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Single Case

Gastric Adenocarcinoma with Enteroblastic Differentiation Resected through Endoscopic Submucosal Dissection: A Case Report

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Gastric cancer · Adenocarcinoma with enteroblastic differentiation · Histopathology · Immunohistochemistry

Abstract
Introduction: Gastric adenocarcinoma with enteroblastic differentiation (GAED) is a rare histological type of gastric adenocarcinoma that occurs in the stomach and is known for its aggressive behavior. GAED is diagnosed histopathologically and is often advanced at the time of diagnosis. ***Case Presentation:*** We report the case of a 70-year-old male with a 20-mm superficial depressed lesion on the anterior wall of the antrum. Histological examination of the endoscopic submucosal dissection specimen revealed that the tumor was composed of dilated or slit-like branching tubules; additionally, the tumor cells had clear cytoplasm resembling that of the fetal digestive tract. Immunohistochemically, the tumor cells were positive for Glypican-3 and alpha-fetoprotein. A pathological diagnosis of GAEDs was established. GAED was found in approximately 30% of all the tumor cells and showed lymphatic invasion. The patient has been under recurrence-free follow-up for approximately 1 year after the endoscopic submucosal dissection. ***Conclusion:*** In order to detect a large number of cases, immunostaining should be aggressively performed if morphological findings are suspicious for GAED.

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Introduction

Gastric adenocarcinoma with enteroblastic differentiation (GAED) is a rare and aggressive cancer [1], known to be highly aggressive. GAED is analogous to hepatoid adenocarcinoma and alpha-fetoprotein (AFP) – producing gastric carcinoma (AFP-GC). Even after radical surgery, the 5-year overall survival rate of hepatoid adenocarcinoma and AFP-GC is 22% and 42%, respectively [2], indicating a poorer prognosis than that of conventional gastric cancer [3]. GAED is characterized by cells with a clear cytoplasm resembling the fetal gastrointestinal epithelium and is immunohistochemically positive for spalt-like transcription factor 4 (SALL4), Glypican-3, and AFP. Because of its aggressive behavior, GAED is often advanced at the time of diagnosis [2], and cases treated with endoscopic submucosal dissection (ESD) are rare. Herein, we describe a case of GAED that was successfully resected using ESD.

Case Presentation

A 70-year-old male with no known comorbidities presented to our hospital with an early gastric cancer in the anterior wall of the gastric antrum (Fig. 1a). The lesion was approximately 20 mm in size and superficially depressed (Fig. 1b). The background gastric mucosa had open-type atrophic gastritis and was previously infected with *Helicobacter pylori*. Magnifying endoscopy with narrow-banding imaging revealed a clear demarcation line and irregular microvascular and microsurface patterns (Fig. 1c). Based on the endoscopic findings, adenocarcinoma was suspected. Endoscopic ultrasonography using a 12-MHz miniature probe revealed that the tumor was within the deep submucosa (Fig. 1d). No special findings were noted in blood biochemistry tests, and serum AFP levels were not measured. Adenocarcinoma was pathologically detected on biopsy of the same site. Endoscopy revealed lesions suggestive of probable cancer invasion of the deep submucosa; however, ESD was performed to assess the risk of lymph node metastasis.

The endoscopically resected specimen was 30 mm in size and showed a superficial depressed tumor, which was found to be 20 mm in size (Fig. 2a). Histological examination revealed that the tumor was composed of dilated or slit-like branching tubules of variable diameters that infiltrated deeply into the submucosa (Fig. 2b). Adhesive glandular ducts and glandular ducts with necrotic material in the lumen were observed inside the tumor (Fig. 2c). The GC was moderately differentiated, which is Grade 2 according to the World Health Organization classification. Atypical glandular ducts with a partially clear cytoplasm were also observed; these resembled the fetal digestive tract (Fig. 2d). This enteroblastic component has been reported in approximately 30% of all cases and is more prevalent in infiltrated areas. Immunohistochemically, the tumor cells were positive for Glypican-3 and AFP, with dot-like staining (Fig. 3a–c).

The pathological diagnosis was GAED. The tumor invasion depth was 2,100 μm into the submucosa (pT1b) with lymphatic invasion. Although an additional gastrectomy was considered, the patient denied any further treatment. The patient was followed up after resection, and no recurrence or metastasis was observed. The patient has been under recurrence-free follow-up for approximately 1 year. The CARE Checklist has been completed by the authors for this case report and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535954).

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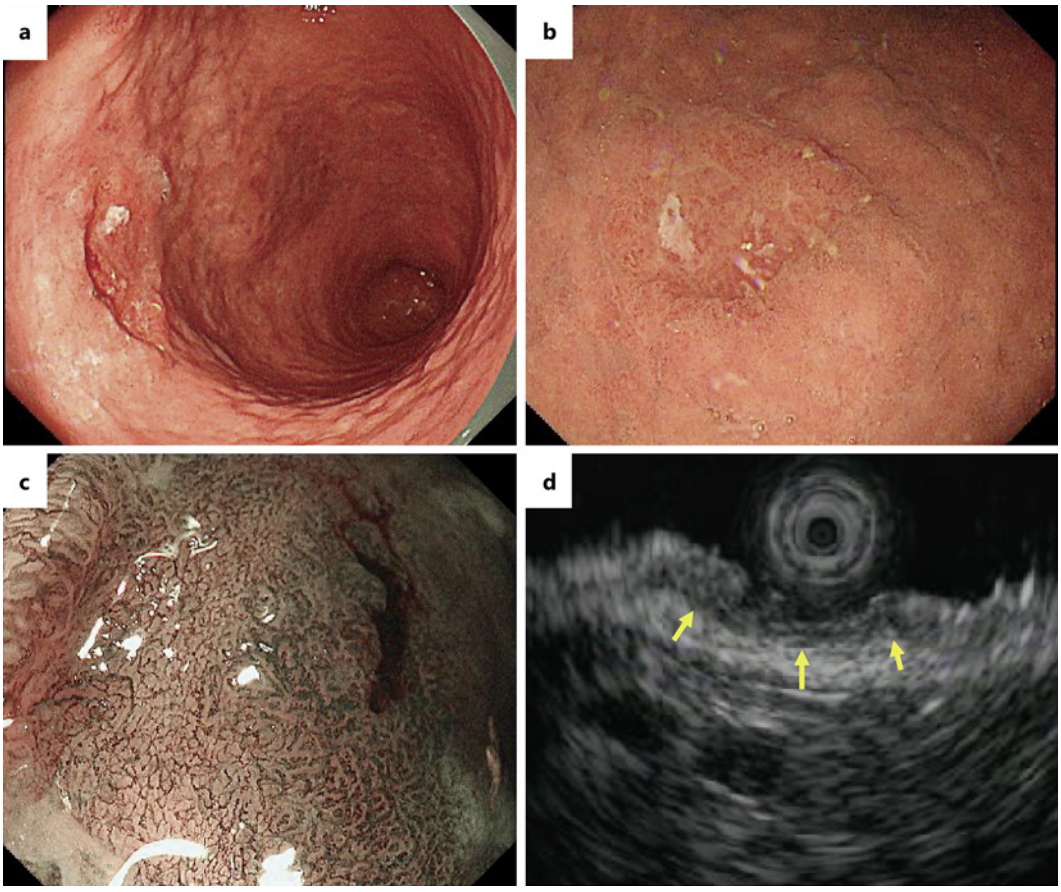

Fig. 1. Endoscopic and gross findings. **a**, **b** White-light imaging revealed that there was a lesion in the anterior wall of the gastric antrum (**a**), which was superficially depressed, with a size of 20 mm (**b**). **c** Magnifying endoscopy with narrow-band imaging shows irregular microsurface patterns and irregular microvascular patterns, with a demarcation line. **d** Endoscopic ultrasonography image using a 12-MHz miniature probe. The arrows indicate the areas of suspected infiltration.

Discussion

This report describes a rare case of GAED in which successful resection was achieved using ESD. Cases of GAED with ESD are rare, and, to our knowledge, this is the 13th case reported in the literature [2, 4–7]. Compared to other gastric cancers, the preferred site and endoscopic features of GAED are not clear at this time [5, 8]. However, this may be due to the lack of an adequate pathological search for gastric cancer ESD cases; the actual number may be much higher.

GAED was initially linked to enteroblastic cells based on the analysis of AFP-positive gastric cancers. Its characteristics are as follows: (1) growth of columnar carcinoma cells primarily in tubulopapillary and glandular patterns; (2) production of abundant glycogen, but not mucin, in the clear cytoplasm; (3) scattering of gut hormone-containing cells among the clear carcinoma cells; and (4) production of oncofetal glycoproteins, including AFP and carcinoembryonic antigen, by the carcinoma cells [9]. Although no AFP measurements were performed prior to ESD in this case, histopathologically typical tumor cells with enteroblastic components and a pale cytoplasm were observed, and AFP was detected via immunostaining. The enteroblastic component in GAED is present in

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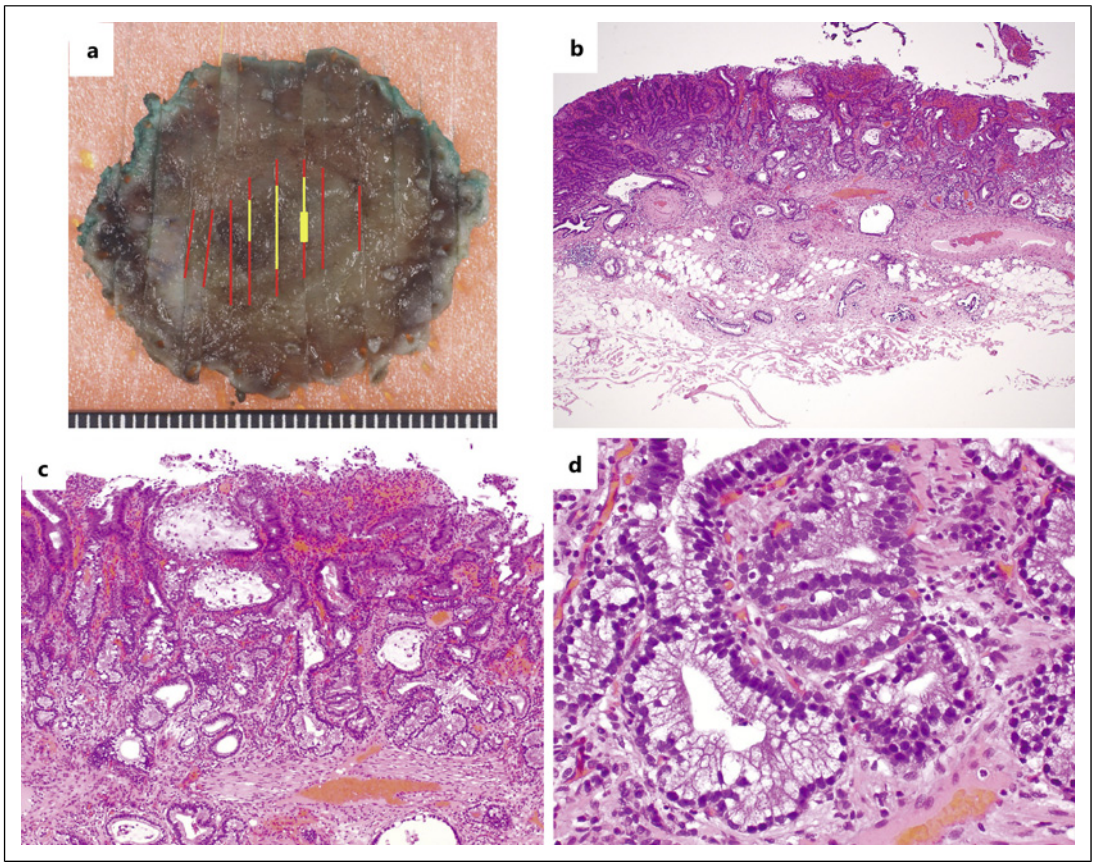

Fig. 2. Pathological findings. **a** Endoscopic submucosal dissection specimen with gross mapping. The tumors were 20 mm in size. The red line area indicates the cancerous area, and the yellow line area indicates where the enteroblastic differentiation was seen on the surface layer. **b** The tumor was composed of dilated or slit-like branching tubules of variable diameter that infiltrated deeply into the submucosa. **c** Inside the tumor, adhesive glandular ducts and glandular ducts with necrotic material in the lumen are observed. **d** The tumor cells show partially clear cytoplasm, resembling the fetal digestive tract. Magnification: ×40 (**b**), ×100 (**c**), and ×400 (**d**).

30–100% of reported cases and has a wide range [7, 8]. In this case, approximately 30% of gastric cancer tissues contained an enteroblastic component. This is a relatively low percentage, and it is possible that this percentage would have been even higher if the tumor had progressed.

However, the molecular mechanisms underlying the development of GAED remain unclear. Gastric cancer is classified according to the mucin phenotype [10], and based on this classification, GAED is classified as an intestinal mucin phenotype [5, 8]. AFP, Glypican-3, and SALL4 are molecular markers' characteristic of GAED and are used as immunostains [5, 8]. The positivity rates of AFP, Glypican-3, and SALL4 are variable, requiring a combination of these markers, in addition to the morphological picture, to make a diagnosis. The difficulty in staining and interpreting immunohistochemical stains for AFP may be another factor that makes GAED identification difficult. Because Glypican-3 and AFP were positive in this case, together with the typical morphology of GAED, a diagnosis of GAED was made.

GAED is basically a rapidly progressing cancer, which is reflected in the significantly deeper invasive depth, lymphatic and venous invasions, and a higher rate of positive margins

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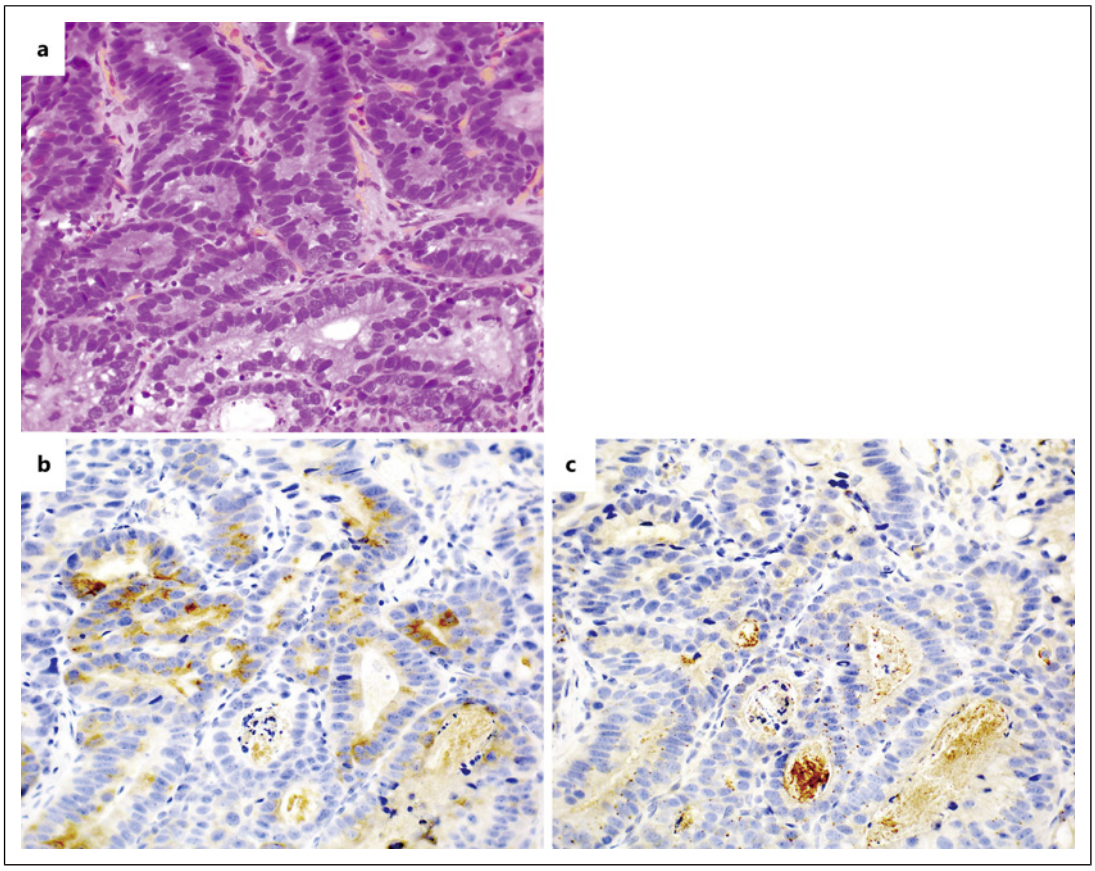

Fig. 3. Immunohistochemical findings. These figures show the same locations on serial sections as much as possible. **a** Hematoxylin and eosin (HE) staining. Tumor cells have eosinophilic or clear cytoplasm. **b** Glypican-3. **c** AFP. Both Glypican-3 and AFP are enteroblastic markers, and both the eosinophilic and clear cytoplasmic portions of HE staining showed areas of expression. Magnification: ×400 (**a–c**).

compared to conventional gastric cancer; a few cases of curative resection were observed in an analysis of 6 cases of GAED with ESD [5]. Lymph node metastasis was observed in 4 of the 10 early-stage gastric cancer cases (40%) [8]. In this case, curative resection was not performed because of lymphatic invasion. Additional gastrectomy is desirable but was not performed because the patient did not provide consent.

In conclusion, we report a rare case of GAED resection via ESD. Among all reported cases treated with ESD, our case has the deepest invasion depth. To improve our knowledge of the clinicopathological dynamics of GAED, it is necessary to aggressively perform immunostaining to diagnose GAED in cases where it is suspected by hematoxylin and eosin staining and to analyze a large number of cases.

Acknowledgments

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Statement of Ethics

This case report was published in accordance with the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with national guidelines. This retrospective review of patient data does not require ethical approval, as stated by the national guidelines.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

Akira Ishikawa: diagnosis and preparation of the manuscript; and Koki Nakamura: case management.

Data Availability Statement

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

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