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Case Report

Well-Differentiated Adenocarcinoma Spreading Widely in the Gastric Submucosa

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Keywords
Ectopic submucosal gastric gland · Gastric cancer · Submucosal tumor · Well-differentiated adenocarcinoma

Abstract
A 56-year-old woman was referred to our hospital due to dry mouth. Diagnostic upper gastrointestinal endoscopy showed slightly elevated lesions both on the anterior wall and lesser curvature in the upper part of the stomach. Biopsy-proven tuble-forming atypical cells in the two lesions led us to treat the presumed early gastric cancers with endoscopic submucosal dissection (ESD). Pathological examination of the ESD specimen showed well-differentiated malignant cells spreading widely in the submucosa with positive lateral and deep margins. On retrospective image re-evaluation after ESD, we noticed the correlation between the presumed early gastric cancers and the multiple submucosal cyst-like lesions in the gastric wall on computed tomography. Under the tentative diagnosis of gastric cancers originating not from orthotopic gastric mucosa but from submucosal ectopic gastric gland, the patient underwent laparoscopic total gastrectomy and regional lymph node dissection, revealing the tumor infiltration to the serosa and regional lymph node swelling. Postoperative pathological evaluation showed lymph node metastases, multiple submucosal cyst-like lesions lined with a single layer of presumably benign epithelium, papillary adenocarcinoma cells in the submucosa, and tubular adenocarcinoma cells both in the mucosal and subserosal regions. The patient was discharged on the postoperative 7th day without any events and completed adjuvant chemotherapy on an outpatient basis. General surgeons should note that cyst-like lesion(s) in the gastric wall might be a predictor of extensive submucosal cancer cell spreading even in a case of well-differentiated gastric adenocarcinoma.

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Introduction

It is well known that well-differentiated gastric adenocarcinomas generally show papillary growth into the gastric lumen, leading to protruding or slightly elevated lesions in the early gastric cancers and sharply demarcated polypoid tumors in the advanced gastric cancers. On the contrary, these tumors often have none or very little, if any, submucosal cancer spreading [1–4]. Well-differentiated early gastric cancers, therefore, are regarded as good candidates for endoscopic submucosal dissection (ESD) [5].

Poorly differentiated adenocarcinomas rarely show papillary growth. On the other hand, they grow in an ulcer-forming fashion and often show extensive submucosal spreading. CDH1-related gastric cancers typically show a Pagetoid spread, i.e., a submucosal-wide extension of poorly cohesive cancer cells [6], of signet-ring atypical cells. These gastric cancers are naturally out of indications for ESD.

Various cancers can invade the gastric wall from outside and ultimately disrupt the mucosa [7]. Therefore, neither endoscopic nor pathological biopsy findings, when the tumors exhibit well-differentiated adenocarcinoma morphology, can accurately judge the target lesion to be caused either by malignant transformation of orthotopic gastric mucosa or by direct exposure of cancer cells to the gastric lumen through mucosal disruption. We herein report a case of well-differentiated gastric adenocarcinoma, presumably submucosal ectopic gastric gland origin, showing submucosal wide spreading.

Case Report

A 56-year-old woman was referred to our hospital due to dry mouth. Diagnostic upper gastrointestinal endoscopy showed slightly elevated two lesions both on the anterior wall and lesser curvature in the upper part of the stomach (Fig. 1). The endoscopic biopsy specimen pathologically showed atypical cells growing in a tuble-forming fashion, leading to the diagnosis of well-differentiated gastric cancer. We, therefore, did ESD in order to resect the two target lesions en block under the presumed diagnosis of early gastric cancers. Pathological evaluation of the ESD specimen also showed atypical cells growing in tubular and papillary fashions. The atypical cells spread extensively under the mucosa with positive lateral and deep margins. We had noticed cyst-like lesions in the gastric wall on computed tomography (CT) but had regarded them not to be correlated with the presumed early gastric cancers before ESD (Fig. 2). Pathological findings of the ESD specimen made the patient undergo laparoscopic total gastrectomy and regional lymph node dissection under the tentative diagnosis of gastric cancer originating from the submucosal ectopic gastric gland. In the operation, we found tumor infiltration to the serosa and lymph node swelling. Postoperative pathological study showed malignant cells growing in tubular and papillary fashions with regional node metastases. Well-differentiated atypical cells distributed from the mucosa to the serosa at the elevated lesions and spread widely, i.e., 150 × 135 mm, in the gastric submucosa (Fig. 3a). The differentiation degree of gastric adenocarcinoma cells was highest, i.e., a papillary form, in the submucosa and decreased as they approached both to the mucosa and serosa. Malignant cells that appeared to originate from the orthotopic gastric mucosa were present just above the most proliferative areas of submucosal lesions. Large cyst-like lesions, lined with a single layer of presumed benign cells, were observed in the gastric submucosa (Fig. 3b–d). Judged by these pathological findings, we highly speculated that well-differentiated invasive adenocarcinoma cells originating from the submucosal ectopic gastric gland spread widely in the submucosa and partially protruded into the gastric lumen through the disruption of the gastric mucosa in this case (Fig. 3e). The patient recovered uneventfully,

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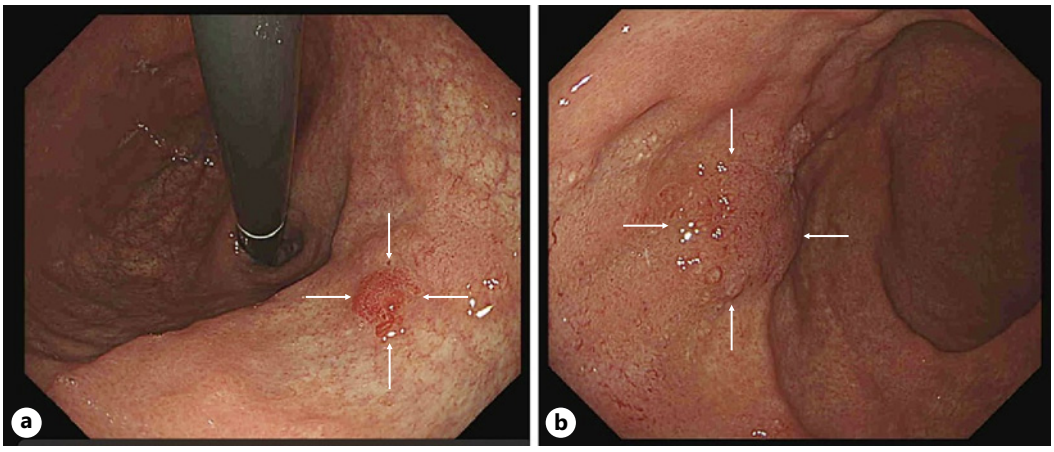

Fig. 1. Endoscopic findings. Slightly elevated lesions both on the anterior wall (arrows (**a**)) and lesser curvature (arrows (**b**)) were endoscopically observed in the upper part of the stomach.

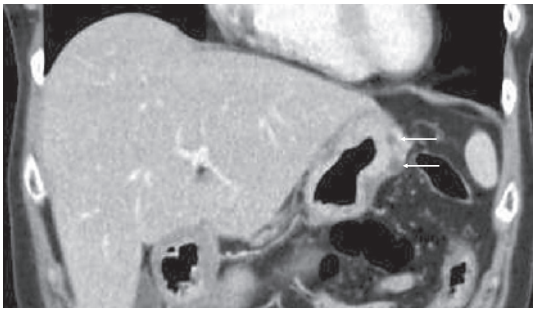

Fig. 2. Computed tomography (CT) of the stomach. Oval cyst-like lesions were observed in the gastric wall (arrows) without any extra-gastric lesions.

received adjuvant chemotherapy on an outpatient basis, and has been well without any recurrences for 14 months. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533363).

Discussion

In routine clinical practice, we judge a gastric lesion as a cancer when the malignant lesion is surrounded by normal gastric mucosa and as a submucosal gastric tumor when covered with normal gastric mucosa [8]. Submucosal tumors, however, sometime lack the overlying normal gastric mucosa when they grow too large to disrupt the overlying normal mucosa. Clinicians, however, never misjudge them as advanced gastric cancers due to the overtly different endoscopic findings reflecting their distinctive pathological growth patterns.

Hepatocellular carcinoma, pancreatic cancer, and colon cancer can invade the stomach. These solid malignancies can sequentially infiltrate the gastric wall in the order of serosa, subserosal layer, proper muscle layer, submucosal layer, muscle layer of the mucosa, and mucosa. Disruption of the mucosa easily leads to the cancer protrusion into the gastric lumen. Pathological findings can easily lead physicians to the misdiagnosis of primary gastric cancer when the protruding tumor from the neighboring organ pathologically shows well-differentiated

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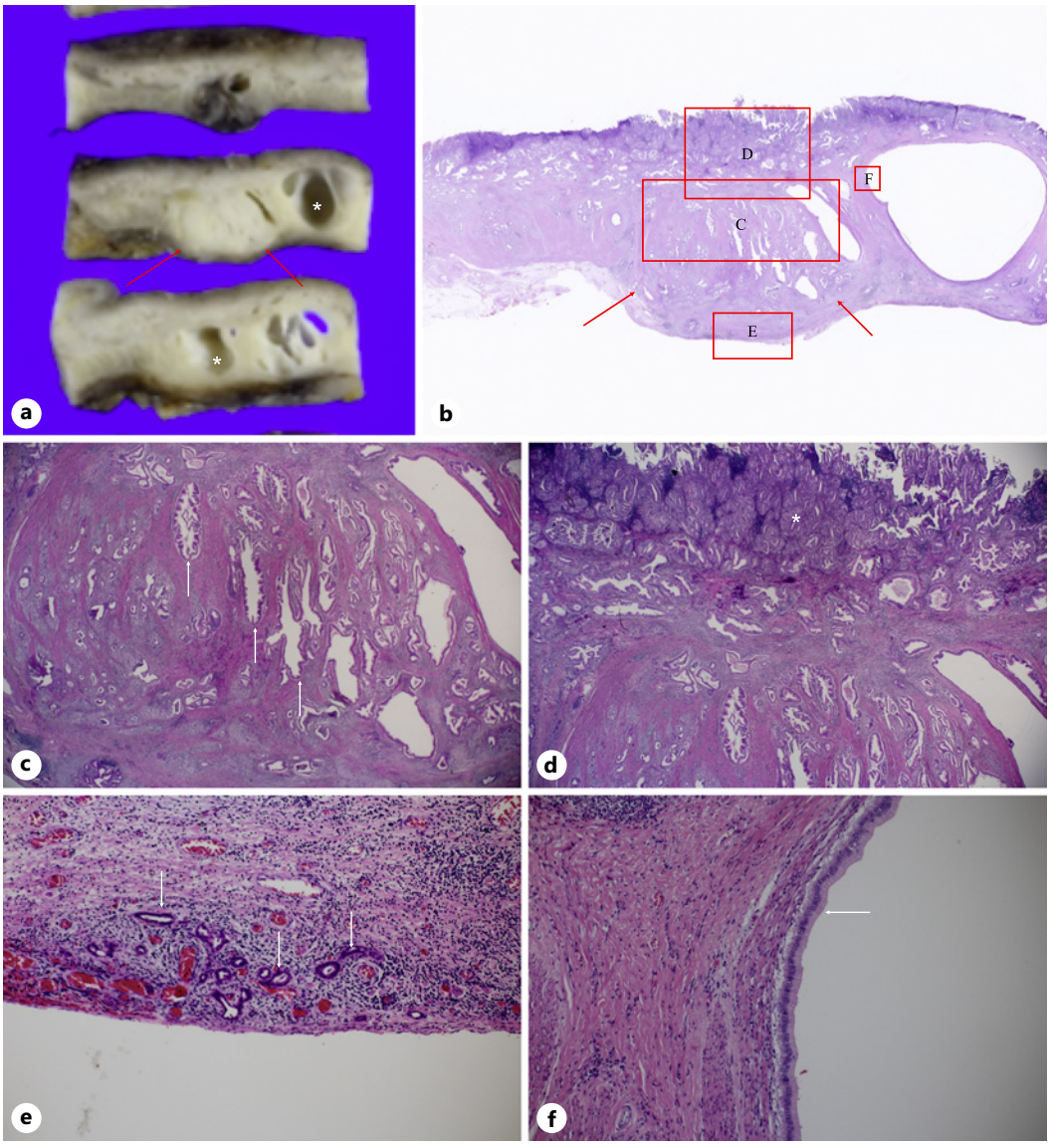

Fig. 3. Pathological findings. **a** Probably due to the ESD, no macroscopic elevated lesions were observed on the gastric luminal surface. A protruded lesion toward the serosa (arrows) and cyst-like lesions (asterisks) were observed in the gastric wall. **b** The externally protruded lesion (arrows) was composed of well-differentiated atypical cells spreading out the gastric wall. **c** Magnified view of the central part of the protruded lesion showed atypical cells growing in a papillary fashion (arrows). **d** Magnified view of the mucosal part of the lesion showed atypical cells growing in a tubular fashion, i.e., a less differentiated form than a papillary growth form (asterisk). **e** Magnified view of the subserosal part of the lesion showed atypical cells with a less differentiated pattern (arrows) than those of mucosal and submucosal lesions. **f** Magnified view showed a cyst-like lesion lined by a single layer of presumed benign cells (arrow).

adenocarcinoma cells. This event, however, is observed only when massive tumor cells engage in this event, i.e., presence of a large extra-gastric tumor invading the stomach, and rarely annoys physicians about how to properly make a therapeutic strategy.

Pathological findings showed that well-differentiated adenocarcinoma cells extended vertically from the mucosa to the serosa at the elevated lesions, while further spreading

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extensively under the mucosa in this case. If the present case was a primary gastric cancer, we cannot explain why the well-differentiated adenocarcinoma cells spread so widely under the mucosa. In addition, in case of primary gastric cancer, the differentiation degree of adenocarcinoma cell clusters should decrease as the depth from the mucosa increases. The speculation of gastric cancer originating from the submucosal ectopic gastric gland [9] can well explain both the submucosal wide spreading of well-differentiated adenocarcinoma cells and atypical cancer cell differentiation patterns, i.e., the presence of most differentiated adenocarcinoma cells in the submucosa.

We cannot deny that an ectopic pancreas in the stomach became cancerous and caused this lesion. Especially, adenocarcinoma arising from a type III ectopic pancreas [10] cannot be ruled out pathologically. It, however, is well known that the size of the ectopic pancreas is up to about 2 cm. In addition, adenocarcinomas arising from the ectopic pancreas generally form protruded lesions without marked submucosal spreading [11, 12]. The absence of normal pancreatic acini and islet cells in this case further suggest that this lesion was not developed in an ectopic pancreas.

No endoscopists can clinically judge gastric adenocarcinomas, whether they originate from the orthotopic gastric mucosa or they protrude into the gastric lumen after mucosal disruption, when these two disorders show similar pathological growth pattern of a well-differentiated adenocarcinoma fashion. We, however, detected the presence of cyst-like lesions in the gastric wall on CT before ESD but unfortunately had no diagnostic idea for the correlation between the cyst-like lesions and the overlying presumed early gastric cancers. Judged by the pathological findings observed in this case, cyst-like lesions in the gastric wall should be one of the important predictors of the presence of submucosal ectopic gastric gland. We should have suspected the relationship between the cyst-like lesions in the gastric wall and the presumed early gastric cancers before ESD. The suspicion should have easily led us to do the endoscopic ultrasound evaluation, having led to the omission of ESD due to the detection of wide-spreading submucosal lesions. Clinicians should carefully evaluate cyst-like lesion(s) in the gastric wall to avoid unnecessary ESD.

Immunostaining with CK7, CK20, TTF-1, thyroglobulin, calretinin, WT-1, CEA, and villin is useful to diagnose cancer of unknown primary origin [13, 14]. For example, CK7 (+), CK20 (−), calretinin (−), WT1 (−), and CEA (−) cancer cells highly suggests their origin from mammary gland. However, these immunostainings, even though having been done to this case, should have been of no use for the definitive diagnosis of gastric lesions due to the similar immunophenotypic expressions of the orthotropic gastric mucosa and the ectopic gastric mucosa.

In conclusion, cyst-like lesions on CT should be an important predictor of the presence of submucosal ectopic gastric gland. Physicians should note that well-differentiated gastric cancer cells originating from submucosal ectopic mammary gland can widely spread submucosally in the gastric wall.

Statement of Ethics

The study was approved by the Kishiwada Tokushukai Hospital Ethics Committee (IRB #Case 23-1). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Naoki Kataoka contributed to the design of the report. Shoji Oura drafted the manuscript. Eisei Nishino evaluated the pathological findings.

Data Availability Statement

All data generated during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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