

Case Report

A 67-year-old man with gastric adenocarcinoma with enteroblastic differentiation in Korea: a case report

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Abstract

We report a rare case of Gastric adenocarcinoma with enteroblastic differentiation (GAED) that was treated with endoscopic submucosal dissection and additional distal gastrectomy with lymph node dissection. A 67-year-old man underwent endoscopic submucosal dissection for a stomach lesion, which was diagnosed as GAED with submucosal invasion and lymphatic invasion. Histologically, GAED exhibits a tubulopapillary growth pattern with clear cells resembling the

primitive fetal gut. Immunohistochemically, GAED variably expresses oncofetal proteins like glypican-3, alpha-fetoprotein, and SALL4. Despite negative margins, additional gastrectomy with lymph node dissection was performed due to deep submucosal invasion. No residual tumor or metastasis was found, and the patient remained disease-free for two years before succumbing to unrelated causes. GAED is known for its aggressive behavior, frequent lymphovascular invasion, and high metastatic potential; therefore, clinicians should be aware of the histopathological diagnosis of this rare tumor and its aggressive behavior. .

Keywords: Adenocarcinoma; alpha-fetoproteins; Endoscopic mucosal resection; Gastrectomy; Transcription Factor 4

Introduction

Gastric adenocarcinoma with enteroblastic differentiation (GAED), also called clear cell gastric carcinoma, is a rare and poorly documented malignancy that accounts for less than 1% of all gastric cancers. [1,2] GAED is a subtype of alpha-fetoprotein (AFP)-producing adenocarcinomas. [1] However, the association between GAED and AFP production remains unclear. [2] The histological characteristic of the tumor is an intestine-like structure composed of cuboidal or columnar neoplastic cells with clear cytoplasm that stain positive for oncofetal proteins, including glypican-3, spalt-like transcription factor 4 (SALL4), and AFP. [3] Compared to conventional adenocarcinoma, GAED is more aggressive with frequent lymphovascular invasion and a high rate of metastasis to the liver and lymphatics. [4] Herein we report a rare case of GAED that was treated with endoscopic submucosal dissection (ESD) and additional distal gastrectomy with lymph node (LN) dissection.

Case presentation

Ethics statement

This case report received exemption from consent and review from the Pusan National University Hospital Research Ethics Review Committee (IRB No. 2402-023-136).

Patient Information

A 67-year-old man visited our hospital for the treatment of high-grade dysplasia in the stomach that was detected during a health checkup esophagogastroduodenoscopy (EGD). He had a history of alcoholic hepatitis and chronic hepatitis B. He was a heavy drinker and had a 40 pack-year history of smoking. The patient was asymptomatic.

Clinical findings

Physical examination results were unremarkable.

Diagnostic assessment

Laboratory findings revealed a slightly elevated liver function test, indicating the presence of alcoholic hepatitis. Tumor markers, including serum AFP, carcinoembryonic antigen, and carbonic anhydrase 19-9 were within the normal ranges. On EGD, there was a 2 cm-sized slightly depressed lesion with nodular mucosal changes at the anterior wall of the gastric prepylorus (Fig 1A).

Magnifying endoscopy with narrow-band imaging (ME-NBI) revealed a clear demarcation line and irregular microsurface (MS) and microvascular (MV) patterns, especially irregular oval/tubular MS and irregular loop MV patterns (Fig. 1B). Endoscopic ultrasonography showed that the lesion was limited to the mucosal layer. Abdominal and chest computed tomography showed no evidence of lymph node or distant metastases.

Therapeutic Intervention and final diagnosis

ESD was performed for complete resection of the lesion (Fig. 1C-E). The gross appearance of the resected specimen showed a 19 mm-sized, IIc lesion with irregular mucosal surface (Fig. 1F). On microscopic examination, the tumor showed a tubulopapillary growth pattern and submucosal invasion (Fig. 2A). Overlaid with conventional adenocarcinoma, the tumor was partially composed of cuboidal or columnar cells with clear cytoplasm resembling the primitive fetal gut, which is characteristic of enteroblastic differentiation (Fig. 2B). On immunohistochemical staining, the tumor cells were negative for glypican-3 and AFP, known as oncofetal proteins (Fig. 2C and D). Although the horizontal and deep resection margins were free of tumor, the tumor invaded the deep submucosa (750 μ m from the muscularis mucosa) with lymphatic invasion. Therefore, additional distal gastrectomy with LN dissection was performed. No residual tumor or LN metastasis was observed in the surgical specimens.

Follow-up and Outcomes

During the follow-up of two years, there was neither local nor distant recurrence. However, three years later, the patient died of necrotizing pneumonia and uncontrolled alcoholic hepatitis.

Discussion GAED, also known as clear cell gastric carcinoma, is rarely observed in the stomach. Clear cell carcinomas are commonly observed predominantly in the lower urinary tract and female reproductive system (endometrium and ovary). Because GAED occurs rarely, its clinicopathologic and immunohistochemical characteristics have not been fully understood. [2,5,6] Histologically, enteroblastic adenocarcinoma is mostly combined with conventional well-differentiated or moderately-differentiated tubular adenocarcinoma in the upper part of all tumors. [2] GAED exhibits a tubulopapillary growth pattern with predominantly clear cells and luminal eosinophilic secretions. [7] The present case showed ME-NBI findings (irregular oval/tubular MS and irregular loop MV patterns) consistent with the histopathological findings of GAED, similar to those of previous reports. [8,9]

With regard to immunohistochemical stain, most of the GAEDs variably express three enteroblastic lineage markers, so-called oncofetal proteins; glypican-3 (a marker for hepatoid gastric carcinoma), AFP (a marker for hepatocellular carcinoma and yolk sac tumor), and SALL4 (a marker for AFP-producing gastric carcinoma). [10-12] For the diagnosis of GAED, glypican-3 is the most sensitive marker, followed by SALL4 and AFP. [2] The present case demonstrated negative stain for glypican-3 and AFP, and SALL4 could not be stained due to the lack of testing equipment. If AFP production is identified in carcinoma cells of the stomach on immunohistochemical stain, the lesion can be called AFP-producing gastric carcinoma, which is associated with poor prognosis due to a high incidence of lymphovascular invasion and liver metastasis. [13]

Clear cells contain abundant cytoplasm of glycogen, lipid, water, or mucin. [6] Most gastric carcinomas with clear cell changes (GCCs) exhibit cytoplasmic accumulation of glycogen and mucin. We previously reported that GCCs secondary to glycogen deposition were associated with

expression of AFP, glypican-3, and CD10, whereas GCCs characterized by mucin deposition were associated with expression of MUC5AC and MUC6. [14] GAED and hepatoid adenocarcinoma are representative histologic subtypes of gastric adenocarcinoma with clear cells. Reportedly hepatoid adenocarcinoma with clear cells is differentiated from GAED based on its poor prognosis, diffuse strong expression of oncofetal proteins, and intestinal mucin phenotype. [7] In contrast, GAED shows focally heterogenous expression of oncofetal proteins and commonly expressed CD10, CDX-2, and MUC6, but not MUC2 and MUC5AC, suggesting both gastric antral/intestinal mucin phenotype and focal enteroblastic differentiation. [7]

Similar to AFP-producing adenocarcinoma, the presence of clear cell changes in gastric cancer is associated with poor prognosis compared to conventional gastric adenocarcinoma. [14] It has been reported that the majority of GAED patients (90%) exhibit lymphatic and/or vascular invasion. [2] Lymph node metastasis is observed in 40% of early stage cases and 84% of advanced cases, surpassing the rates observed in conventional gastric adenocarcinoma (20-45%).

In conclusion, GAED is a rare malignancy with distinct histopathological features. Compared to conventional adenocarcinoma, GAED is known to have aggressive features, such as frequent lymphovascular invasion and metastasis to the liver and lymph nodes, resulting in a poor prognosis. Therefore, clinicians should be aware of the histopathological diagnosis of this rare tumor and its aggressive behavior.

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Conflict of interest

No potential conflict of interest relevant to this article was reported

Funding

Not applicable.

Data availability

Not applicable.

Acknowledgments

Not applicable.

Supplementary materials

Not applicable.

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FIGURE LEGENDS

Fig. 1. Endoscopic submucosal dissection for early gastric cancer. (A) A 2 cm-sized slightly depressed lesion with nodular mucosal changes is observed at the anterior wall of the gastric prepylorus on conventional endoscopy and indigo carmine chromoendoscopy. (B) Magnifying endoscopy with narrow-band imaging reveals irregular microsurface and microvascular patterns. (C) Marking dots are made around the lesion. (D) Circumferential incision and submucosal dissection is performed using an IT knife. (E) The lesion is completely removed. (F) Resected specimen.

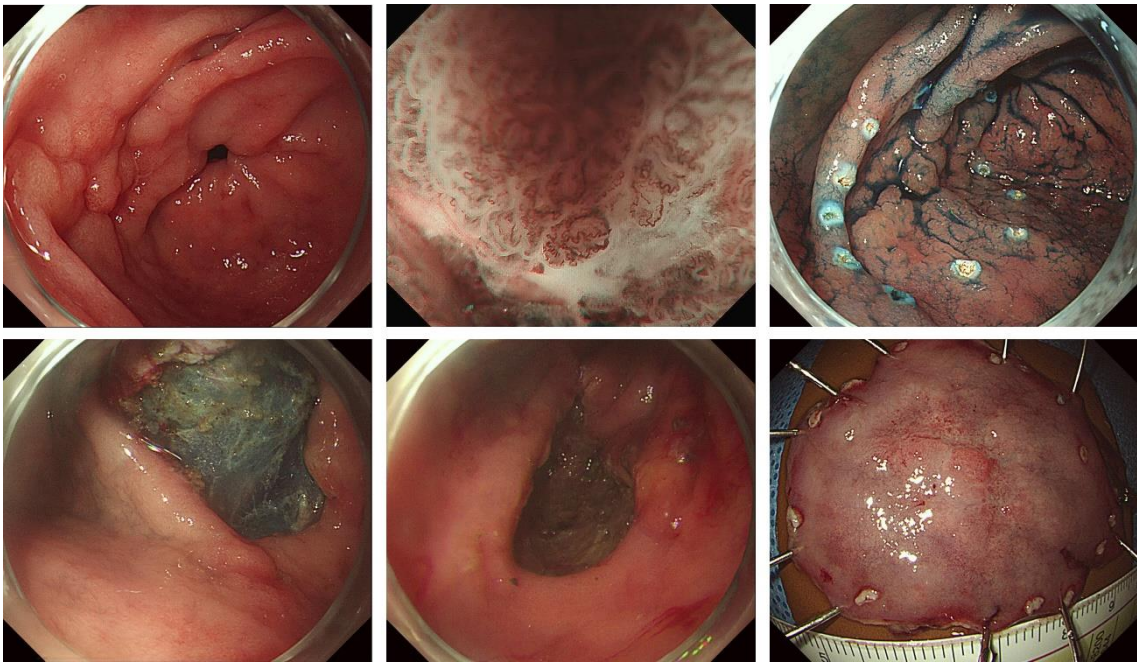


Fig. 2. Histopathological findings. (A) Tumor reveals a tubulopapillary growth pattern and invades the submucosa (H&E stain, x40). (B) The tumor cells have clear cytoplasm with a tubular pattern, characteristics of enteroblastic adenocarcinoma (H&E stain, x200). (C and D) The tumor cells are negative for glypican-3 (C) and alpha-fetoprotein (D) stain (immunohistochemical stain, x40).

