastroscopy	Leiomyoma, ectopic pancreas	Pylorus, muscular layer	No	Locally surgical resection	-	(9)
Nakano <i>et al</i> , 1987	Japanese	72	Anorexia and hungry epigastric pain	Japanese	Gastroscopy and upper gastrointestinal series examination	GC	Anterior and posterior walls of the lesser curvature	Yes	Total gastrectomy	-	(10)
Present report	English	47	Acid reflux, heartburn with abdominal distension and diarrhea (5-10 times a day) for more than 10 years	Chinese	Gastroscopy	Leiomyoma, ectopic pancreas, gastrointestinal stromal tumor, early GC	Gastric body	No	ESD	Alive after 5 weeks	-

GC, gastric cancer; ESD, endoscopic submucosal dissection.

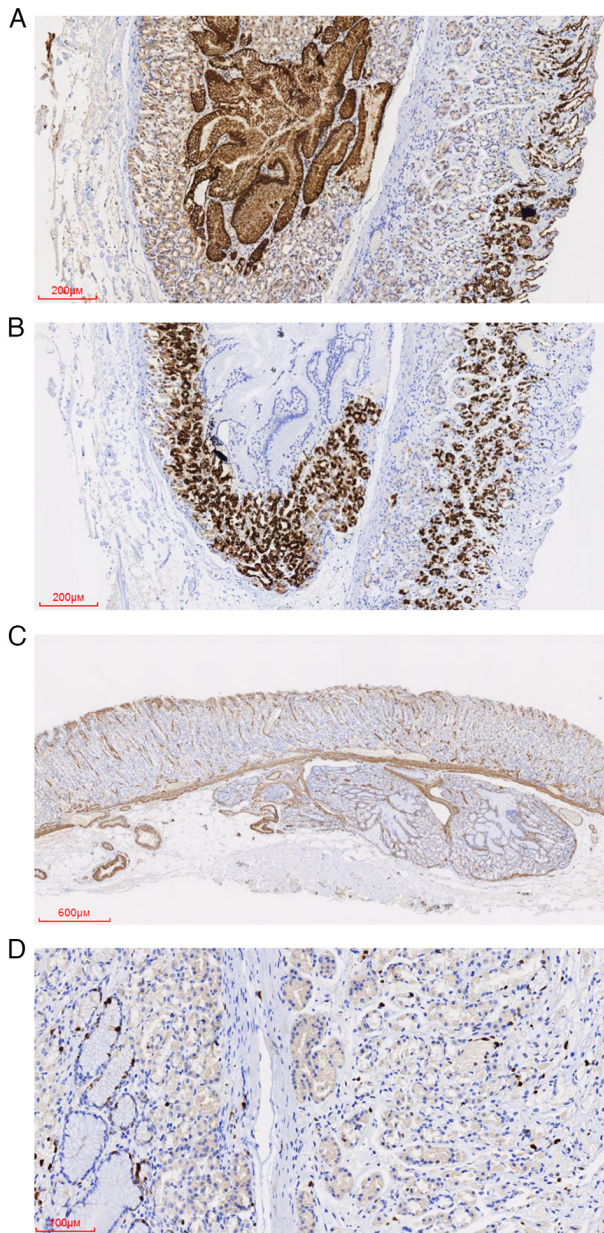


Figure 3. Immunohistochemical staining of the ectopic gastric mucosa. (A) MUC-5AC was expressed in the surface mucus cells of normal and ectopic gastric mucosa. Magnification, x50; scale bar, 200 μ m. (B) MUC-6 was expressed in the mucous neck cells of normal and ectopic gastric mucosa. Magnification, x50, scale bar, 200 μ m. (C) SMA is expressed in the mucosal muscle and interstitial vascular wall. Magnification, x20, scale bar, 600 μ m. (D) The Ki-67 proliferating index in normal and ectopic gastric mucosa was low; EGM on the left and normal mucosa on the right. Magnification, x200, scale bar, 100 μ m. MUC, mucin; SMA, smooth muscle actin.

atypia is unapparent or mild (13), and mitotic images are rare. The gastric pit epithelial cells on the atypical gland surface are normal. The glands with structural dysplasia are deep in the lamina propria. The glands are dilated and irregular; some may be sieve-shaped. The disease is diagnosed when the glands with slight cell atypia but prominent structural atypia invade the submucosa. In the present case, no cell atypia or structural atypia was observed, neither in the glands of the mucosa lamina propria nor the ectopic submucosal gland. Thus, the present case was distinct from gastric adenocarcinoma of the fundic gland type.

Second, EGM is distinguished from neuroendocrine tumor grade G1. In neuroendocrine tumor grade G1, the tumor cells are uniform in size and shape, with a round, oval, or short spindle shape, light to moderate nuclear dysplasia, granular nuclear chromatin, rare mitotic images, and tumor cells sometimes arranged in nests and chordates, Ki-67 proliferating index is low ($\leq 1\%$) (14). In the present case, IHC staining revealed positive expression of Syn, CD56, and CgA; the mucous, main, and parietal cells were the primary components, whereas the neuroendocrine cells were scattered in ectopic glands. Thus, the present case was distinct from neuroendocrine tumor grade G1.

Third, EGM is distinguished from gastritis cystica profunda, where the glands are composed of similar, normal gastric pits and glands of the lamina propria. The gastritis cystica profunda is usually continuous with the glands of the lamina propria, and the glands are expanded to varying degrees (15). Lymphocytes may be present gathered in the stroma around the glands. The present case lacked these manifestations.

Fourth, EGM is separate from ectopic pancreas. An ectopic pancreas is typically comprised of one or more components of the pancreatic acinus, duct, and islet (16). IHC staining of the pancreatic acinar components was positive for lipase, trypsinogen, and amylase, additionally, neuroendocrine markers of islet components were positive. The case comprised gastric pits rich in mucus, main, and parietal cells, with notably no pancreatic component.

Finally, EGM is distinct from inverted hyperplastic polyp (IHP). IHP is rare and was considered heterotopic or hamartomatous until the 1990s. It is characterized by inverted growth of the hyperplastic mucosa under the normal mucosa and can be pedicled (17). Most of the glands in IHP are cystic dilatation, a key distinguishing feature of EGM.

As EGM can become cancerous, it must be completely removed as soon as reasonably possible when something suspicious is found. It is vital to examine the infiltration depth of malignant components, vascular invasion, and the incised edge to determine whether additional surgery is required. According to the literature review performed for the present report, the prognosis of patients is often very good. However, follow-up is also essential according to the existing data, as no evidence exists that EGM will not recur.

In summary, EGM is a rare lesion with unique morphological features. As it can become cancerous, efforts should be made to avoid its misdiagnosis. Complete resection is required during treatment, and patients are advised to have regular follow-ups.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JHX and XJY drafted the manuscript and conceived the study. JHX, NYS and WJG performed the research and analyzed the data. JHX wrote the manuscript. XJY and NYS revised the manuscript. XJY and WJG confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Sunshine Union Hospital (approval no. 2023-06-0008).

Patient consent for publication

The patient provided written informed consent for the case study to be published.

Competing interests

The authors declare that they have no competing interests.

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