

# Gastric Adenocarcinoma with Enteroblastic Differentiation

Ádám Ferenczi<sup>a</sup> Levente Kuthi<sup>b,c</sup> Anita Sejbén<sup>a</sup>

<sup>a</sup>Department of Pathology, University of Szeged, Szeged, Hungary; <sup>b</sup>Department of Surgical and Molecular Pathology, National Institute of Oncology, Budapest, Hungary; <sup>c</sup>Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

## Established Facts

- Gastric adenocarcinoma with enteroblastic differentiation (GAED) is a rare entity among gastric carcinomas, and it is characterized by a fetal gut-like histological architecture and the tumor cells displaying a clear cytoplasm rich in glycogen.
- Due to the enteroblastic differentiation, these tumors would tend to be positive for alpha-fetoprotein (AFP), Sal-like protein 4 (SALL4), and Glypican 3 immunohistochemical markers.
- When characterized by molecular pathological examinations, next-generation sequencing (NGS) in GAEDs resulted in a high frequency of v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2) amplification and mutated tumor protein 53. A reduction in the expression of Smad family member 4 (SMAD4) was also observed, which might correlate with the more aggressive behavior of GAED, when compared to CGA. A gene alteration of neurotrophic tyrosine receptor kinase (NTRK) has also been described by Pu et al. [J Clin Pathol. 2024;77(9): 608–13].

## Novel Insights

- We present a case of a 68-year-old woman who presented at the general practitioner with abdominal pain; therefore, gastroscopy was performed, which confirmed malignancy.
- Alcian blue and PAS stains demonstrated positivity for acidic and neutral mucins. P53 IHC was negative, indicative of null-phenotype, while Syntaxin-1 and Chromogranin showed focal positivity. SALL4 and Glypican 3 were positive; however, AFP displayed only minimal, uncertain positivity. The Ki67 labeling index was 70%. Due to the morphological and immunohistochemical characteristics, the tumor was concluded as GAED with neuroendocrine marker positivity.
- WES was carried out revealing 4 pathogenic, including TP53, KLHL7, RAPSN, and ACTA1, and 3 likely pathogenic mutations, encompassing PNKP, HNF1A, and ADNP.

## Keywords

Gastric adenocarcinoma with enteroblastic differentiation · Neuroendocrine marker expression · Whole-exome sequencing

## Abstract

**Introduction:** Gastric adenocarcinoma with enteroblastic differentiation (GAED) is a rare entity with worse prognosis compared to conventional gastric adenocarcinomas. Its histological characteristics are fetal gut-like architecture and tumor cells with cytoplasmic clearing, as well as positive immunohistochemical reaction to at least one of the enteroblastic markers. Hereby, we present a case of GAED with neuroendocrine marker positivity, with whole-exome sequencing (WES), and an updated literature review. **Case Presentation:** A 68-year-old woman presented at the general practitioner with abdominal pain. Abdominal ultrasound described gastric wall thickening raising suspicion of gastric cancer; thus, gastroscopy was performed, and biopsy samples were taken, which confirmed malignancy. Neoadjuvant systemic chemotherapy was initiated, and total gastrectomy was performed. Microscopically, pleomorphic polygonal cells were visible with clear cytoplasm and high-grade cellular atypia. Alcian blue and PAS stains demonstrated positivity for acidic and neutral mucins. P53 IHC was negative, indicative of null-phenotype, while Syntaxin-1 and Chromogranin showed focal positivity. SALL4 and Glypican 3 were positive; however, AFP displayed only minimal, uncertain positivity. The Ki67 labeling index was 70%. Due to the morphological and immunohistochemical characteristics, the tumor was concluded as GAED with neuroendocrine marker positivity. WES was carried out revealing 4 pathogenic, including TP53, KLHL7, RPSN, and ACTA1, and 3 likely pathogenic mutations, encompassing PNKP, HNF1A, and ADNP. **Discussion:** GAED is a rare subtype of gastric adenocarcinomas, representing 0.3–5.4% of all cases, and has an unclarified etiology. Our WES results identified new pathogenic and likely pathogenic mutations. From a differential diagnostic point of view, hepatoid adenocarcinoma and the possibility of metastatic origin have to be excluded.

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architecture and the tumor cells displaying a clear cytoplasm rich in glycogen. According to the current World Health Organisation (WHO) Classification of Tumours, GAED is currently classified into the hepatoid adenocarcinomas and related entities, more precisely to the alpha-fetoprotein (AFP) producing tumors. The WHO states that the frequency of this gastric adenocarcinoma subgroup is between 0.3 and 5.4%. Regarding the etiology of GAED, no significant risk factors have been associated so far [1].

Multiple growth patterns have been described in GAED, including cuboidal, columnar cell, tubulopapillary, or solid [2]; furthermore, solid growth pattern has been associated with worse prognosis [3]. Due to the enteroblastic differentiation, these tumors would tend to be positive for Sal-like protein 4 (SALL4) and Glypican 3 immunohistochemical (IHC) markers, as well, alongside the above mentioned AFP. Besides the typical clear cytoplasm morphology, for the definitive diagnosis, positivity for at least 1 of the 3 aforementioned IHC stains is mandatory. However, it has to be emphasized that these tumors almost always coexist with a conventional gastric adenocarcinoma (CGA) component.

When characterized by molecular pathological examinations, next-generation sequencing (NGS) in GAEDs resulted in a high frequency of v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2) amplification and mutated tumor protein 53 (TP53) [4]. A reduction in the expression of Smad family member 4 (SMAD4) was also observed, which might correlate with the more aggressive behavior of GAED, when compared to CGA [5]. A gene alteration of neurotrophic tyrosine receptor kinase (NTRK) has also been described by Pu et al. [6].

As for the clinical aspects, it is noteworthy that GAED tends to be more aggressive with a poor outcome when compared to CGA, with a 5-year survival rate of 46.6% and also a higher frequency of lymphovascular invasion, lymph node, and liver metastases [3, 5, 7–10]. According to the Trastuzumab for Gastric Cancer (ToGA) study, as GAED often harbors ERBB2/HER2 amplification, trastuzumab therapy may be used [11].

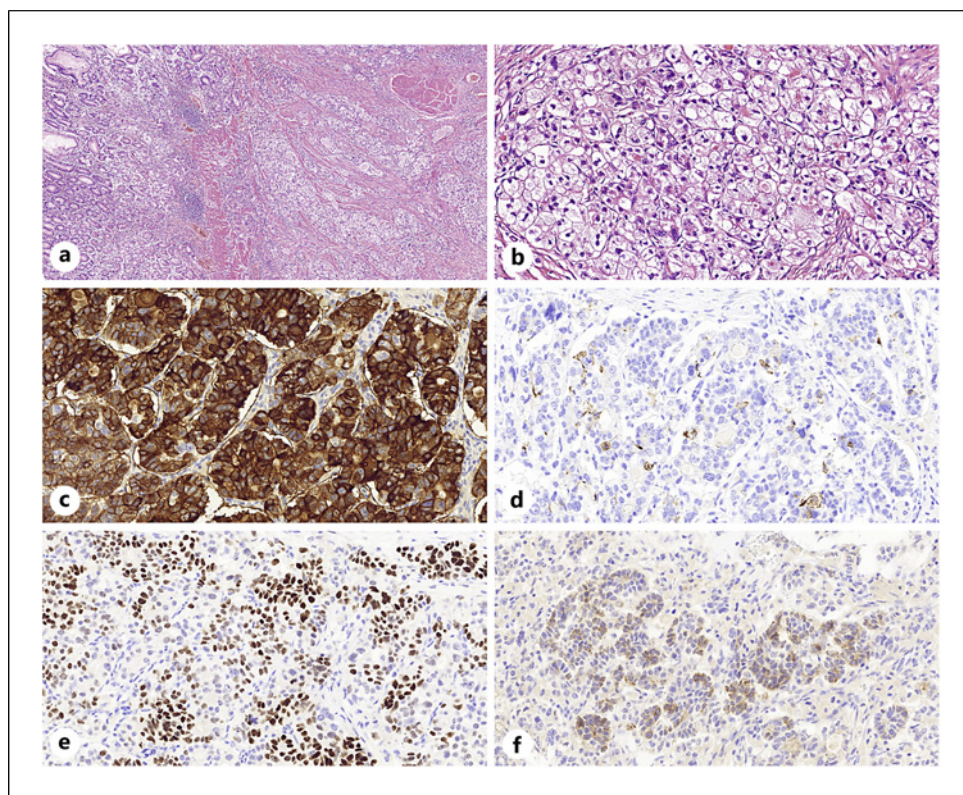
## Introduction

Gastric adenocarcinoma with enteroblastic differentiation (GAED) is a rare entity among gastric carcinomas, and it is characterized by a fetal gut-like histological

## Case Presentation

A 68-year-old female patient presented at the general practitioner in 2021 with abdominal pain, localized to the right hypochondriac region, and was referred to

**Fig. 1.** Microscopic finding of our case. **a** GAED (HE,  $\times 5$ ). **b** Higher magnification of the tumor reveals classic atypical cells with clear cytoplasm (HE,  $\times 20$ ). **c** Focal Syntaxin positivity was observed in the tumor cells (Syntaxin,  $\times 20$ ). **d** Focal Chromogranin A positivity was visible as well (Chromogranin A,  $\times 20$ ). **e** SALL4 revealed focal positivity in the cancer cells (SALL4,  $\times 20$ ). **f** Glypican 3 reflected focal positivity (Glypican 3,  $\times 20$ ). HE, hematoxylin and eosin; SALL4, Sal-like protein 4.



ultrasound examination, which revealed thickening of the gastric wall, raising suspicion for gastric cancer. Consequently, endoscopy was performed, describing a tumor size of 6 cm localized to the lesser curvature of the gastric body, in 5 cm distance from cardia. The tumor was ulcerated and showed focal bleeding, giving the impression of malignancy. During the procedure, 6 biopsies were taken from the tumorous mass. The esophagus, cardia, and duodenum were histologically unremarkable, while the corpus-pylorus sample revealed moderate, chronic, inactive gastritis with intestinal metaplasia. The biopsy from the suspicious area was signed out as high-grade intestinal type adenocarcinoma. IHC examination revealed diffuse, cytoplasmic positivity for cytokeratin (CK) AE1/AE3 and CK19, alongside negativity for HER2. *Helicobacter pylori* was not identified in any slide by immunohistochemistry.

Following the diagnosis, neoadjuvant 5-FU, leucovorin, oxaliplatin, docetaxel (FLOT) regime protocol was initiated, and later the patient underwent surgery. A total gastrectomy was performed at the Surgery Department of the University of Szeged Albert Szent-Györgyi Clinical Center, and the surgical specimen was sent to the Department of Pathology alongside the

resection rings and lymph nodes from the coeliac trunk.

Macroscopically, the tumor penetrated the muscular layer by 9 mm, and its greatest diameter proved to be 29 mm. Microscopically, multiple patterns were observed. Tubular areas comprising pleomorphic polygonal cells displaying a high grade of cellular atypia were seen alongside atypical cells with clear cytoplasm, positive for acidic and neutral mucin with Periodic acid-Schiff and Alcian blue stains. Multiple mitotic figures and atypical mitoses could be observed in these areas. However, other parts of the tumor showed nests forming monomorphic cells with eosinophilic and granulated cytoplasm. Hepatoid areas were not present. The growth pattern was predominantly infiltrative, and lymphovascular and perineural invasion was present as well (Fig. 1a, b). Four lymph nodes from the lesser curvature contained adenocarcinoma metastasis, and the lymph nodes from the coeliac trunk remained negative. Mismatch repair protein proficiency was observed, implying microsatellite stable tumor. P53 IHC proved to be negative, indicative of null-phenotype, while Syntaxin-1 and Chromogranin were focally positive in the clear cell component and diffusely positive in the nest-forming areas (Fig. 1c, d). The oncofetal markers (SALL4, Glypican 3) were focally positive,

**Table 1.** Summary of pathogenic and likely pathogenic mutations found in our case

| Gene         | Variant allele frequency, % | ClinVar significance | Coding impact |
|--------------|-----------------------------|----------------------|---------------|
| <i>TP53</i>  | 36.5                        | Pathogenic           | SNV           |
| <i>KLHL7</i> | 13.6                        | Pathogenic           | SNV           |
| <i>RAPSN</i> | 13.2                        | Pathogenic           | SNV           |
| <i>ACTA1</i> | 11.4                        | Pathogenic           | SNV           |
| <i>PNKP</i>  | 27.2                        | Likely pathogenic    | Insertion     |
| <i>HNF1A</i> | 15.6                        | Likely pathogenic    | SNV           |
| <i>ADNP</i>  | 10.0                        | Likely pathogenic    | SNV           |

ACTA1, actin alpha 1; ADNP, activity-dependent neuroprotective protein; HNF1A, hepatic nuclear factor 1 alpha; KLHL7, Kelch-like protein 7; PNKP, polynucleotide kinase-phosphatase; RASPN, receptor-associated protein of the synapse; SNV, single nucleotide variant; TP53, tumor protein 53.

while AFP reflected solely minimal, uncertain positivity (Fig. 1e, f). Moreover, homeobox protein CDX-2 (CDX2) and Cluster of differentiation 10 (CD10) were also positive. Negativity was observed with mucin 2 (MUC2), mucin 6 (MUC6), and mucin 5AC (MUC5AC) reactions. The Ki67 reflected proliferation activity of 70%. HER2 remained negative in the surgical specimen as well. Due to the morphology and the IHC profile, the tumor was concluded as GAED with neuroendocrine marker expression. Signs of tumor regression were barely visible. During the surgery R0 resection was achieved. Due to the rarity of this entity, whole-exome sequencing (WES) was carried out.

From the patient's surgical specimen, 10 serial sections of 10- $\mu$ m thickness per FFPE sample were taken, and deparaffinization and proteinase K treatment were performed overnight at 55°C. Extracted DNA was purified by using 0.5 vol KAPA PureBead (Roche) and eluted in 20  $\mu$ L of 10 mM Tris-HCl pH 8 buffer. DNA concentration was measured by Quant-iT 1x dsDNA HS Assay kit (Thermo Fisher Scientific) with Fluostar Omega (BMG Labtech) plate reader. For WES library construction, Twist Library Preparation EF Kit 2.0 with Universal Adaptor System and Exome 2.0 Panel (Twist Bioscience) was applied according to the manufacturer's protocol. The fragment size distribution of the pre-capture and postcapture libraries was determined by capillary electrophoresis on LabChip GX Touch HT Nucleic Acid Analyzer by using X-Mark HT Chip and DNA NGS 3K Assay kit (PerkinElmer). The libraries were quantified by Quant-iT 1x dsDNA HS Assay kit (Thermo Fisher Scientific) with Fluostar Omega (BMG Labtech). Pooled libraries were diluted to 1.5 nM for 2  $\times$

150 bp paired-end sequencing with 300-cycles S4 Reagent Kit on NovaSeq 6000 Sequencing System (Illumina) according to the manufacturer's protocol. In average, more than 24 Gbp raw data were generated per sample, and demultiplexing, adapter trimming, Q30-filtering, and somatic variant calling of the sequenced data were performed on Dragen Bio-IT platform (Illumina). Genomic variants of Vcf files were annotated by using the Nirvana Software package. A custom variant filter was applied, including only non-synonymous variants with coding consequences and a read depth greater than 50. Variants classified as benign according to the ClinVar database were excluded. The remaining subset of variants was manually reviewed, and suspected artifactual variants were also excluded.

Altogether, 4 pathogenic mutations were identified, including tumor protein 53 (*TP53*), Kelch-like protein 7 (*KLHL7*), receptor associated protein of the synapse (*RAPSN*), and actin alpha 1 (*ACTA1*). Three likely pathogenic mutations were found, encompassing polynucleotide kinase-phosphatase (*PNKP*), hepatic nuclear factor 1 alpha (*HNF1A*), and activity-dependent neuroprotective protein (*ADNP*). All pathogenic and likely pathogenic mutations are listed in Table 1.

## Discussion with Literature Review

AFP-producing tumors are rare entities among gastric adenocarcinomas and this especially applies for GAED; while, according to the current WHO Classification, its incidence remains 0.3–5.4%, however, literature data suggest a higher frequency of 2.2–10.9% [1, 3, 9].

**Table 2.** Summary of literature review regarding GAED

| Author and year of publication | Case, <i>n</i> | Gender (m = male, f = female) | Age                    | Localization (cardia, corpus, fundus, antrum, pylorus) | Result of immunohistochemical stainings                                                                     | Result of molecular examination, if applicable                                                | Nontumorous gastric mucosa |
|--------------------------------|----------------|-------------------------------|------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------|
| Yamabuki et al. [9] (2014)     | 1              | f                             | 75                     | Pylorus                                                | AFP+, CEA+, CDX2+, CD10+, Synaptophysin-, Chromogranin A-, CD56-, MUC2-, MUC5AC-                            | NA                                                                                            | NA                         |
| Matsumoto et al. [17] (2016)   | 6              | m = 5, f = 1                  | 61; 75; 77; 78; 80; 83 | Upper: 2; middle: 2; lower: 2                          | AFP: 1; Glypican 3: 5; SALL4: 2; MUC2: 1; MUC5AC: 1; MUC6: 4; CD10: 6                                       | NA                                                                                            | NA                         |
| Murakami et al. [18] (2016)    | 29             | m = 23, f = 6                 | Average: 73+/-7.5      | Upper: 6; middle: 9; lower: 14                         | AFP: 13; Glypican 3: 24; SALL4: 20                                                                          | NA                                                                                            | NA                         |
| Fujimoto et al. [19] (2018)    | 19             | m = 14, f = 5                 | Average: 67            | Upper: 8; middle: 4; lower: 7                          | AFP+, Glypican 3+, SALL4+, HER2+: 8                                                                         | NA                                                                                            | NA                         |
| Yamada et al. [20] (2018)      | 1              | f                             | 73                     | Corpus                                                 | AFP+, Glypican 3+, SALL4+, Synaptophysin-, HER2-                                                            | NA                                                                                            | NA                         |
| Akazawa et al. [2] (2018)      | 51             | m = 42, f = 9                 | Average: 71            | Upper: 15; middle: 12; lower: 24                       | AFP+: 16; Glypican 3+: 42; SALL4: 41                                                                        | NGS: 24; TP53 mutant: 35; CTNNB1: 2; APC: 1; ATM: 1; FBXW7: 1; GNAS: 1; HER2 amplification: 9 | NA                         |
| Kuroda and Yorita [21] (2018)  | 10             | m = 9, f = 1                  | Average: 69            | Upper: 3; middle: 3; lower: 3, NA: 1                   | AFP+: 10; Glypican 3+: 2; SALL4: 8                                                                          | NA                                                                                            | NA                         |
| Yatagai et al. [4] (2019)      | 51             | m = 42, f = 9                 | Average: 70 and 72     | Upper: 15; middle: 12; lower: 24                       | Reduced SMAD4: 31                                                                                           | Sanger sequencing; SMAD4 LOH freq: 23                                                         | NA                         |
| Yatagai et al. [5] (2019)      | 51             | m = 42, f = 9                 | Average: 70 and 72     | Upper: 15; middle: 12; lower: 24                       | p53 mutant: 28                                                                                              | Sanger sequencing; ATM: 1; p53 promoter methylation: 9; TP53 locus LOH: 19                    | NA                         |
| Kwon et al. [22] (2019)        | 28             | m = 22, f = 6                 | Average: 63            | Upper: 2; middle: 8; lower: 18                         | AFP+: 10; Glypican 3+: 13; SALL4+: 28; CD10+: 20; CDX2+: 27; MUC6+: 9; MUC5AC-: all cases; MUC2-: all cases | NA                                                                                            | NA                         |
| Ikezawa et al. [7] (2020)      | 1              | f                             | 77                     | Antrum                                                 | AFP-, Glypican 3+, SALL4+                                                                                   | NA                                                                                            | NA                         |
| Kimura et al. [14] (2020)      | 1              | m                             | 70                     | Corpus                                                 | AFP-, Glypican 3+, SALL4+                                                                                   | NA                                                                                            | NA                         |

Table 2 (continued)

| Author and year of publication   | Case, <i>n</i> | Gender (m = male, f = female) | Age          | Localization (cardia, corpus, fundus, antrum, pylorus) | Result of immunohistochemical stainings                                                 | Result of molecular examination, if applicable                                                          | Nontumorous gastric mucosa                                     |
|----------------------------------|----------------|-------------------------------|--------------|--------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
| Li et al. [23] (2020)            | 11             | NA                            | NA           | NA                                                     | AFP+: 5; Glypican 3+: 7; SALL4+: 8; CDX2+: 11; CD10+: 8; MUC2+: 3                       | FISH; HER2 amplification: 3                                                                             | NA                                                             |
| Ochi et al. [10] (2020)          | 1              | m                             | 76           | Antrum                                                 | AFP+, SALL4+                                                                            | NA                                                                                                      | NA                                                             |
| Li et al. [24] (2021)            | 12             | m = 12, f = 2                 | Median: 66.5 | NA                                                     | AFP+: 5; Glypican 3+: 9; SALL4+: 12; CDX2+: 8; CD10+: 3                                 | FISH; HER2 amplification: 2                                                                             | NA                                                             |
| Dias et al. [25] (2021)          | 1              | m                             | 78           | Corpus                                                 | AFP-, Glypican 3+, SALL4+                                                               | NA                                                                                                      | NA                                                             |
| Kato et al. [13] (2021)          | 2              | m                             | 82; 83       | Cardia; angulus                                        | Case 1: AFP-, Glypican 3+, SALL4+; Case 2: AFP-, Glypican 3-, SALL4+                    | NA                                                                                                      | <i>H. pylori</i> -associated, atrophic gastritis in both cases |
| Kataoka et al. [26] (2020)       | 24             | NA                            | NA           | NA                                                     | DNT3A+: 120                                                                             | EBER-ISH; positive: 7                                                                                   | NA                                                             |
| Zhao et al. [27] (2023)          | 1              | m                             | 66           | Antrum                                                 | AFP+; Glypican 3-; SALL4+                                                               | NA                                                                                                      | NA                                                             |
| Abe et al. [3] (2023)            | 94             | m = 76, f = 18                | Average: 72  | Upper: 34; middle: 21; lower: 39                       | AFP+: 29; Glypican 3+: 65; SALL4+: 76                                                   | NA                                                                                                      | NA                                                             |
| Li et al. [15] (2024)            | 1              | m                             | 68           | Antrum                                                 | AFP-; Glypican 3-; SALL4+; CDX2+; CD10+; MUC2+; MLH1+; MSH2+; MSH6+; PMS2+; CK7-; CK20- | NA                                                                                                      | NA                                                             |
| Ngan [28] (2023)                 | 1              | m                             | 61           | Corpus                                                 | AFP+; SALL4+; CDX2+; HER2+                                                              | NA                                                                                                      | NA                                                             |
| Pu et al. [6] (2023)             | 90             | NA                            | Average: 63  | NA                                                     | NA                                                                                      | FISH, NGS; NTRK1 amplification: 1; NTRK3 amplification: 1; TPM3-NTRK1 fusion: 1; NTRK2-SMCHD1 fusion: 1 | NA                                                             |
| Wang et al. [16] (2023)          | 37             | m = 29, f = 8                 | Median: 66   | Cardia-fundus: 6; corpus: 9; antrum-pylorus: 22        | APF+: 17; Glypican 3+: 27; SALL4+: 33                                                   | NGS; MSS: 10; MLH1: 1; EPCAM: 1; PMS2: 1; MSH2: 1; TP53: 9                                              | NA                                                             |
| Ishikawa and Nakamura [8] (2024) | 1              | m                             | 70           | Antrum                                                 | AFP+, Glypican 3+                                                                       | NA                                                                                                      | NA                                                             |
| Iwata et al. [29] (2024)         | 1              | m                             | 77           | Antrum                                                 | AFP+, Glypican 3+, SALL4+                                                               | NA                                                                                                      | NA                                                             |

Table 2 (continued)

| Author and year of publication | Case, <i>n</i> | Gender (m = male, f = female) | Age | Localization (cardia, corpus, fundus, antrum, pylorus) | Result of immunohistochemical stainings                                                                                | Result of molecular examination, if applicable                                                         | Nontumorous gastric mucosa                                                                                                |
|--------------------------------|----------------|-------------------------------|-----|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| Our case (2024)                | 1              | f                             | 68  | Corpus                                                 | pMMR, p53-, Syntaxin-1+, Chromogranin-A+, SALL4+, GPC3+, AFP+, CDX2+, Ki67: 70%, CK+, CK19+, HER2-, <i>H. pylori</i> - | WES; TP53, KLHL7, RAPSN, ACTA1 (pathogenic mutations); PNKP, HNF1A, ADNP (likely pathogenic mutations) | Chronic, inactive gastritis with severe atrophy, complete and incomplete intestinal metaplasia. <i>H. pylori</i> negative |

AFP, alpha-fetoprotein; APC, adenomatous polyposis coli; ATM, ataxia telangiectasia mutated; CDX2, homeobox protein, CDX-2; CD10, cluster of differentiation 10; CD56, cluster of differentiation 56; CEA, carcinoembryonic antigen; CK7, cytokeratin 7; CK20, cytokeratin 20; CTNNB1, catenin B1; DNT3A, DNA-methyltransferase 3A; EBER-ISH, Epstein-Barr encoding region in situ hybridization; EPCAM, epithelial cell adhesion molecule; FBXW7, F-box and WD repeat domain containing 7; FISH, fluorescent in situ hybridization; GNAS, GNAS complex locus; HER2, human epidermal growth factor receptor-2; LOH, loss of heterozygosity; MLH1, MutL homolog 1; MSH2, MutS homolog 2; MSH6, MutS homolog 6; MSS, microsatellite stable; MUC2, mucin 2; MUC5AC, mucin 5AC; MUC6, mucin 6; NA, not applicable; NGS, next-generation sequencing; NTRK1, neurotrophic tyrosine receptor kinase 1; NTRK3, neurotrophic tyrosine receptor kinase 3; PMS2, postmeiotic segregation increased 2; SALL4, Sal-like protein 4; SMAD4, Smad family member 4; SMCHD1, structural maintenance of chromosomes flexible hinge domain containing 1; TP53, tumor protein 53; TPM3, alpha-tropomyosin-3; WES, whole-exome sequencing; MMR, mismatch repair.

A literature review was conducted in PubMed with “stomach,” “gastric,” “adenocarcinoma,” and “enteroblastic” keywords. There are currently 26 articles that are summarized in Table 2. The first reported case of AFP-producing gastric cancer with liver metastasis was published by Bourreille et al. [12]; however, the earliest article with a detailed description of GAED was published in 2014 by Yamabuki et al. [9], characterizing the tumor as more aggressive and displaying a higher frequency of serosal invasion, lymph node, and liver metastases, and generally being higher stage (e.g., III or IV). The authors specify the criteria for GAED diagnosis based on IHC results (AFP, CEA, CDX-2, CD10), while serum AFP elevation is mentioned as an uncertain diagnostic factor [9, 12]. So far, 5 articles contain literature reviews on GAED [9, 13–16]; nevertheless, solely 2 of them summarize their data in a table (Kato [12 cases], Kimura [41 cases]).

Regarding the etiology of GAED, none of the reviewed literature notes any possible factor or cause; however, molecular examinations have already been performed. Akazawa et al. [2] identified TP53 mutation, and amplification of ERBB2, with NGS. Furthermore, mutations in Catenin B1 (CTNNB1), Adenomatous polyposis coli

(APC), Ataxia telangiectasia mutated (ATM), F-box and WD repeat domain containing 7 (FBXW7), and GNAS complex locus (GNAS) were also described. Sanger sequencing was carried out, noting a loss of heterozygosity (LOH) of SMAD4 and TP53, promoter methylation of TP53 at a lower frequency, and mutation of ATM [4]. Li et al. [23] described the previously observed amplification of ERBB2 with FISH, while Kataoka et al. [26] noted positive cases for Epstein-Barr encoding region in situ hybridization as well. Pu et al. [6] reported the role of NTRK3 amplification, alpha-tropomyosin-3 TMP3::NTRK1 fusion, and NTRK2-Structural maintenance of chromosomes flexible hinge domain containing 1 (SMCHD1) fusion in GAED using FISH, and Wang et al. [30] identified mutations of epithelial cell adhesion molecule, MutL homolog 1 (MLH1), postmeiotic segregation increased 2 (PMS2), MutS homolog 2 (MSH2), and TP53 using NGS.

According to the data, the patients’ mean age was 68.7 years (range: 61–83 years) and the male:female ratio was 25:6. Regarding nationality, no precise data are available; however, it has to be emphasized that the majority of articles are from Asia. Localization was noted specifically, mentioning the exact anatomic regions, or

Table 3. Summary of the immunohistochemical results of all GAED cases in our literature review

| Author and year of publication   | Case, n | AFP       | Glypican 3 | SALL4     | CEA  | CDX2      | CD10     | MUC2      | MUC5AC    | MUC6     | HER2     | MLH1 | MSH2 | MSH6 | PMS2 | Synaptophysin A | Chromogranin A | CD56         | SMAD4     | p53  | CK7  | CK20 | CK19 | Syntaxin-1 | Ki67 | H. pylori |
|----------------------------------|---------|-----------|------------|-----------|------|-----------|----------|-----------|-----------|----------|----------|------|------|------|------|-----------------|----------------|--------------|-----------|------|------|------|------|------------|------|-----------|
| Yamabuki et al. [9] (2014)       | 1       | Pos.      | NA         | NA        | Pos. | Pos.      | Pos.     | Neg.      | Neg.      | NA       | NA       | NA   | NA   | NA   | NA   | Neg.            | Neg.           | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Matsumoto et al. [17] (2016)     | 6       | Pos. (1)  | Pos. (5)   | Pos. (2)  | NA   | NA        | Pos. (6) | Pos. (1)  | Pos. (1)  | Pos. (4) | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Murakami et al. [18] (2016)      | 29      | Pos. (13) | Pos. (24)  | Pos. (20) | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Fujimoto et al. [19] (2018)      | 19      | Pos.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | Pos. (8) | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Yamada et al. [20] (2018)        | 1       | Pos.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | Neg.     | NA   | NA   | NA   | NA   | Neg.            | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Akazawa et al. [2] (2018)        | 51      | Pos. (16) | Pos. (42)  | Pos. (41) | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Kuroda and Yoria [21] (2018)     | 10      | Pos. (10) | Pos. (2)   | Pos. (8)  | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Yatagai et al. [4] (2019)        | 51      | NA        | NA         | NA        | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | Reduced (31) | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Yatagai et al. [5] (2019)        | 51      | NA        | NA         | NA        | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | Neg. (28) | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Kwon et al. [22] (2019)          | 28      | Pos. (10) | Pos. (13)  | Pos. (28) | NA   | Pos. (27) | NA       | Neg. (51) | Neg. (51) | Pos. (9) | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Ikezawa et al. [7] (2020)        | 1       | Neg.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Kimura et al. [14] (2020)        | 1       | Neg.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Li et al. [23] (2020)            | 11      | Pos. (5)  | Pos. (7)   | Pos. (8)  | NA   | Pos. (11) | NA       | Pos. (3)  | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Ochi et al. [10] (2020)          | 1       | Pos.      | NA         | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Li et al. [24] (2021)            | 12      | Pos. (5)  | Pos. (9)   | Pos. (12) | NA   | Pos. (8)  | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Dias et al. [25] (2021)          | 1       | Neg.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Kato et al. [13] (2021)          | 2       | Neg. (2)  | Pos. (1)   | Pos. (2)  | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Kataoka et al. [26] (2020)       | 24      | NA        | NA         | NA        | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Zhao et al. [27] (2023)          | 1       | Pos.      | Neg.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Abe et al. [3] (2023)            | 94      | Pos. (29) | Pos. (65)  | Pos. (76) | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Li et al. [15] (2024)            | 1       | Neg.      | Neg.       | Pos.      | NA   | Pos.      | NA       | Pos.      | NA        | NA       | NA       | Pos. | Pos. | Pos. | Pos. | NA              | NA             | NA           | NA        | NA   | Neg. | Neg. | NA   | NA         | NA   | NA        |
| Ngan [28] (2023)                 | 1       | Pos.      | NA         | Pos.      | NA   | Pos.      | NA       | NA        | NA        | NA       | Pos.     | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Pu et al. [6] (2023)             | 90      | NA        | NA         | NA        | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Wang et al. [16] (2023)          | 37      | Pos. (17) | Pos. (27)  | Pos. (33) | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Ishikawa and Nakamura [8] (2024) | 1       | Pos.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Iwata et al. [29] (2024)         | 1       | Pos.      | Pos.       | Pos.      | NA   | NA        | NA       | NA        | NA        | NA       | NA       | NA   | NA   | NA   | NA   | NA              | NA             | NA           | NA        | NA   | NA   | NA   | NA   | NA         | NA   | NA        |
| Our case (2024)                  | 1       | Pos.      | Pos.       | Pos.      | NA   | Pos.      | NA       | NA        | NA        | NA       | Neg.     | Pos. | Pos. | Pos. | Pos. | NA              | Pos.           | NA           | NA        | Neg. | Pos. | NA   | Pos. | Pos.       | 70%  | Neg.      |

AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; CDX2, homeobox protein; CDX-2; CD10, cluster of differentiation 10; CD56, cluster of differentiation 56; CK, cytokeratin; CK7, cytokeratin 7; CK19, cytokeratin 19; CK20, cytokeratin 20; HER2, human epidermal growth factor receptor-2; Ki67, proliferation marker; MLH1, Mismatch repair protein 1; MUC2, mucin 2; MUC5AC, mucin 5; MUC6, mucin 6; MSH2, Mismatch repair protein 2; MSH6, Mismatch repair protein 6; NA, not applicable; Neg., negative; Pos., positive; p53, tumor protein 53; PMS2, postmeiotic segregation increased 2; SALL4, Sal-like protein 4; SMAD4, Smad family member 4.

divided as upper, middle, and lower parts of the stomach. Regarding the exact anatomical regions, the majority of the cases were localized to the antropyloric region ( $n = 29$ ), followed by the corpus body ( $n = 14$ ), cardia ( $n = 7$ ), and the angulus ( $n = 1$ ). Based on the other classification, the majority of tumors were confined to the lower region ( $n = 131$ ), followed by the upper ( $n = 85$ ), and the middle areas ( $n = 71$ ). Both localization schemes correlate with one another [1–36].

The most representative microscopic features of GAED are tumor cells with clear cytoplasm and positive IHC staining for at least one of the enteroblastic markers (i.e., AFP, SALL4, and Glypican 3). The tumor cells displaying clear cytoplasm almost always coexist with a CGA component [3]. It is also notable that GAED is regarded as high grade and shows a more aggressive clinical behavior, compared to CGA. Alcian blue and periodic acid-Schiff staining have been performed in 2 of the articles, Yamabuki et al. [9] observed negative staining, alongside the negativity of tumor cells with MUC2 and MUC5AC, while Yamada et al. [20] described the presence of abundant cytoplasmic glycogen. The results of the IHC examinations are summarized in Table 3. The most commonly observed positive reactions in decreasing tendency were SALL4 ( $n = 240$ ), Glypican 3 ( $n = 202$ ), AFP ( $n = 114$ ), CDX2 ( $n = 49$ ), CD10 ( $n = 39$ ), MUC6 ( $n = 13$ ), and HER2 ( $n = 9$ ). The negative IHC reactions noted were SMAD4 ( $n = 31$ ), MUC2 ( $n = 29$ ), MUC5AC ( $n = 29$ ), and p53 ( $n = 28$ ). Neuroendocrine marker positivity has not been noted in any of the articles included in our literature review; however, Yamabuki et al. [9] and Yamada et al. [20] report negative staining for Synaptophysin and Chromogranin A in their presented case. Table 2 highlights the IHC profile of the cases included in our literature review. Electron microscopic examination has not yet been carried out.

The main differential diagnostic options are hepatoid adenocarcinoma of the stomach, displaying clear cells in a hepatoid growth pattern, diffusely positive IHC reaction for AFP, Glypican 3, and SALL4 contrary to the focal positivity commonly observed in GAED, and expression of HepPar-1 [22, 28]. Furthermore, clear cell renal cell carcinoma metastasis has to be excluded, as well as metastasis of pancreatobiliary adenocarcinoma, which can also show clear cell change and glandular differentiation, while expressing CK7, CA19-9, and MUC1. Lastly, primary clear cell adenocarcinoma of the stomach also has to be ruled out, in which case we cannot observe positivity for IHC

markers of enteroblastic differentiation. Moreover, according to Abe et al. [3], there may be another entity, entitled gastric adenocarcinoma with enteroblastic markers, in which there is no clear cytoplasm characteristic present, but enteroblastic differentiation can be proven with IHC markers. The prognosis of this carcinoma is similar to GAED's.

To summarize, in our work we report the case of a 68-year-old female patient who presented at the general practitioner with abdominal pain, leading to ultrasonography which raised suspicion of gastric tumor. The biopsies taken during gastroscopy from the ulcerated, bleeding lesion confirmed the cancer diagnosis and neoadjuvant FLOT chemotherapy regimen was initiated, after which total gastrectomy was performed. Macroscopically, the tumor penetrated the muscular wall. During microscopic evaluation, multiple patterns could be identified, such as tubular areas with polygonal cells displaying high-grade dysplasia and other areas with atypical cells with clear cytoplasm. The tumor was mismatch repair proficient, p53 immunohistochemistry indicated a null-phenotype, neuroendocrine marker positivity could also be observed, and Ki67 was 70%. The oncofetal markers SALL4 and Glypican 3 were focally positive; however, AFP showed only uncertain positivity. The case was concluded as GAED and WES has been carried out revealing 4 pathogenic mutations, such as TP53, KLHL7, RPSN, and ACTA1 as well as 3 likely pathogenic mutations, namely PNKP, HNF1A, and ADNP. TP53 mutation has been identified in GAED by Akazawa et al. [2]. KLHL7 mutation has been associated with gastric cancer and has been identified as a bad prognosticator, with inversely proportional effect on overall survival [30]. RPSN has been so far connected to lung and breast carcinomas [31, 32], and ACTA1 has been linked to early gastric cancer by solely one publication [33]. PNKP-like factor has been observed to be upregulated in chemo- or radiotherapy-treated gastric carcinomas [34]. HNF1A has been proven to promote Fluorouracil resistance in gastric carcinomas [35], and ADNP has been associated with unfavorable prognosis in gastric cancer [36].

GAED is a rare subtype of gastric adenocarcinomas, representing 0.3–5.4% of all cases, has an unclarified etiology, and has more aggressive behavior compared to CGA. Hereby we present an unusual manifestation of GAED with neuroendocrine marker expression, and for the first time in the literature, with results of WES, that identified new pathogenic and likely pathogenic mutations, and an updated literature review.

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## Statement of Ethics

Written informed consent was obtained from the patient for the publication of the details of their medical case and any accompanying images. This study protocol was reviewed and approved by Institutional Ethical Committee of the Albert Szent-Györgyi Clinical Centre of the University of Szeged (4988).

## Conflict of Interest Statement

The authors declare no conflict of interest.

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## Author Contributions

Data collection, writing, and review and editing: Ádám Ferenczi, Anita Sejbén, and Levente Kuthi; interpretation of the results of whole-exome sequencing, and conceptualization: Levente Kuthi and Anita Sejbén; and funding acquisition: Anita Sejbén.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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