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Original Article

Gastric adenocarcinoma with intestinal progenitor cell differentiation: a morphologically underdiagnosed and more invasive distinctive type of gastric adenocarcinoma

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Abstract: This study aims to explore the clinical and pathological characteristics, prognosis, diagnosis, and differential diagnosis of gastric adenocarcinoma with enteroblastic differentiation (GAED) in elderly patients. A total of 16 cases of GAED diagnosed from August 2019 to August 2022 at the First Affiliated Hospital of Nanchang University were retrospectively collected to analyze their clinical and pathological features. A control group of 360 cases of conventional gastric adenocarcinoma diagnosed during the same period was used for comparison. Among the 16 GAED patients, 11 were male and 5 were female, with ages ranging from 64 to 89 years (median age 75.5 years). Clinical manifestations of these patients included symptoms such as abdominal pain, bloating, hematemesis, and melena. The macroscopic classification revealed 11 cases of ulcerative lesions, 4 protruded lesions, and 1 diffusely infiltrative lesion. Tumor sizes varied from 3 to 9.5 cm in diameter, with a median diameter of 4.75 cm. Microscopically, the tumor cells exhibited tubular, papillary, and cribriform arrangements, with cuboidal or columnar morphology, relatively distinct cell boundaries, and cytoplasm that appeared clear or weakly acidophilic. Immunophenotyping analysis revealed the expression of SALL4 (15/16), Glypican-3 (12/16), CDX2 (12/16), CD10 (10/16), and p53 (12 cases exhibiting mutant expression, 4 cases exhibiting wild-type expression) within the tumor cells. There was no loss of mismatch repair proteins (MLH1, PMS2, MSH2, MSH6). The Ki-67 proliferation index ranged from 50% to 95%. In comparison to conventional gastric adenocarcinoma, GAED was frequently found in the gastric antrum ($P<0.001$) and exhibited a higher incidence of intravascular cancer emboli ($P<0.001$). Significant differences were noted in the Lauren classification, invasion depth, differentiation degree ($P<0.01$), and macroscopic type ($P<0.05$). However, no significant differences were found regarding age, gender, tumor diameter, neural invasion, or lymph node metastasis ($P>0.05$). The postoperative follow-up ranging from 5 to 29 months revealed one death and 15 cases of disease-free survival. GAED is a special subtype of gastric adenocarcinoma characterized by a combination of embryonal and intestinal differentiation immunophenotypes, as well as its increased propensity for biological invasion. Accurate identification of GAED is crucial in pathological practice, as it helps differentiate between GAED and conventional adenocarcinoma and aids in the evaluation of tumor malignancy. Furthermore, it is imperative to conduct a differential diagnosis that involves hepatoid adenocarcinoma, yolk sac tumor-like adenocarcinoma, and metastatic hepatocellular carcinoma.

Keywords: Gastric tumor, intestinal progenitor cell differentiation, immunohistochemistry

Introduction

Gastric adenocarcinoma with enteroblastic differentiation (GAED) is a rare type of gastric adenocarcinoma, also known as clear cell gastric adenocarcinoma or fetal-type intestinal adenocarcinoma [1, 2]. The 2019 "World Health Organization Classification of Tumours of the Digestive System" has specifically categorized it as a subtype of gastric adenocarcinoma. GAED is characterized by distinct histomorphological and immunophenotypic characteristics; however, it also exhibits certain resemblances to hepatoid adenocarcinoma and yolk sac tumor-like gastric cancer, which may lead to diagnostic challenges [3, 4]. Patients often

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present with elevated serum alpha-fetoprotein (AFP) levels. Given GAED's tendency to invade blood vessels, liver metastasis is frequently observed, which underscores the importance of distinguishing it from hepatocellular carcinoma [5, 6]. In this study, we retrospectively analyzed the clinical data from 16 elderly patients with GAED, explored their clinical and pathological characteristics, and compared them with 360 cases of traditional gastric adenocarcinoma diagnosed concurrently, aiming to provide a basis for clinical diagnosis, treatment, and prognosis. This study is innovative in its comprehensive exploration of histopathological and immunohistochemical research in GAED patients, an area that has been underexplored in previous studies. Research on GAED patients is currently sparse, and their immunohistochemical profiles have not been thoroughly studied. Takashi Murakami et al. conducted a study that delved into the immunohistochemical features of GAED; however, this paper builds upon this foundation by enhancing the selection of antibodies in immunohistochemical analyses and providing a more focused discussion on the identification of diagnostic markers for elderly patients with GAED.

Materials and methods

Study design

A total of 16 cases of GAED diagnosed from August 2019 to August 2022 at the First Affiliated Hospital of Nanchang University were collected to analyze their clinical pathological features. A control group of 360 cases of conventional gastric adenocarcinoma diagnosed during the same period was used for comparison. Patients were eligible for the GAED group if they were diagnosed with gastric adenocarcinoma based on pathological findings, had complete medical records, and underwent radical surgical resection. Patients were ineligible if they had incomplete imaging data or poor-quality images, presented with concomitant tumors in other locations, were pregnant or lactating women, exhibited poor clinical compliance, or were unable to comply with the study protocol.

Patients were eligible for the non-GAED group if they had complete imaging and surgical data, and were diagnosed with gastric adenocarcinoma based on postoperative pathological findings. Patients were ineligible if they had incomplete clinical data and poor-quality images, were pregnant or lactating women, or had a history of concomitant malignancies in other locations.

Source of data

Clinical pathological data were collected from gastrectomy specimens diagnosed between August 2019 and August 2022 at the Department of Pathology, the First Affiliated Hospital of Nanchang University, Jiangxi Province. This study was approved by the Institutional Review Board and Research Ethics Committee of the First Affiliated Hospital of Nanchang University, and was conducted in compliance with the Declaration of Helsinki.

Methods

The patient samples obtained during radical resection surgery were subjected to histopathological and immunohistochemical analyses. The specimens were incised and fixed in 10% neutral formalin for 24 hours before processing, followed by dehydration, paraffin embedding, sectioning at 4 μm, and H&E staining for observation under light microscopy [7]. Immunohistochemical staining was performed using the EnVision two-step method, employing antibodies such as spalt-like transcription factor 4 (SALL4) (ZM-0393), Glypican-3 (TA327687), HepPar-1 (ZM-0131), CD10 (ZM-0283), caudal-type homeobox 2 (CDX2) (ZA-0520), p53 (ZM-0408), Ki-67 (ZM-0166), human epidermal growth factor receptor 2 (HER2) (ZM-0065), mutL homolog 1 (MLH1) (ZM-0154), postmeiotic segregation increased 2 (PMS2) (ZA-0542), MutS Homolog 2 (MSH2) (ZA-0702), and MutS Homolog 6 (MSH6) (ZM-0367). Antibody kits from Beijing Zhongshan Golden Bridge Biotechnology were used, and procedures were carried out following the manufacturer's instructions. The detection of EB virus was conducted through in situ hybridization to identify EBV-encoded RNA (EBER) with reagent kits purchased from Leica (PB0589) as per the provided instructions. The histological, immunohistochemical, and EBER in situ hybridization results were jointly observed and interpreted by two pathologists.

Follow-up and prognosis

All cases were tracked through medical record systems or phone contacts to collect data on disease progression and survival status, with the follow-up ending on July 20, 2022.

Statistical analysis

The statistical software SPSS 22.0 was used. Quantitative data were represented by median values, while categorical data were expressed as frequency n (%). The comparison of categorical variables was conducted using the chi-square test or Fisher's exact probability method, with a significance level set at $P<0.05$.

Results

Clinical data

The clinical pathological data and follow-up information of the 16 GAED cases (**Table 1**) indicate that the cohort included 11 males and 5 females, with ages ranging from 64 to 89 years (median age 75.5 years). Primary clinical symptoms of these patients were abdominal pain, melena, and hematemesis. Abdominal computed tomography (CT) scans revealed irregular thickening of the gastric wall with heterogeneous density, and enhanced scans showed uneven enhancement or distinct mass-like, cauliflower-like tumor shadows. Elevated serum alpha-fetoprotein was noted in 14 cases. All patients underwent radical surgical resection, with 8 receiving chemotherapy postoperatively and 1 receiving postoperative radiotherapy. Gross examination identified 11 cases of ulcerative lesions, 4 cases of protruding lesions, and 1 case of diffuse infiltrative lesion. Tumor locations included the cardia (n=4), gastric body (n=4), and gastric antrum (n=8), with tumor maximum diameters ranging from 3 to 9.5 cm (median diameter 4.75 cm). Follow-up period for the 16 GAED cases ranged from 5 to 29 months, with one case of death from pancreatic metastasis, and 15 cases showing disease-free survival.

Microscopic observation

Pathological feature analysis of the 16 GAED cases (**Figure 1**; **Table 2**) showed morphological similarities, with tumor cells arranged in a tubular, papillary, and cribriform pattern (**Figure 1A**). The cells were cuboidal or columnar with relatively distinct cell boundaries, and abundant clear or lightly acidophilic cytoplasm, resembling the morphology of embryonic development of intestinal epithelium. The cell nuclei were round or oval, featuring distinct nucleoli and slightly coarse chromatin (**Figure 1B**). One case concurrently exhibited tubular adenocarcinoma, low adhesion carcinoma, and hepatoid adenocarcinoma. Most cases displayed intravascular tumor emboli (15/16), neural invasion (10/16), and lymph node metastasis (10/16).

Immunohistochemistry

The immunohistochemical phenotypes of the 16 GAED cases (**Figure 1**; **Table 3**) demonstrated that the tumor cells associated with GAED exhibited positive expression for SALL4 (15/16, **Figure 1D**), Glypican-3 (12/16, **Figure 1F**), AFP (10/16), CDX2 (12/16, **Figure 1C**), CD10 (11/16), p53 (mutant expression in 12 cases, **Figure 1E**), and HER2 (3/16, 2+; 4/16, 1+; 9/16, 0). There was no loss of mismatch repair proteins (MLH1, PMS2, MSH2, MSH6), and the Ki-67 positivity index ranged from 50% to 95%.

Comparison of clinical pathological features between GAED and non-GAED

The incidence of vascular invasion in GAED was 87.5% (14/16), which was significantly higher than the 32% (116/360) in conventional gastric adenocarcinoma, indicating a statistically significant difference ($P<0.05$). Furthermore, GAED was predominantly located in the gastric antrum compared to conventional gastric adenocarcinoma ($P<0.01$). There were significant differences in Lauren classification, invasion depth, differentiation degree ($P<0.01$), and gross classification ($P<0.05$) between GAED and conventional gastric adenocarcinoma. However, no significant differences were observed in age, gender, tumor diameter, neural invasion, and lymph node metastasis ($P>0.05$) (**Table 4**).

Discussion

GAED is a rare subtype of AFP-producing gastric cancer, first identified by Motoyama T et al. in 1993 [8]. Currently, AFP-producing gastric cancers are classified into three subtypes: GAED, hepatoid adenocarcinoma, and yolk sac tumor-like gastric cancer. These subtypes

Table 1. Clinical pathological data of 16 GAED cases

Case No.	Gender	Age (years)	Location	Tumor Size (cm)	Macroscopic Type	Preoperative Serum AFP Level	Treatment	Follow-Up
1	Female	73	Gastric Antrum	4.5×3×1	Ulcerative Type	Elevated	Surgery	No recurrence
2	Female	89	Gastric Antrum	7.5×6.8×3.4	Ulcerative Type	Elevated	Surgery+Chemotherapy	No recurrence
3	Female	80	Residual Stomach, Cardia and Fundus	7.2×5.8×3.6	Elevated Type	Elevated	Surgery+Radiation Therapy	No recurrence
4	Male	69	Near Gastric Angularis and Antrum	3.5×2.8×1.5	Elevated Type	Elevated	Surgery	No recurrence
5	Male	75	Gastric Antrum	3.5×3×0.7	Ulcerative Type	Elevated	Surgery	No recurrence
6	Male	74	Gastric Antrum	3.5×3×2	Ulcerative Type	Elevated	Surgery+Chemotherapy	No recurrence
7	Female	83	Cardia and Fundus	9.1×5.9×1.2	Ulcerative Type	Elevated	Surgery	No recurrence
8	Male	75	Gastric Antrum	5×4×2	Elevated Type	Elevated	Surgery+Chemotherapy	Deceased 1 year later (Pancreatic metastasis)
9	Male	69	Greater Curvature of Stomach Body	4×2.5×1.5 cm	Ulcerative Type	Elevated	Surgery+Chemotherapy	No recurrence
10	Male	76	Lesser Curvature of Stomach	6.5×6.5×0.9 cm	Ulcerative Type	Normal	Surgery+Chemotherapy	No recurrence
11	Male	64	Gastric Antrum	3×2.5×2 cm	Elevated Type	Elevated	Surgery+Chemotherapy	No recurrence
12	Male	78	Gastric Antrum	9.5×4.6×4.6 cm	Diffuse Infiltrating Type	Normal	Surgery	No recurrence
13	Male	76	Cardia	3.7×3×0.7 cm	Ulcerative Type	Elevated	Surgery+Chemotherapy	No recurrence
14	Male	82	Subcardia and Stomach Body	4×4×1 cm	Ulcerative Type	Elevated	Surgery+Chemotherapy	No recurrence
15	Male	77	Lesser Curvature of Gastric Antrum	6×4.5×1	Ulcerative Type	Elevated	Surgery	No recurrence
16	Female	65	Cardia	3×2.2×0.6 cm	Ulcerative Type	Elevated	Surgery	No recurrence

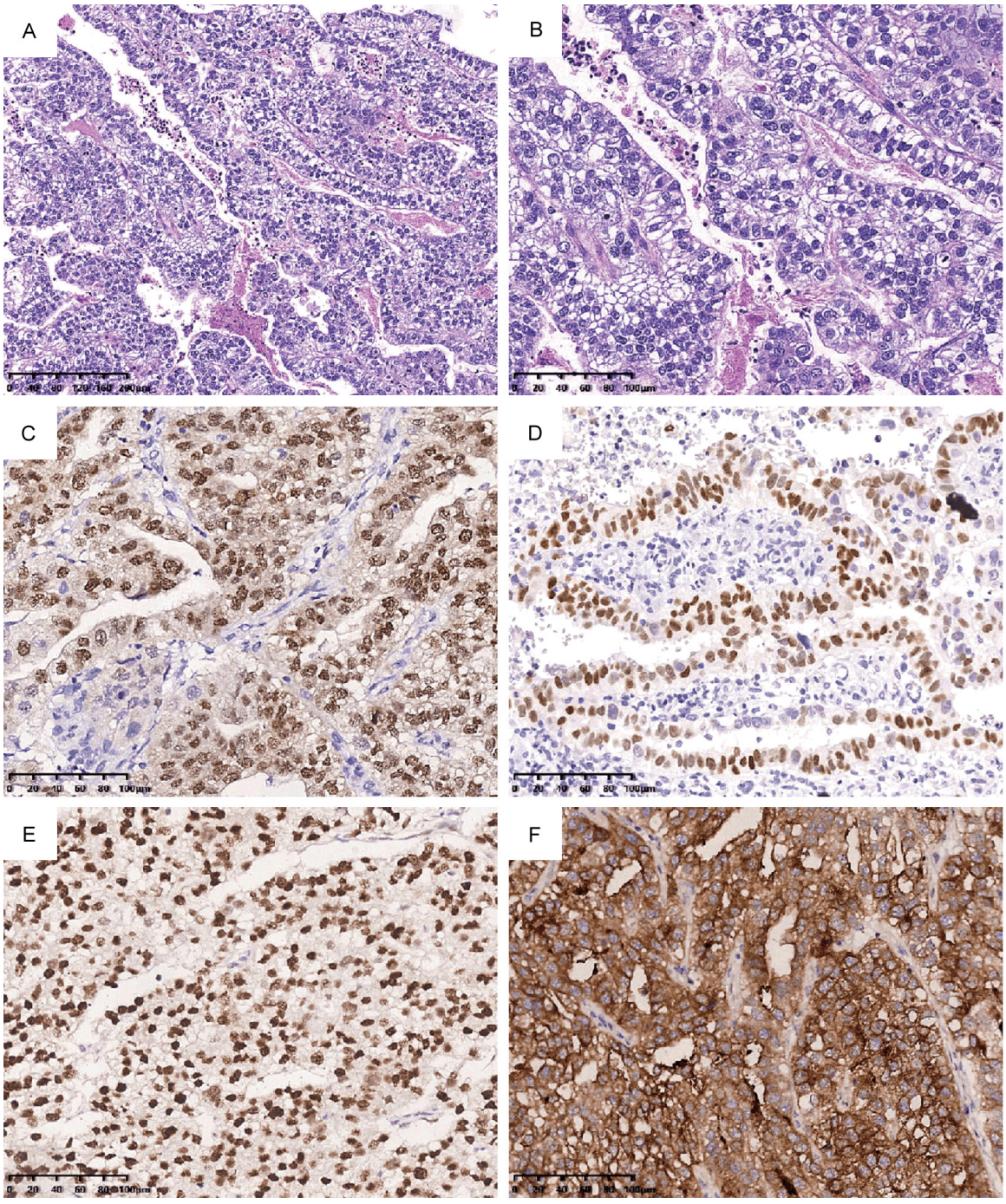

Figure 1. Pathological features and immunohistochemistry of GAED. A. Tumor cells were arranged in a tubular, papillary, and cribriform pattern; B. Cell nuclei were round or oval, with distinct nucleoli and slightly coarse chromatin; C. GAED tumor cells expressed CDX2; D. GAED tumor cells expressed SALL4; E. GAED tumor cells expressed p53; F. GAED tumor cells expressed Glypican-3.

exhibit morphological and immunophenotypic similarities, which may cause diagnostic confusion. GAED mainly affects individuals between the ages of 59 and 85 years (average 73 years), with a male predominance (male:female =23:6). The lesions are commonly found in the middle to lower third of the stomach. In this study, the patients' ages ranged from 64 to 89 years (median age 75.5 years), with a male-to-female ratio of 11:5, GAED was predominantly

Table 2. Pathological features of 16 GAED cases

Case No.	Tumor Infiltration Depth	Tumor Differentiation	Vascular Thrombosis	Nerve Invasion	Lymph Node Metastasis	Liver Metastasis	TNM Stage
1	Submucosal	Moderate	Present	Present	Groups 5, 6, 7, 8 lymph nodes 1/1, 2/2, 1/1, 1/1, Lesser curvature 2/8, Greater curvature 1/8	Absent	T3N3M0
2	Submucosal	Low	Present	Present	Lesser curvature 2/32, Greater curvature 0/3, 4 cancer nodules	Absent	T3N2M0
3	Submucosal	Moderate	Present	Present	Perigastric lymph nodes 5/10	Absent	T3N2M0
4	Mucosal Sublayer	Moderate	Present	Absent	Lesser curvature 4/22, Greater curvature 0/3	Absent	T1bN2M0
5	Muscular Layer	Moderate	Present	Present	Lesser curvature 2/10, Greater curvature 0/2	Absent	T2N1M0
6	Submucosal	Moderate	Present	Absent	Lesser curvature 0/20, Greater curvature 0/3	Present (1 nodule)	T3N0M1
7	Muscular Layer	Absent	Absent	Absent	Lesser curvature 0/13, Greater curvature 0/9	Absent	T2N0M0
8	Submucosal	Low	Present	Present	Lesser curvature 0/16, Greater curvature 0/4, 1 cancer nodule in Greater curvature	Absent	T3N1M1
9	Muscular Layer	Low	Present	Present (on the Greater curvature side: 3/15)	Absent	Lesser curvature 0/13, Greater curvature 0/9	T2N2M0
10	Subserosal	Moderate	Present	Present	No cancer metastasis observed	Absent	T4N0M0
11	Muscular Layer	Moderate	Absent	Absent	No cancer metastasis observed	Absent	T2N0M0
12	Subserosal	Moderate	Absent	Absent	Lesser curvature 1/8, Greater curvature 1/10	Absent	T4N1M0
13	Intrinsic Muscular Layer	Moderate	Present	Present	No cancer metastasis observed	Absent	T2N0M0
14	Submucosal	Low	Present	Present	Groups 3, 9, 11 lymph nodes 4/10, 1/2, 1/2	Absent	T3N2M0
15	Subserosal	Low	Absent	Absent	Perigastric, Groups 1, 3, 5, 7-9 lymph nodes 1/6, 3/5, 2/6, 3/9, 1/1	Absent	T4aN3aM0
16	Mucosal Sublayer	Low	Absent	Absent	No cancer metastasis observed	Absent	T1bN0M0

Table 3. Immunophenotype of 16 cases of GAED

Case No.	SALL4	AFP	Glypican-3	CDX-2	HER2	CD10	MMR	P53	Ki-67
1	+	-	+	-	0	+	pMMR	Mutant Type	80%
2	+	+	+	+	2+	+	pMMR	Mutant Type	80%
3	+	-	+	+	1+	-	pMMR	Mutant Type	80%
4	-	+	+	+	2+	+	pMMR	Mutant Type	50%
5	+	+	-	+	1+	+	pMMR	Mutant Type	50%
6	+	+	-	+	0	-	pMMR	Wild Type	70%
7	+	+	+	+	1+	-	pMMR	Mutant Type	80%
8	+	+	+	-	0	+	pMMR	Mutant Type	60%
9	+	-	+	+	1+	+	pMMR	Mutant Type	70%
10	+	-	-	+	0	+	pMMR	Mutant Type	70%
11	+	+	+	-	0	+	pMMR	Wild Type	80%
12	+	-	-	+	0	+	pMMR	Mutant Type	95%
13	+	+	+	+	0	-	pMMR	Wild Type	75%
14	+	+	+	-	0	+	pMMR	Mutant Type	90%
15	+	+	+	+	2+	+	pMMR	Mutant Type	80%
16	+	-	+	+	0	-	pMMR	Wild Type	70%

found in the gastric antrum (8/16). GAED presents with nonspecific clinical manifestations, primarily characterized by gastrointestinal symptoms. Radiologically, GAED often exhibits irregular thickening of the gastric wall or distinct space-occupying lesions with uneven enhancement post-contrast, possibly accompanied by lymphadenopathy, resembling the imaging features typically seen in conventional gastric adenocarcinoma [9]. Although serum AFP elevation is common in GAED cases, it's not a prerequisite for diagnosis, which mainly relies on histomorphology and immunophenotype. The prognosis for GAED is poorer than for conventional gastric adenocarcinoma, with a median survival of only 29 months [10, 11]. Li QZ et al. [12] compared 11 cases of GAED with 289 cases of conventional gastric adenocarcinoma. They found a significantly shorter progression-free survival in GAED patients, indicating a faster disease progression, with a higher likelihood of vascular and/or lymphatic invasion, and a higher rate of lymph node metastasis (62.5% vs 44%). They also confirmed a significantly higher rate of vascular invasion in the GAED group compared to the conventional gastric adenocarcinoma group ($P<0.001$). Recent studies have found a high incidence of SMAD4 gene loss in GAED patients, which is strongly associated with advanced tumor progression and lymph node metastasis. Currently, the treatment for GAED primarily involves radical surgical resection, supplemented by chemotherapy or radiotherapy for metastatic cases [13, 14].

GAED is primarily seen as ulcerative tumors, exhibiting morphological characteristics of enteroblastic differentiation. It has both embryonal (expressing SALL4, Glypican-3, AFP) and intestinal (expressing CD10, CDX2, and MUC6) phenotypes [15]. Akazawa et al. [16] reported that the positive rates of SALL4 and Glypican-3 in GAED were 80.4% and 82.4%, respectively. In this study, the positive rates of SALL4 and Glypican-3 were 15/16 (93.7%) and 12/16 (75%), respectively. This finding aligns with previous research, supporting that both SALL4 and Glypican-3 are sensitive markers for the diagnosis of GAED. The ultrastructural analysis revealed the presence of well-developed microvilli and core filaments, occasionally forming terminal webs. These characteristics are in line with the absorptive epithelium found in the fetal intestine or mature intestinal cells. The cytoplasmic organelles exhibited poor development, with scarce mucin granules, resembling undifferentiated primitive intestinal cells. Additionally, a large number of dispersed glycogen granules were observed. Some scholars believe that hepatoid adenocarcinoma may represent a solid subtype or a terminally differentiated manifestation of GAED, thus suggesting its classification as solid GAED [17, 18]. However,

Table 4. Comparison of clinical pathological features between GAED and non-GAED

Clinical Pathological Parameters	GAED	non-GAED	T or c^2	P
Age	75.31±6.56	73.52±7.36	0.956	0.340
Tumor Diameter (cm)	5.22±2.15	3.27±1.75	4.313	0.148
Gender			0.381	0.537
Male	11 (69%)	272 (76%)		
Female	5 (31%)	88 (24%)		
Location			43.115	<0.001
Cardia	4 (25%)	5 (1.4%)		
Gastric Body	4 (25%)	256 (71%)		
Gastric Antrum	8 (50%)	99 (27.6%)		
Lauren Classification			49.414	<0.001
Intestinal Type	9 (56%)	308 (86%)		
Diffuse Type	2 (13%)	0 (0)		
Mixed Type	5 (31%)	52 (14%)		
Tumor Depth			10.592	0.014
T1	2 (12.5%)	151 (42%)		
T2	5 (31.3%)	41 (11.4%)		
T3	6 (37.5%)	74 (21%)		
T4	3 (18.7%)	94 (25.6%)		
Vascular Invasion			20.693	<0.001
Present	14 (87.5%)	116 (32%)		
Absent	2 (12.5%)	244 (68%)		
Nerve Invasion			2.507	0.113
Present	9 (56.3%)	132 (37%)		
Absent	7 (43.7%)	228 (63%)		
Lymph Node Metastasis			2.214	0.137
Present	10 (62.5%)	157 (44%)		
Absent	6 (37.5%)	203 (56%)		
Macroscopic Type			24.555	<0.001
Elevated Type	4 (25%)	18 (5%)		
Ulcerative Type	10 (62.5%)	338 (94%)		
Infiltrative Type	2 (12.5%)	4 (1%)		
Differentiation			33.144	<0.001
High	0 (0)	0 (0)		
Moderate	5 (31%)	309 (86%)		
Low	11 (69%)	51 (14%)		

studies have shown that compared to GAED, about 57.5% of hepatoid adenocarcinoma cases had multiple distant metastases, predominantly affecting the liver, at the time of diagnosis (P<0.001). Furthermore, survival analyses revealed that the overall survival and recurrence-free survival of patients with hepatoid adenocarcinoma (averaging 25 months and 53 months, respectively) were significantly shorter than those of GAED patients (averaging 107 months and 118 months, respectively) (P<0.001). These findings support the classification of GAED as an independent pathological subtype of gastric cancer, distinguished by variations in pathological morphology and prognosis [19]. In this cohort, one case displayed features of GAED, tubular adenocarcinoma, low-cohesive carcinoma, and hepatoid adenocarcinoma, indicating a potential morphological relationship among these entities. Nevertheless, given the limited number of cases, further research is warranted to ascertain if the bio-

logical behavior and clinical prognosis of GAED patients with mixed components align with those of patients with pure GAED.

In our routine pathological diagnostic practice, we have noticed that the morphology of certain tumor tissues bears a striking resemblance to that of embryonic tissues. Some scholars [20] have speculated that these tumors may activate specific embryonic developmental programs. They have also introduced the concept of "embryonic remnants", implying that these tumors arise from quiescent embryonic-like cells in mature tissues. These tumors not only exhibit morphological characteristics akin to primitive cells, but also demonstrate an upregulation of genes associated with primitive cell-like properties. Given that these primitive cells possess attributes such as self-renewal, multipotential differentiation, and unlimited proliferation capacity, tumors of this nature exhibit a high degree of invasiveness. In 2014, The Cancer Genome Atlas (TCGA) [21] classified gastric adenocarcinoma into four molecular subtypes: chromosomal instability (CIN), genomically stable (GS), Epstein-Barr virus (EBV) positive, and microsatellite instability (MSI). The molecular subtyping of gastric cancer is instrumental in the selection of targeted drugs for individualized treatment. Yamazawa et al. [22] found that the molecular subtype of gastric adenocarcinoma with enteroblastic differentiation is classified as "chromosomal instability". This subtype often manifests as aneuploidy and the amplification of receptor tyrosine kinases (RTK). The aneuploidy is related to a high incidence of mutations of the P53 gene (occurrence rate about 71%). Yatagai N et al. [23] found that the methylation of the TP53 promoter plays a role in the downregulation of p53 expression. Additionally, aberrant methylation of TET1 and 5-hydroxymethylcytosine (5-hmC) may be related to the development of invasive GAED. In this study, 12 out of 16 GAED cases had P53 mutations (75%), corroborating findings reported by Yamazawa. Furthermore, molecular genetic studies have revealed a high prevalence of HER2 gene amplification (22%-34.6%) in GAED, exceeding that of conventional gastric adenocarcinoma, with 3 cases of HER2 expression 2+ and 4 cases of HER2 expression 1+. Consequently, patients with HER2 amplification may benefit from improved overall survival rates through targeted therapy with trastuzumab [24]. Kataoka I [25] showed that gastric cancer with overexpression of DNA methyltransferase 3A (DNMT3A) has several clinical and pathological characteristics, such as intestinal type, biological invasion, and enteroblastic differentiation. DNMT plays a crucial role in tumor development, and has emerges as a target for cancer treatment, with certain inhibitors already being utilized in clinical settings. Therefore, DNMT3A may also be a potential target for GAED treatment.

Although this study offers valuable insights, it is also important to acknowledge its limitations. The restricted sample size and the single-center study design may affect the generalizability and applicability of the results to broader healthcare contexts. Future investigations should aim to mitigate this limitation by employing larger sample sizes and conducting multicenter studies. Additionally, the follow-up period ended on July 20, 2022, which may compromise the prognosis accuracy. Extending the follow-up duration in subsequent studies could provide more insights into long-term outcomes such as recurrence and mortality rates in patients.

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Disclosure of conflict of interest

None.

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