Case Report

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Pathology Section

Gastric Adenocarcinoma With Enteroblastic Differentiation: A Clear Cell Conundrum

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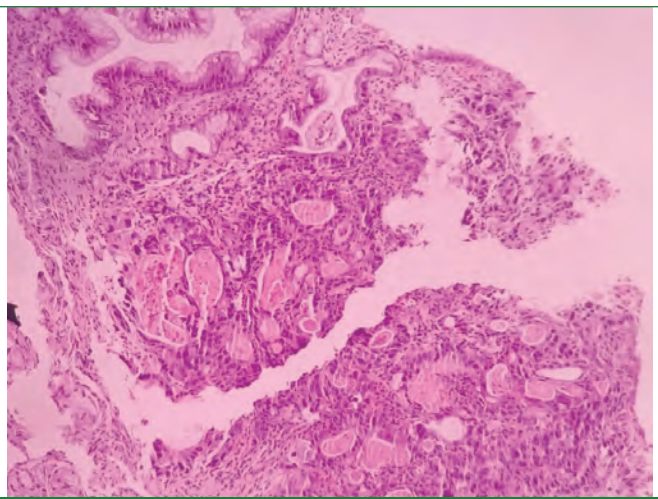
ABSTRACT

Gastric Adenocarcinoma with Enteroblastic Differentiation (GAED) is an aggressive and rare subtype of Gastric Carcinoma (GC). The authors report a case of 65-year-old male presented with complaints of upper Gastrointestinal tract (GI) bleeding for two months. Endoscopy revealed an ulceroproliferative growth in the incisura and distal body of stomach. Small biopsy was suggestive of adenocarcinoma. Patient underwent D1 subtotal gastrectomy. Gross specimen had an ulcerative growth in the lesser curvature. Histopathology showed malignant neoplasm consisting of tubules lined by cuboidal to columnar cells with clear cytoplasm resembling primitive foetal gut epithelium. Periodic Acid-Schiff (PAS) staining highlighted the glycogen rich clear cytoplasm. Oncofoetal Immunohistochemical (IHC) markers such as Glypican-3 (GPC3) and Spalt-like transcription factor (SALL-4) were positive supporting enteroblastic differentiation. Tumour penetrated the subserosal tissue and showed lymph node metastasis. Compared to conventional GCs, GAED has aggressive behavior and poor prognosis with tumour showing early deep tumour invasion, lymph node and distant metastasis. Serum tumour marker such as Alpha-fetoprotein (AFP) can be elevated aiding in diagnosis and follow up. Further prognostic markers such as Human Epidermal Growth Factor Receptor 2 (HER2/neu) was done and was negative and tumour protein p53 (p53) showed mutant type staining underscoring GAEDs aggressive nature. Recognition of this histologic subtype is crucial, to differentiate it from other AFP producing and clear cell tumours such as hepatoid gastric adenocarcinoma, metastatic clear cell renal cell carcinoma, yolk sac tumour-like adenocarcinoma, well differentiated tubular or papillary adenocarcinoma with clear cell features, and in case of patient presenting with early liver metastasis from primary hepatocellular carcinoma. The present case highlighted the importance of considering GAED as a differential on encountering clear cells in a gastric cancer which also resembled foetal intestinal epithelium. Histochemical staining such as PAS and IHC staining like AFP for antigen markers like, GPC3, SALL-4, Hepatocyte Paraffin 1 (HepPar1) and sometimes cytokeratin can help with the diagnosis and to exclude other clear cell tumours. HER2/neu was negative and p53 IHC showed mutant-type expression. Early diagnosis of this rare aggressive subtype is essential to guide further follow up, improving patient outcome and further understanding of its clinicopathologic spectrum.

Keywords: Carcinoma stomach, Foetal gut epithelium, Alpha-fetoprotein, Glypican 3

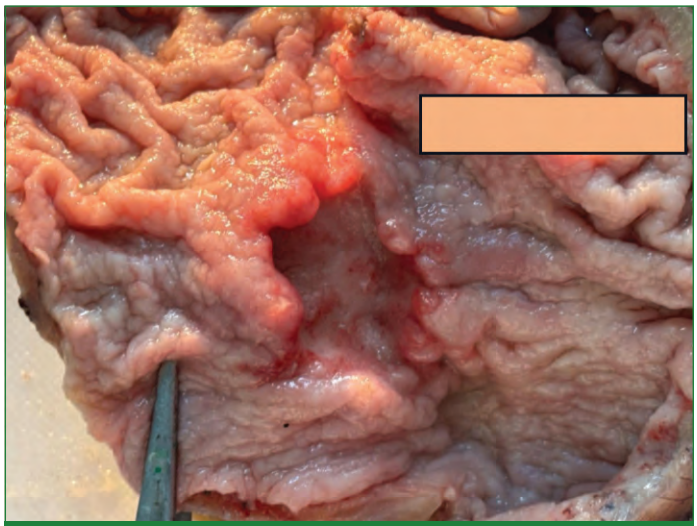
CASE REPORT

A 65-year-old male presented with complaints of abdominal pain, loss of appetite, and weight loss for the past two months, along with haematemesis for two days. He visited the Surgical Gastroenterology Outpatient Department and underwent upper gastrointestinal endoscopy, which revealed an ulceroproliferative growth in the distal body of the stomach and incisura, extending into the antrum. A provisional clinical diagnosis of carcinoma stomach was made, and endoscopic biopsy was performed, which was reported as infiltrating adenocarcinoma, moderately differentiated [Table/Fig-1].



[Table/Fig-1]: Endoscopic biopsy shows a moderately differentiated infiltrating adenocarcinoma (Haematoxylin and Eosin (H&E) x100).

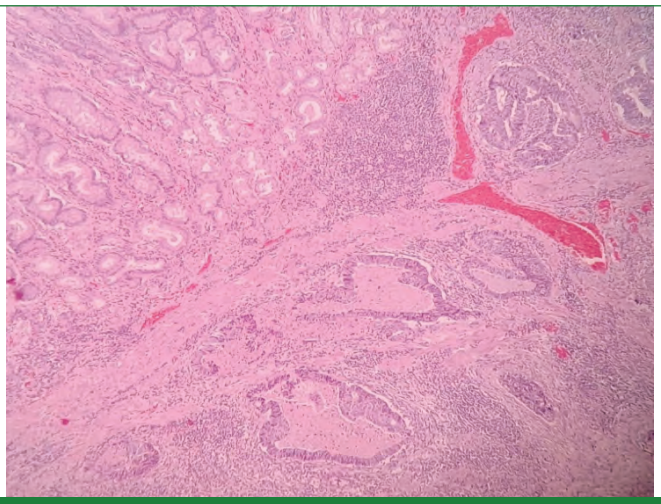
The patient subsequently underwent D1 subtotal gastrectomy. The resected specimen measured 15 cm along the greater curvature and 10 cm along the lesser curvature, with an attached greater omentum measuring 24×22×1 cm. The external surface showed intact serosa. On opening the specimen, a 4×2.3×1 cm ulceroinfiltrative lesion was identified along the lesser curvature [Table/Fig-2].



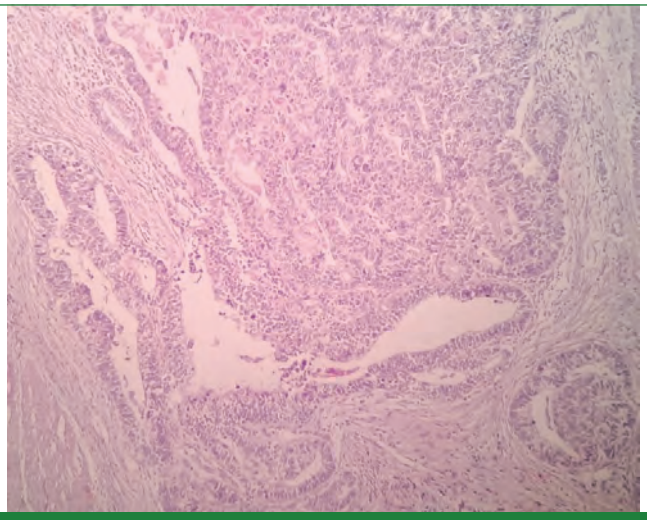
[Table/Fig-2]: Gross subtotal gastrectomy specimen with cut surface showing an ulceroinfiltrative lesion.

Representative sections were taken for histopathological examination. Microscopy revealed gastric mucosa infiltrated by a

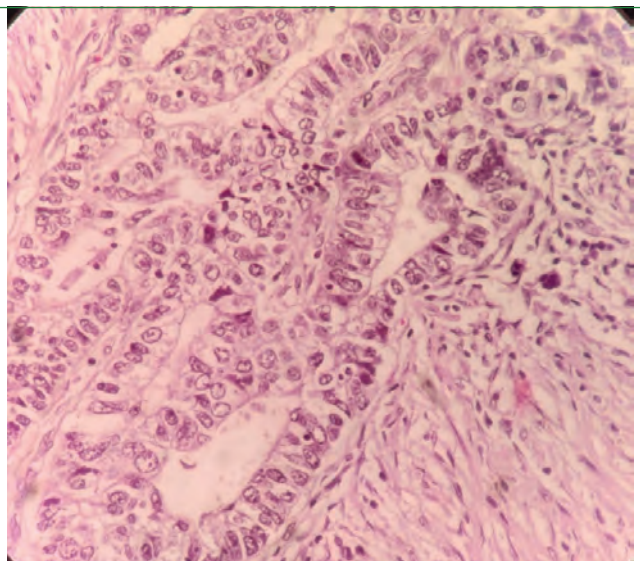
malignant neoplasm arranged predominantly in tubules and glands [Table/Fig-3,4]. The tubules were lined by cuboidal to columnar cells with moderate to abundant clear cytoplasm and round to oval vesicular nuclei exhibiting moderate atypia [Table/Fig-5,6]. The tumour was seen penetrating into the subserosal connective tissue without invasion of the visceral peritoneum.



[Table/Fig-3]: Microscopic view of gastric mucosa with an infiltrating malignant neoplasm arranged in tubules and glands (H&E x40).

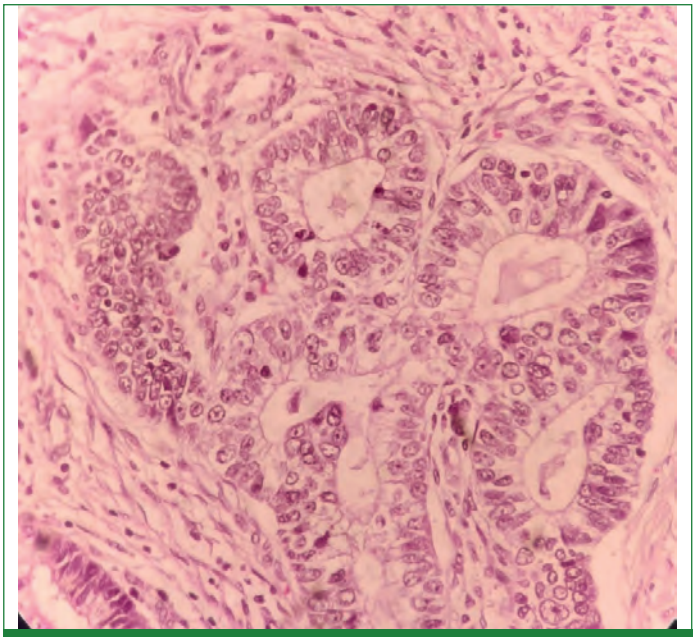


[Table/Fig-4]: Microscopy shows malignant neoplasm arranged in tubules and glands lined by cuboidal to columnar cells having clear cytoplasm (H&E x100).

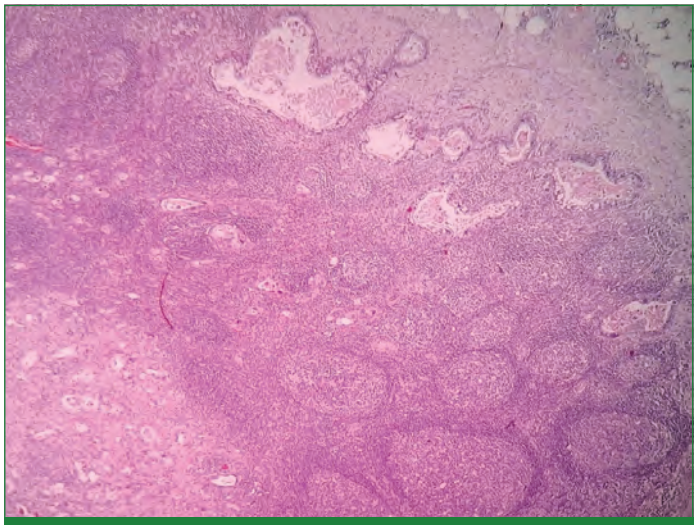


[Table/Fig-5]: High power view shows malignant tubules lined by columnar cells having clear cytoplasm similar to foetal intestinal epithelium (H&E x400).

Two out of eleven lymph nodes harvested contained metastatic tumour deposits with similar morphology [Table/Fig-7].



[Table/Fig-6]: High power view shows malignant tubules lined by columnar cells having clear cytoplasm similar to foetal intestinal epithelium (H&E x400).



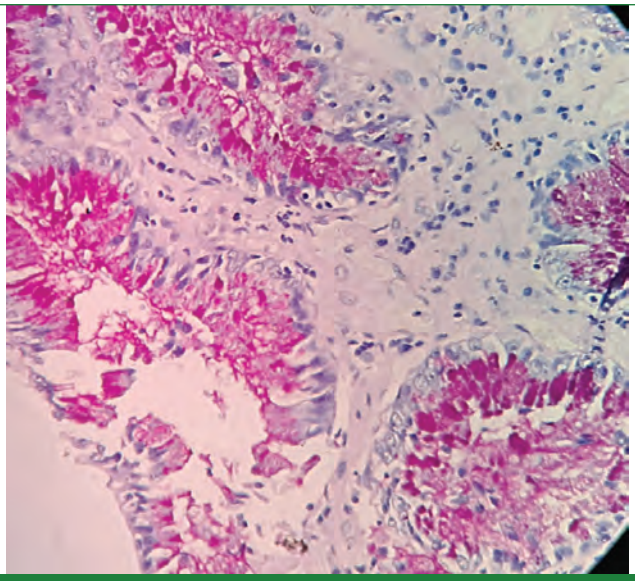
[Table/Fig-7]: Lymph node metastasis showing tumour with similar clear cell morphology (H&E x40).

Due to the clear cell morphology of the tumour, an array of histopathological differential diagnoses was considered, including tubular adenocarcinoma with clear cell features, poorly cohesive carcinoma with signet-ring morphology, hepatoid adenocarcinoma, yolk sac tumour-like adenocarcinoma, and adenocarcinoma with enteroblastic differentiation. As the histologic features closely resembled primitive foetal gut epithelium, the diagnosis was narrowed to adenocarcinoma with enteroblastic differentiation, and histochemical as well as immunohistochemical analyses were pursued.

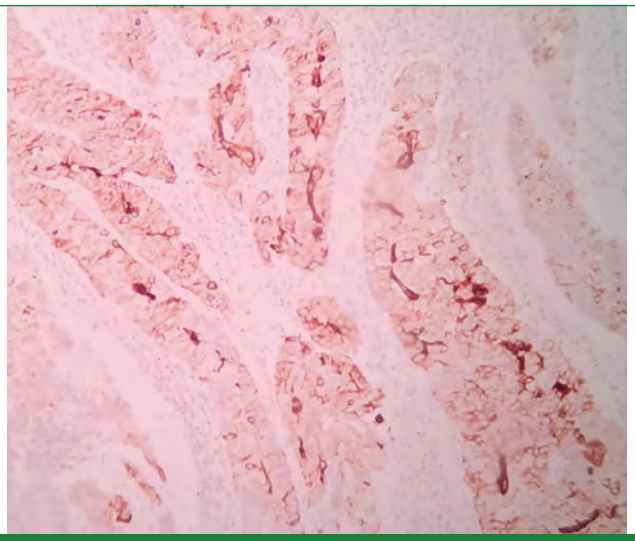
The PAS staining was positive in the glycogen-rich clear cells [Table/Fig-8]. To confirm the diagnosis, a panel of oncofetal immunohistochemical markers was applied. GPC3 showed moderate to strong membranous and cytoplasmic positivity in 50% of tumour cells [Table/Fig-9]. SALL-4 exhibited strong nuclear positivity in 70-80% of tumour cells [Table/Fig-10]. AFP and HepPar-1 were negative.

Based on the histomorphology, histochemical, and immunohistochemical profile, a final diagnosis of gastric adenocarcinoma with enteroblastic differentiation, with a pathological stage of pT3N1, was made.

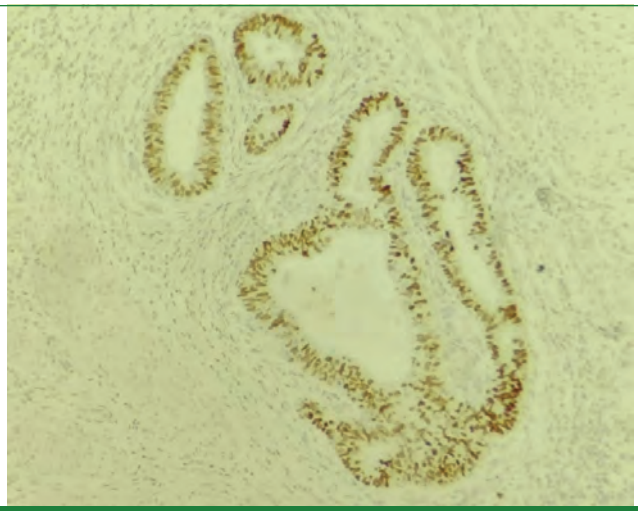
For prognostic assessment and molecular profiling, additional immunohistochemical markers were performed. HER2/neu was negative [Table/Fig-11]. p53 showed diffuse, strong nuclear and cytoplasmic positivity in more than 80% of tumour cells [Table/Fig-12].



[Table/Fig-8]: Histochemical stain PAS highlighting the glycogen rich clear cells (PAS x400).



[Table/Fig-9]: GPC3 shows moderate to strong membranous and cytoplasmic positivity in 50% of tumour cells (IHC x100).

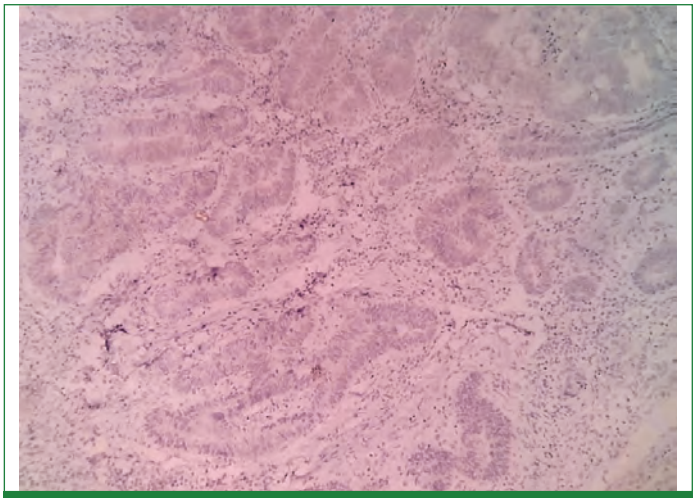


[Table/Fig-10]: SALL-4 shows strong nuclear positivity in 70% of tumour cells (IHC x100)

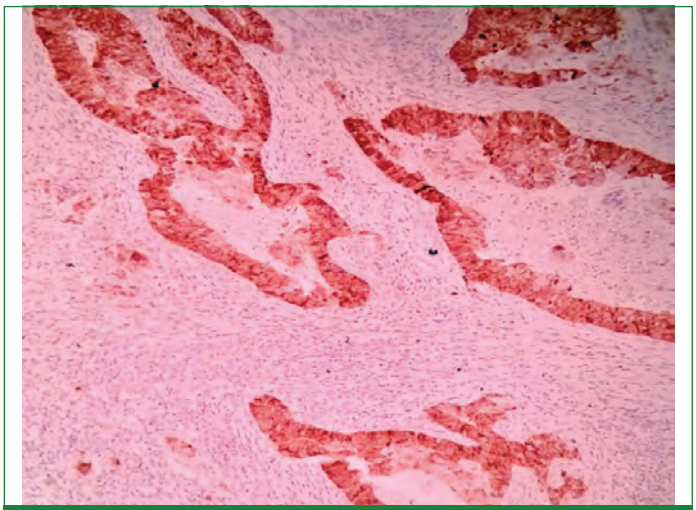
At the time of writing this report, the patient is under medical oncology care and has completed two cycles of the Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel (FLOT) chemotherapy regimen.

DISCUSSION

The GAED is a rare subtype of gastric adenocarcinoma, with an incidence ranging from 0.3% to 5.4% [1]. Clinically, patients present



[Table/Fig-11]: HER2/neu negative in tumour cells (IHC x100).



[Table/Fig-12]: p53 shows mutant type staining with strong nuclear and cytoplasmic positivity in 80% of tumour cells (IHC x100).

with nonspecific symptoms such as weight loss, anorexia, abdominal pain, and upper gastrointestinal bleeding. Serum tumour markers such as AFP, Carcinoembryonic Antigen (CEA), Human Chorionic Gonadotropin (hCG), and Des-gamma-Carboxy Prothrombin (DCP) may be elevated, particularly when GAED coexists with hepatoid adenocarcinoma or yolk sac tumour-like adenocarcinoma. However, elevated serum markers are not essential for diagnosis [2,3].

Microscopically, GAED is characterised by a tubular or tubulopapillary architecture lined by columnar cells with clear cytoplasm resembling foetal gut epithelium. Immunohistochemically, tumour cells express oncofetal markers such as SALL-4, GPC3, and AFP, as well as intestinal differentiation markers such as CDX2. GAED is associated with early deep tumour invasion, high rates of lymphovascular spread, lymph node metastasis, early distant metastasis (especially to the liver), and an overall poor prognosis [1-13].

GAED was previously categorised under AFP-producing gastric carcinoma. However, since some of these tumours do not produce AFP, GAED is now recognised as a distinct entity under Hepatoid Adenocarcinoma and Related Entities in the WHO Classification of Digestive System Tumours, 5th Edition (2019) [13].

Matsunou et al., first described the histopathological and immunohistochemical features of GAED in 1994 as a case of AFP-producing gastric carcinoma with enteroblastic differentiation [12]. When compared with previously reported series [Table/Fig-13], the present case shares similar features such as male predominance, clear cell histomorphology, and expression of at least one of the oncofetal markers (GPC3, SALL4, or AFP). These findings further underscore the aggressive nature of GAED, with a higher frequency of lymphovascular invasion and lymph node metastasis compared to conventional gastric adenocarcinomas [1,2,4-10].

Study	Year	No. of cases	Mean age	Gender/ M:F	Immunohistochemical markers (AFP, Glypican3, SALL-4)	HER2/neu positivity	p53 expression
Ferenczi et al., [1]	2025	1	68	Female	SALL4+, Glypican3+, AFP variable	Negative	Mutant
Ge x et al., [2]	2024	16	Median: 75.5	11:5	SALL4+ > Glypican3+ > AFP+	Negative	Mutant 12/16
Wang et al., [4]	2023	37	Median: 66	29:8	SALL4+ > Glypican3+ > AFP+	Positive	Mutant
Abe et al., [5]	2023	94	Median: 72	76:18	SALL4+ >Glypican3+ > AFP+	NR	NR
Li et al., [6]	2021	12	Median: 66.5	12:2	SALL4+ >Glypican3+ > AFP+	Positive 2/12	Mutant 10/12
Takahashi et al., [7]	2024	1	82	Male	Glypican3+, SALL4+, AFP-	Negative	Mutant
Ishikawa et al., [8]	2024	1	70	Male	AFP+, Glypican3+, SALL4-	NR	NR
Iwata et al., [9]	2023	1	77	Male	AFP+, Glypican3+, SALL4+	NR	NR
Nakayama et al., [10]	2024	1	39	Female	SALL4+, AFP+	NR	NR
Present case	2025	1	65	Male	SALL4+, Glypican3+, AFP-	Negative	Mutant

[Table/Fig-13]: Comparison of present case with published GAED series [1,2,4-10].
M:F: Male:Female ratio; NR: Not reported

Wang et al., in 2023, studied the molecular characteristics of 37 patients with GAED and reported high HER2 expression (10-35%), frequent p53 mutations, Epstein-Barr virus (EBV) negativity, and Microsatellite Stability (MSS). They proposed a molecular classification of HER2+/TP53+/EBV-/MSS as a chromosomally unstable subtype, although this has not yet been incorporated into the the Cancer Genome Atlas (TCGA) classification [4]. In the present case, immunohistochemistry showed mutant-type p53 expression; however, HER2/neu was negative. Despite this, the tumour exhibited aggressive features such as subserosal invasion and nodal metastasis.

Gastric carcinomas with clear cell morphology must be evaluated for GAED using a comprehensive immunohistochemical panel, as misdiagnosis may lead to delayed recognition, with patients potentially presenting later with liver metastasis and elevated AFP levels-findings that may be mistaken for primary hepatocellular carcinoma [2,7].

The pathogenesis of GAED is not yet fully understood. However, the primitive nature of the tumour suggests that dedifferentiation of gastric stem cells into a foetal intestine–like phenotype, along with frequent chromosomal instability, likely plays a contributory role [2].

This case represents the first reported instance of GAED at our institution. Although there are no established criteria regarding the percentage of clear cells required for diagnosis, the presence of a gastric carcinoma composed of glycogen-rich clear cells resembling foetal gut epithelium, along with positive staining for at least one oncofetal marker such as GPC3, SALL4, or AFP, is considered essential [3-6].

CONCLUSION(S)

This case is presented for its rarity, underscoring the inherent diagnostic complexity, particularly in differentiating GAED from other gastric tumours with clear cell morphology. Accurate diagnosis requires meticulous histomorphological assessment of clear cells, corroborated by a comprehensive immunohistochemical panel, and supported by therapeutic and molecular profiling.

Further accumulation of well-documented cases and clinicopathological correlations is imperative to enhance understanding of the biological behavior of GAED, establish standardised diagnostic criteria, and explore potential targeted therapeutic strategies for improved patient outcomes.

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