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Case Report

Gastric Adenocarcinoma With Enteroblastic Differentiation: Lessons From a Rare Case

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Introduction: Gastric adenocarcinoma with enteroblastic differentiation (GAED), also known as clear cell carcinoma or fetal gut-like adenocarcinoma, is a special type of adenocarcinoma characterized by primitive intestine-like structures. GAED partially overlaps with α-fetoprotein–producing gastric carcinoma (APGC). There is insufficient information on the biologic behavior of GAED, which has a worse prognosis compared with conventional gastric carcinoma (GC).

Case presentation: We introduce an 82-year-old man who presented 4 years ago with severe epigastralgia; the patient then underwent distal gastrectomy for a large GC. The patient received an initial diagnosis of well-to-moderately differentiated gastric adenocarcinoma with lymphatic invasion and without nodal involvement, resulting in a TNM classification of T1N0M0, stage IB. Follow-up computed tomography 31 months after the gastrectomy revealed a hepatic lesion. Lateral segmentectomy of the liver was performed for therapeutic diagnosis. Pathology specimens from the resected tissue were characterized by glycogen-rich neoplastic cells with eosinophilic cytoplasm with a focal glandular component on hematoxylin-eosin staining and periodic acid–Schiff staining. By retrospective analysis using

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immunohistochemical staining, Glypican 3 was partially positive and spalt-like transcription factor 4 (SALL-4) was strongly positive in the resected GC and metastatic hepatic carcinoma, indicating that GAED metastasized to the liver.

Conclusions: Although exceedingly rare, surgeons should recognize GAED as one of the special types of GC. Treatment guidelines for GAED have not yet been established; however, pathological confirmation of GAED when encountering an APGC by immunohistochemical staining for Glypican 3 and SALL-4 is essential to recognize its malignant biological behavior unlike conventional GC.

Key words: Alpha-fetoprotein–producing gastric carcinoma – Gastric adenocarcinoma with enteroblastic differentiation – Glypican 3 – Hepatoid adenocarcinoma – SALL-4

Gastric adenocarcinoma with enteroblastic differentiation (GAED) was first proposed by Matsunou *et al*[1] as a rare variant of α-fetoprotein (AFP)–producing gastric cancer[1]; however, the clinicopathologic characteristics of GAED have not been well established. This subtype of gastric adenocarcinoma has been histologically characterized as having a primitive intestine-like structure, composed of cuboidal or columnar cells with clear cytoplasm. It is generally recognized that GAED produces AFP in the serum or in the tumor cells. Yet, some cases of GAED are negative for AFP production, and the relationship between GAED and AFP production remains unclear.[2] Although GAED is known to be distinct from other conventional gastric carcinomas (GCs), clinical information on GAED has been quite limited. In this study, we report an exceedingly rare case of GAED with AFP production treated twice with surgical intervention and diagnosed by retrospective analysis using immunohistochemical staining for Glypican 3 and spalt-like transcription factor 4 (SALL-4).

Case Presentation

We present the case of an 82-year-old man who presented 4 years ago with epigastralgia and was admitted to our hospital for suspected acute cholecystitis. He had no family history of malignancy. Laboratory data showed elevated hepatobiliary enzymes: aspartate aminotransferase level of 360 IU/mL (normal range [NR], 8–38 IU/L), alanine transaminase of 145 IU/mL (NR, 4–44 IU/L), γ-glutamyl transpeptidase of 731 IU/mL (NR, 18–66 IU/L), total bilirubin of 2.1 mg/mL (NR, 0.2–1.2 mg/dL), direct bilirubin of 1.5 mg/mL (NR, 0.0–0.3 mg/dL), and amylase of 35 IU/L (NR, 40–129 IU/L). The hepatobiliary enzymes were likely elevated because of a gallstone in the common bile duct and a history of nonalcoholic fatty liver disease. Although stones were not detected in the common bile duct on endoscopic retrograde cholangiopancreatography, we judged that the stones might have passed through the common bile duct. The hepatobiliary enzymes returned to nearly normal levels afterward. The patient had a mildly elevated fasting plasma glucose of 125 mg/dL (NR, 70–109 mg/dL), and an HbA1c of 5.9% (NR, 4.7%–6.2%). Carcinoembryonic antigen was 3.7 ng/mL (NR, 0–5.0 ng/mL) and serum carbohydrate antigen was 12.1 U/mL (NR, 0–37 U/mL), both within normal range. AFP was mildly elevated at 13.6 ng/mL (NR, 0–9.9 ng/mL). Computed tomography revealed remarkable thickening in the walls of the gallbladder (Fig. 1A), gastric antrum, and corpus (Fig. 1B), suggesting acute cholecystitis and GC. Upper endoscopy revealed a large elevated mass measuring 90 mm at the antrum of the stomach (Fig. 2). The lesion was biopsied and pathology revealed a moderately differentiated adenocarcinoma. We gave the patient a preoperative diagnosis of acute cholecystitis and conventional-type GC with a TNM classification of T2N0M0 stage IB. The patient underwent cholecystectomy and distal gastrectomy with lymph node dissection. Postoperative pathology revealed well-to-moderately differentiated tubular adenocarcinoma measuring 90 mm in diameter with invasion into the muscularis propria and the lymphatic system. There was no metastasis to lymph nodes. The final staging was T1N0M0 stage IB. The patient received no adjuvant chemotherapy on the grounds of the early stage of GC as per the Gastric Cancer Treatment Guidelines 2018.[4] Two years after the initial operation, no recurrence or metastasis was detected. Abdominal ultrasound revealed a 40-mm–sized mass at the lateral segment of the liver 31 months postoperatively. The mass was negative for fluorine-18-fluorodeoxyglucose by fluorodeoxyglucose-positron emission tomography (Fig. 3). Contrast-enhanced

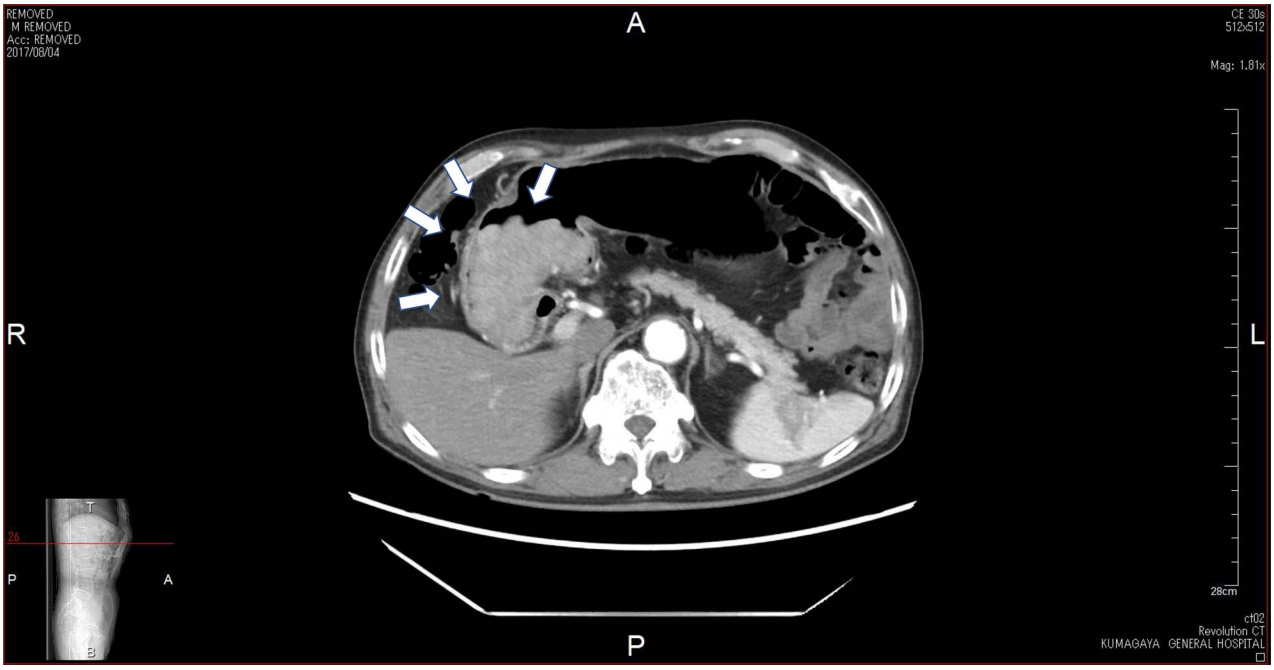

Fig. 1 Computed tomography revealed a remarkable wall-thickening (white arrows) occupying the antrum of the stomach.

magnetic resonance imaging done 33 months after the gastrectomy revealed a highly enhancing mosaic mass that grew to 60 mm in size on T1-weighted imaging (Fig. 4). Serum carcinoembryonic antigen levels were mildly elevated at 9.6 ng/mL (NR, 0–5.0 ng/mL), serum carbohydrate antigen levels were within NR (2.8 U/mL [NR, 0–37 U/mL]), and serum AFP levels were highly elevated at 376 ng/mL (NR, 0–9.9 ng/mL). Therefore, a hepatectomy instead of a liver biopsy was indicated, because the mass was well vascularized; a biopsy poses a higher risk of hemorrhage. Moreover, the mass had the possibility of being a malignancy, such as hepatocellular carcinoma, metastatic carcinoma, or liver angiosarcoma; or of being a benign mass, including hepatic adenoma or hematoma. Performing a biopsy in these cases increases the risk of tumor cell dissemination. We performed an extended left lobectomy of the liver for therapeutic diagnosis at about 34 months after the first operation. The hepatic specimens and the prior resected gastric specimens were retrospectively analyzed. Pathology revealed neoplastic cells with eosinophilic cytoplasm with a focal glandular component on hematoxylin-eosin staining. Periodic acid–Schiff staining revealed acidophilic cytoplasm, suggesting glycogen-rich clear neoplastic cells (Fig. 5). These characteristic findings drove us to analyze the specimens with immunohistochemical staining for markers of enteroblastic

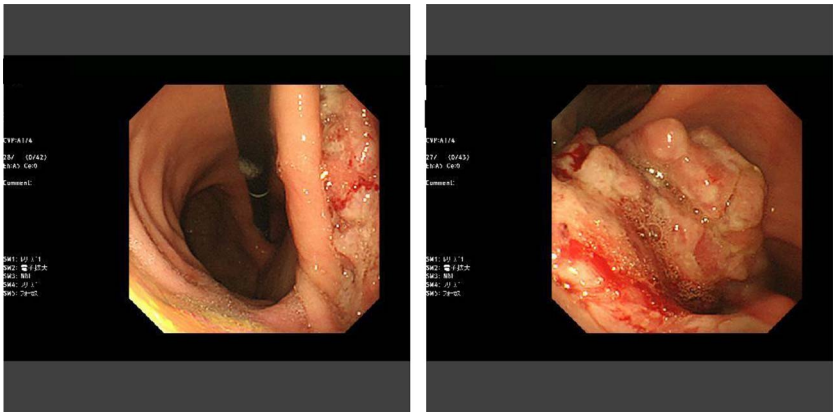

Fig. 2 Upper endoscopy showed circular ulcerative lesion at the antrum of with spreading to the angulus of the stomach.

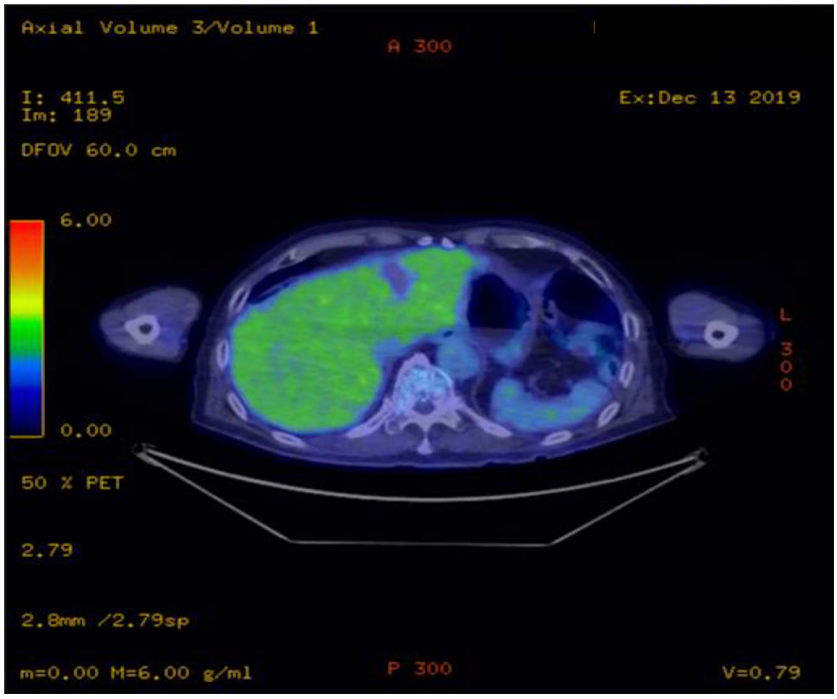

Fig. 3 Positron emission tomography–computed tomography showed no significant accumulation of fluorine-18-fluorodeoxyglucose at the mass.

differentiation (ED). To confirm GAED, we examined immunohistochemical positivity for 3 markers: AFP (rabbit polyclonal, 1:600; Dako, Glostrup, Denmark), Glypican 3 (rabbit, polyclonal, 1G12, 1:200; BioMosaics, Burlington, Vermont), and SALL4 (mouse, clone 6E3, 1:1000, Abnova, Taipei, Taiwan). The gastric and hepatic specimens stained strongly positive for Glypican 3 and sporadically positive for SALL-4 but negative for AFP (Fig. 6). Thus, the primary gastric tumor was retrospectively rediagnosed as GAED. The resected hepatic lesion was also diagnosed as metastatic GAED in the same manner (Fig. 7). For genetic analysis of the tumor, we performed next-generation sequencing (NGS) using the Next Seq 2000 (Illumina Inc, San Diego, California). Genomic DNA was extracted from the tumor specimens using the QIAamp formalin-fixed, paraffin-embedded gastric and hepatic specimens. Next-generation sequencing identified mutations in the *TP53* gene and loss of the *APC* gene. The *ERBB2/HER2* amplification status was not identified (HER2/CEP ratio 1.49 <1.7) by fluorescence in situ hybridization.

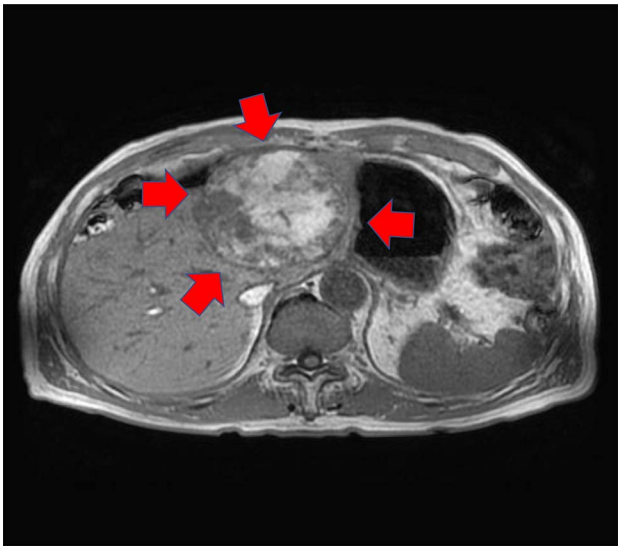

Fig. 4 Contrast-enhanced magnetic resonance imaging revealed the mass was enlarged to 60 mm in size with highly enhancing mosaic mass (red arrows) on T1-weighted image 33 months after the gastrectomy.

Thereafter, the patient remained well, and radiologic examination revealed no recurrence occurred for 6 months after the hepatectomy. The serum level of AFP remained normal (7.3 ng/mL) for 10 months after hepatectomy. However, the patient experienced an acute cerebral infarction, the cause of which is unrelated to metastatic gastric adenocarcinoma, and died 44 months after the initial surgery.

Discussion

Reports on individual clinical courses of GAED have been scarce. To understand GAED, we should

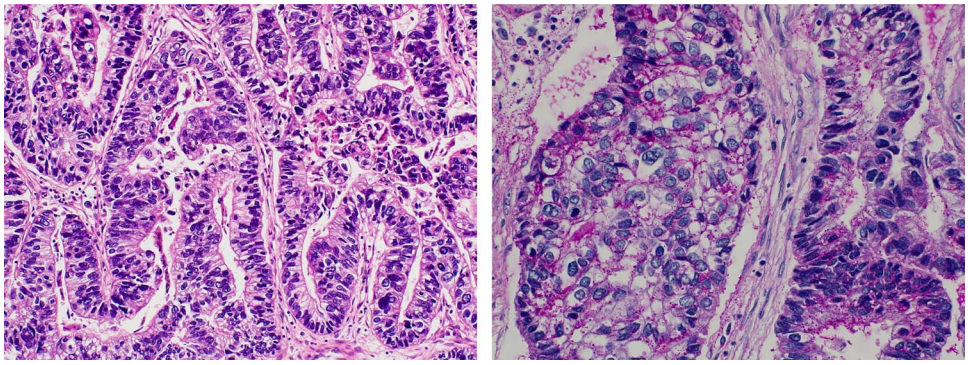

Fig. 5 Neoplastic cells with eosinophilic cytoplasm with a focal glandular component on hematoxylin-eosin staining. Periodic acid–Schiff staining revealed acidophilic cytoplasm suggesting rich glycogen clear neoplastic cells in the reevaluated gastric specimen, suggesting gastric adenocarcinoma coexisted with GAED in the gastric specimen.

shed light on the terminology used historically for APGC, because the terms "AFP-producing gastric carcinoma," "hepatoid adenocarcinoma (HAC)," and "GAED" have been used interchangeably. The term "HAC" was first used for an APGC with hepatic differentiation features in 1985 by Ishikura *et al*.[5] Afterward, in 1990, Ooi *et al*[6] pointed out a variant type with a clear cell component that resembled fetal gut in an AFP-producing HAC. Matsunou *et al*[1] coined the term "enteroblastic differentiation" for an APGC with clear cytoplasm and reported its blastomatous characteristics for the first time. However, these terms have not been systematically classified, because the terms were not defined by considering the morphologically and functionally overlapping features. Subsequently, Glypican 3 and SALL4 were recognized as significant markers for HAC with ED by Ushiku et al[7,8]. SALL-4 is a sensitive marker for APGCs and is especially useful to diagnose hepatoid GC or GC with retrodifferentiation to fetal gut[8]. Glypican 3 is also a sensitive marker for the hepatoid components of an APGC[7]. Therefore, GAED has been most recently defined as immunohistochemical positivity for at least 3 of these markers for enteroblastic linage: AFP, Glypican3, and SALL-4. Though we did not perform immunohistochemistry for claudin-6, it is also known as an enteroblastic lineage marker useful in distinguishing hepatic metastases from GAED from other hepatic tumors[9]. Our specimen was positive for Glypican3, and SALL-4, suggesting GAED as a diagnosis. Akazawa *et al*[10] documented that the immunohistochemical positivity rates for AFP, Glypican 3, and SALL-4 were 31.4%, 82.4%, and 80.4% respectively, and Murakami *et al*[2] reported that Glypican 3 is the most sensitive marker for GAED (83%), followed by SALL4 (72%), and AFP (45%); conventional gastric cancer was not positive for these markers. The pathologic features of GAED include the proliferation of tubular, papillary, or solid cells with a clear cytoplasm rich in glycogen. GC with ED was coexistent with conventional adenocarcinoma.[10] Our resected gastric

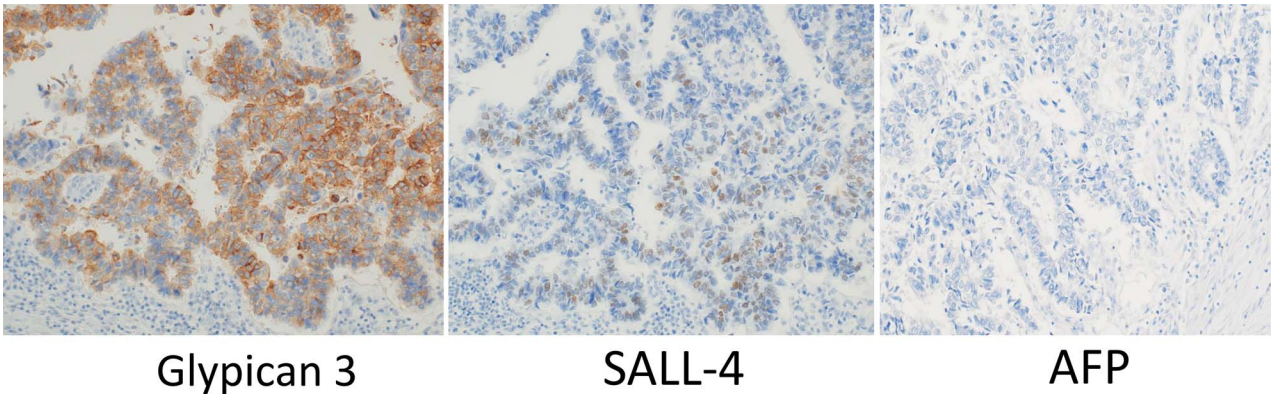

Fig. 6 The gastric specimen showed strongly positive for Glypican 3 and sporadically positive for SALL-4, and negative for AFP in immunohistochemistry.

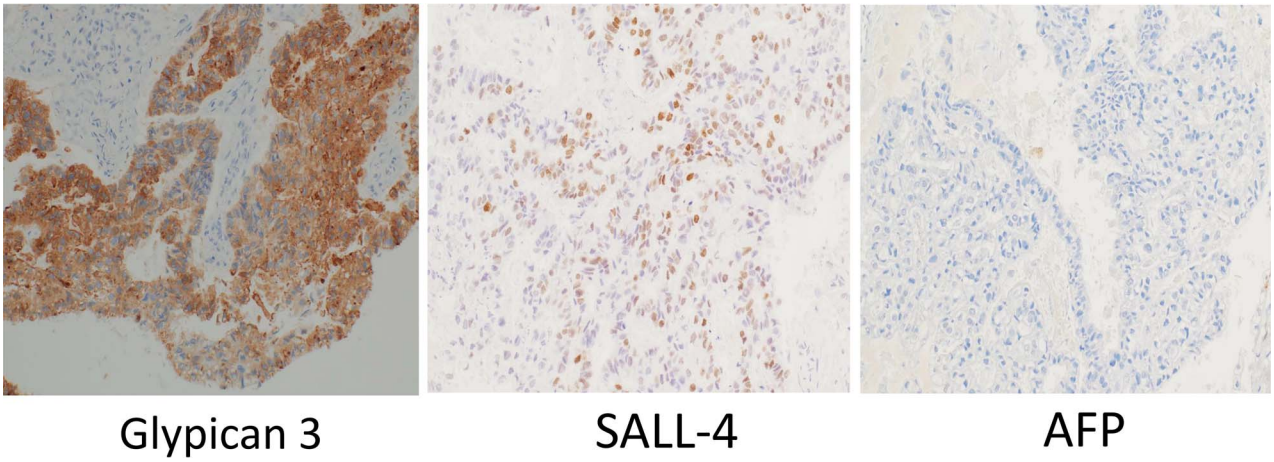

Fig. 7 The hepatic specimen showed immunohistochemical aspects similar to those of gastric specimen.

specimens showed a well-to-moderately differentiated adenocarcinoma coexisting with a clear cell carcinoma as a major component. The pathologic characteristics were consistent with the diagnostic features for GAED.

Strictly speaking, hepatoid adenocarcinoma (HAC) differs from adenocarcinoma with ED, but they both share the ability to produce AFP. Previously, Akazawa *et al*[10] retrospectively demonstrated that all gastric cases diagnosed as HAC were classified as solid-type adenocarcinoma with ED by histologic reevaluation with immunohistochemical staining using enteroblastic lineage marker of AFP, Glypican 3 and SALL-4. Furthermore, genetic analysis revealed a high *TP53* mutation frequency. Therefore, they stated that HAC can be subcategorized as solid-type adenocarcinoma with ED.[10] As for the tumorigenesis of GAED, histologic analysis supports the speculation that GAED develops from conventional GC, acquiring hepatoid or primitive gut features during its course.[2] Adenocarcinoma with ED is often encountered in the stomach, sporadically in the colorectum,[11,12] and in the cervical esophagus, the ampulla of Vater, and the gallbladder.[13–15] We believe that this is because immunohistochemical staining using Glypican 3 and SALL-4 is being applied commonly, and adenocarcinoma with ED may be recognized if reevaluation using immunohistochemical analysis is performed on previously published data that had diagnosed conventional adenocarcinoma, which could suggest that adenocarcinoma with ED can possibly occur in a multitude of organs. From a different perspective, Lu *et al*[16] described recent data on somatically derived yolk sac tumors (YSTs) that significantly overlapped with APGCs. The YST cells showed clear cytoplasm and subnuclear vacuolization, resembling endometrial and fetal-gut epithelium. In addition, the somatically derived YSTs showed immunophenotypes of AFP, Glypican 3, and SALL-4 similar to those of HAC and GAED. Thus, they hypothesized that GAED and HAC are subtypes of APGC, and they may arise from somatically derived YSTs.[16–18]

Moreover, we studied the genetic characteristics of GAED using next-generation sequencing and fluorescence in situ hybridization. Our results identified a *TP53* gene mutation and a loss of *APC*. Akazawa *et al*[10] reported that the most frequently mutated gene was *TP53,* and almost all cases with missense mutations showed *p53* overexpression.

In general, HAC exhibits elevated serum AFP levels and usually presents with extensive vascular invasion, frequent liver metastasis, and advanced pTNM staging, all of which contribute to an extremely poor prognosis.[19] Similarly, GAED is rare and highly malignant. GAED has higher vascular invasion and metastasis rates compared with conventional GC.[2] Even if early diagnosis as GAED could be made at the initial pathologic examination, treatment would be the same, because a specific treatment for GAED has never been established, and we have no choice but to indicate the current treatment guidelines in clinical practice. Surely, there is a report of GAED cases treated by endoscopic submucosal dissection[20]; however, treatment results by long-term follow-up have not been verified, considering the highly malignant behaviors of GAED. Yet, we should make the observation interval for GAED shorter than for conventional GCs in consideration of aggressive behaviors. However, prognosis will not improve unless gene-targeted therapy is developed. Targeted HER2 therapy with trastuzumab

may play an important therapeutic role in HER2$^+$ GC. There is growing evidence that HER2 is an important biomarker and key driver of tumorigenesis in GC, with studies demonstrating amplification or overexpression in 7% to 34% of all GCs; the ToGA trial revealed 22.1% in GC without geographic difference.[21] Although our case was negative for HER2, Fujimoto *et al*[22] reported that HER2 is frequently overexpressed in HAC (31.1%) and GAED (42.1%), compared with other GCs (13.8%).[22] We think that these data imply that HER2 expression may allow the proliferation of primitive neoplastic cells in a manner that would predispose the neoplastic growth to eventually growing into HAC or GAED.

Concerning the prognosis of stage I gastric cancers, overall survival rates between the laparoscopic group (94.2% [95% CI, 92.4%–96.0%]) and the open surgery group (93.3% [95% CI, 91.4%–95.2%]) were similar and satisfactory (log-rank $P = 0.64$; difference, 0.9 percentage points; 1-sided 97.5% CI, −1.6 to infinity).[23] Our case was stage IB according to TNM classification. Unexpectedly, metastasis to the liver occurred in the early postoperative period. The solitary metastatic hepatic lesion was resected; however, the patient died 44 months postoperatively, not due to GAED but due to a cerebrovascular event. Compared with conventional GCs, GAED has a poor prognosis of 2 to 39 months (median, 18 months) in any of its stages.[2] Therefore, tumor-specific treatment, including HER2 targeted therapy when indicated, should be considered.

Finally, we want to emphasize the most important lessons from our case. (1) If the serum levels of AFP are elevated or the clinical course is evidently different from that of conventional GC, pathology should be reconsidered to include GAED in the differential diagnosis. (2) Immunohistochemistry for Glypican 3 and SALL-4 should be performed to confirm GAED. (3) If the serum level of AFP is increasing, tumors with ED should be a candidate wherever tumors are located. (4) Because adenocarcinoma with ED has been sporadically reported in organs other than the stomach, we speculate that the neoplastic transformation acquiring ED can occur across organs.

Conclusions

Tumors with ED may produce AFP, and thus have immunopositivity for Glypican 3 or SALL-4 across organs. Our results emphasize that clinicians should keep this highly malignant tumor variant in mind when considering differential diagnoses for GC histologic subtypes. Research exploring modalities for reliable GAED diagnosis and effects of GAED is needed for earlier detection and better management.

Acknowledgments

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