

Clinicopathological and Genomic Analysis of Hepatoid Alpha-Fetoprotein-Producing Gastric Cancer with Concurrent Multiple Targetable Molecular Aberrations

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Short Report

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Abstract

Alpha-fetoprotein-producing gastric cancer (AFPGC) represents a rare, highly aggressive subtype of gastric adenocarcinoma, with its hepatoid variant conferring dismal clinical outcomes. Despite accumulating genomic data for AFPGC, the hepatoid subtype concurrently bearing Epstein-Barr virus (EBV) infection, *ERBB2* amplification and multiple driver molecular alterations remains poorly characterized, and its pathological mechanisms are incompletely elucidated. We performed integrated molecular-pathological profiling on one hepatoid AFPGC case using immunohistochemistry, in-situ hybridization, FISH, and a 425-gene NGS panel. A 79-year-old male presented with severe anemia and elevated serum AFP (431 ng/mL), alongside locally advanced gastric carcinoma and regional lymph-node metastasis. Histopathological evaluation identified moderately-to-poorly differentiated adenocarcinoma featuring typical hepatoid differentiation and prominent intratumoral lymphoid stroma. Immunophenotypic assessment revealed focal AFP positivity, diffuse HepPar-1 reactivity, strong HER2 overexpression (3+, 90% tumor cells), PD-L1 CPS of 15, and positive EBER signals. Tumor cells displayed reduced membranous β -catenin expression without nuclear or cytoplasmic translocation. FISH confirmed *ERBB2* amplification. NGS uncovered three pathogenic somatic events: *ERBB2* amplification, *ARID1A* nonsense mutation (p.R1276*), and activating *PIK3CA* mutation (p.P449L), together with microsatellite stability and a TMB of 6.2 mutations/Mb. Following short-course induction therapy and subsequent S-1 maintenance, the patient achieved a partial response accompanied by normalized AFP and negative EBV serology, maintaining remission at 4-month follow-up. Our findings characterize this rare composite molecular phenotype of EBV-associated hepatoid AFPGC. Altered β -catenin expression may correlate with hepatoid transdifferentiation, EBV-mediated pathway perturbation and *ARID1A* deficiency, supporting precise pathological subtyping; this case broadens the molecular spectrum of hepatoid AFPGC and informs clinical diagnosis and individualized treatment.

1. Introduction

Alpha-fetoprotein-producing gastric cancer (AFPGC) is a rare subtype of gastric adenocarcinoma, accounting for 1.3% to 15% of all gastric malignancies. Histologically, it is classified into hepatoid, yolk sac tumor-like, fetal gastrointestinal and mixed subtypes, among which the hepatoid variant exhibits the highest aggressiveness, with a propensity for early lymph node and liver metastasis and significantly worse long-term survival than conventional gastric adenocarcinoma^[1–2]. With the widespread application of high-throughput sequencing, the genomic landscape of AFPGC has been increasingly delineated. Previous large-cohort studies have demonstrated that AFPGC is enriched with driver events such as *TP53* mutations and *ERBB2* amplifications, and shows significantly higher chromosomal instability than conventional gastric cancer^[3–5]. In 2014, The Cancer Genome Atlas (TCGA) project categorized gastric adenocarcinoma into four molecular subtypes: EBV-positive, microsatellite instability-high, genomically stable and chromosomally unstable (CIN). The EBV-positive subtype is characterized by *PIK3CA* mutations, widespread DNA hypermethylation and high PD-L1/PD-L2 expression, and is highly sensitive to immune checkpoint inhibitors. The CIN subtype is marked by

frequent receptor tyrosine kinase gene amplifications, among which *ERBB2* amplification is the most clinically actionable target^[6]. A large domestic cohort study showed that EBV infection and HER2 overexpression are independent molecular events in conventional gastric cancer and rarely co-occur^[7]. To date, no hepatoid AFPGC case with both intact EBV molecular features and HER2-driven amplification has been documented in published genomic cohorts of AFPGC. Herein, we comprehensively characterize the histopathological, immunohistochemical and genomic features of a hepatoid AFPGC case with concurrent EBV positivity, *ERBB2* amplification, *ARID1A* nonsense mutation and *PIK3CA* gain-of-function mutation, and discuss the potential pathological mechanism underlying the aberrant β -catenin expression, to supplement the molecular heterogeneity spectrum of this rare subtype. To date, no hepatoid AFPGC case with concurrent EBV positivity and *ERBB2* amplification has been reported. This study presents comprehensive multimodal profiling of this unique tumor and provides novel pathological and therapeutic insights.

2. Materials and Methods

2.1 Ethics and study design

This is a retrospective single-case molecular pathological study. The study protocol was approved by the Institutional Ethics Committee of our institution (approval No. LC2016102) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the patient for the use of clinical data and pathological specimens for research purposes. Complete clinical data, including medical history, laboratory tests, imaging findings, endoscopic results and follow-up records, were collected and compiled into a standardized clinical database. This case report was prepared in accordance with the CARE reporting guidelines. This work is a retrospective case analysis and does not constitute a clinical trial, so clinical trial registration is not applicable.

2.2 Pathological and molecular examinations

Endoscopic biopsy specimens were fixed in 4% neutral buffered formalin and embedded in paraffin. Hematoxylin and eosin (HE) staining was performed on 4- μ m sections, and the final diagnosis was independently reviewed by two senior pathologists. Immunohistochemistry (IHC) was performed using standard laboratory protocols to detect AFP, HepPar-1, SALL4, HER2, PD-L1, β -catenin, CK7, CK20 and mismatch repair proteins (MLH1, MSH2, MSH6, PMS2). EBV-encoded small RNA (EBER) was detected by in situ hybridization (ISH). All staining results were independently interpreted by two senior pathologists blinded to clinical information, in accordance with domestic and international diagnostic guidelines. HER2 gene amplification status was verified by fluorescence *in situ* hybridization (FISH), and a HER2/CEP17 ratio > 2.0 was defined as positive amplification. Genomic DNA was extracted from formalin-fixed paraffin-embedded tumor tissue and subjected to NGS using a 425-gene panel, covering single nucleotide variants, insertions/deletions, copy number variations and gene fusions. Tumor mutational burden (TMB) and microsatellite status were analyzed simultaneously.

2.3 Treatment evaluation and follow-up

The treatment regimen was formulated by a multidisciplinary team of gastrointestinal oncology. Therapeutic efficacy was evaluated according to RECIST v1.1 criteria, and adverse events were graded according to CTCAE version 5.0. The patient was followed up via regular outpatient visits, with the endpoints defined as disease progression or the last follow-up date.

3. Results

3.1 Clinical baseline characteristics

The index patient was a 79-year-old male with well-controlled type 2 diabetes mellitus. He presented with intermittent fatigue for 1 year and decreased appetite for 3 months, accompanied by 5 kg of unintentional weight loss. Baseline laboratory tests showed severe anemia (hemoglobin 63 g/L), elevated serum AFP (431 ng/mL), positive EBV serology, and normal liver and renal function. Contrast-enhanced abdominal CT and PET-CT revealed irregular thickening of the gastric body wall with regional lymphadenopathy, without distant metastasis, corresponding to locally advanced gastric adenocarcinoma. No relevant family history of gastrointestinal malignancy or hereditary tumor-related disease was reported.

3.2 Histopathological and immunophenotypic features

Microscopically, the tumor showed infiltrative growth with nested, sheet-like and irregular glandular structures. Tumor cells were large with abundant eosinophilic cytoplasm, consistent with typical hepatoid differentiation. Prominent lymphocytic infiltration was observed in the tumor stroma, forming a prominent lymphoid stroma background. IHC profiling showed the following: hepatoid differentiation markers revealed focal AFP positivity and diffuse HepPar-1 positivity, with negative SALL4; HER2 showed strong complete membranous staining (3+, 90% of tumor cells); PD-L1 (SP263 clone) had a TPS of 10% and CPS of 15; mismatch repair proteins were all intact (proficient mismatch repair, pMMR); EBER ISH was diffusely positive in tumor cell nuclei. Notably, β -catenin showed markedly reduced membranous expression in tumor cells compared with adjacent normal gastric epithelium, without definite nuclear or cytoplasmic translocation. Both CK7 and CK20 were negative in tumor cells. The final pathological diagnosis was moderately to poorly differentiated adenocarcinoma of the gastric body, with histological and immunophenotypic features consistent with hepatoid alpha-fetoprotein-producing gastric cancer (Figure 1).

3.3 Genomic alteration profiles

FISH confirmed *ERBB2* gene amplification, with a HER2/CEP17 ratio of 4.2 and average HER2 copy number of 8.6 per cell, which was consistent with the IHC 3+ result. NGS identified three pathogenic somatic driver alterations: (1) *ERBB2* copy number amplification (CN = 8.6); (2) *ARID1A* nonsense mutation c.3826C>T (p.R1276*), resulting in complete loss of protein function; (3) *PIK3CA* missense

mutation c.1345C>T (p.P449L), a known gain-of-function pathogenic variant. The TMB was 6.2 mutations/Mb, and the tumor was microsatellite stable (MSS). No pathogenic germline variants were detected.

3.4 Treatment response and follow-up

The patient received short-course induction therapy with combined anti-HER2 targeted therapy, PD-1 inhibitor and S-1 chemotherapy. Due to treatment-related adverse events (cardiotoxicity and cutaneous reaction), targeted therapy and immunotherapy were discontinued sequentially, and the patient switched to maintenance S-1 monotherapy. After 3 cycles of treatment, re-evaluation showed partial response (PR) according to RECIST v1.1 criteria: serum AFP decreased to 1.67 ng/mL (within normal range), EBV serology turned negative, and the primary gastric lesion and metastatic lymph nodes shrank by more than 30%. At the last follow-up (4 months after initial treatment), the patient remained in good general condition with sustained disease remission(Figure 2).

4. Discussion

4.1 Novelty of the molecular phenotype and subtyping

This case report describes an unprecedented molecular phenotype of hepatoid AFPGC with combined EBV infection and high-level *ERBB2* amplification, expanding the molecular spectrum of this rare gastric malignancy. Hepatoid AFPGC is associated with the poorest prognosis among all gastric cancer subtypes, and no standardized precision treatment strategy has been established^[1-2]. To our knowledge, this is the first comprehensive molecular pathological characterization of hepatoid AFPGC harboring concurrent EBV positivity, high-level *ERBB2* amplification, *ARID1A* nonsense mutation and *PIK3CA* gain-of-function mutation, which has not been described in previous large AFPGC cohorts^[3-4]. Systematic comparison with the TCGA molecular classification system reveals that the core features of this case are highly consistent with the EBV-positive subtype: positive EBER ISH as the diagnostic gold standard, co-occurrence of *PIK3CA* and *ARID1A* mutations commonly seen in EBV-positive tumors, MSS status, relatively low TMB, high PD-L1 expression and prominent lymphoid stroma^[6,8]. Meanwhile, this case harbors high-level *ERBB2* amplification, a hallmark event of the CIN subtype. A large cohort of 2504 patients confirmed that EBV infection and HER2 overexpression are statistically independent events in conventional gastric cancer and rarely coexist^[7]. Given the inherent chromosomal instability of AFPGC^[3-5], we propose that this case represents a unique molecular subset within the EBV-positive subtype, with superimposed CIN features resulting from the inherent genomic instability of hepatoid differentiation combined with EBV infection. From a clinical perspective, *ERBB2* amplification is the most clear-cut actionable target in this case. The incidence of HER2 amplification is slightly higher in AFPGC than in conventional gastric cancer, and is associated with hepatoid differentiation^[3-4]. The dramatic AFP reduction after one cycle of anti-HER2 therapy directly confirms HER2 as the core oncogenic driver. *ARID1A*, a core subunit of the SWI/SNF chromatin remodeling complex, contributes to tumorigenesis through aberrant chromatin remodeling and DNA repair defects when functionally lost, and also

enhances tumor immunogenicity and response to immunotherapy^[9-12]. *PIK3CA* mutation is a common driver event in EBV-positive gastric cancer and participates in regulating hepatoid differentiation programs. Although it may mediate resistance to anti-HER2 therapy, the remarkable short-term response in this case suggests that the mutation has not yet conferred primary resistance^[6,13].

4.2 Pathological mechanism of aberrant β -catenin expression

A notable histopathological finding in this case was markedly downregulated membranous β -catenin expression in tumor cells, without the nuclear or cytoplasmic translocation typically observed in canonical Wnt pathway activation. This pattern differs from the conventional β -catenin nuclear accumulation seen in intestinal-type gastric adenocarcinoma. Based on previously published evidence, the potential mechanisms underlying this non-classical phenotype may be explained from three perspectives^[1,14]:

First, hepatoid transdifferentiation is accompanied by remodeling of epithelial adhesion molecules. β -catenin exists in two relatively independent functional pools: the membranous pool binds to E-cadherin to maintain epithelial adhesion, while the cytoplasmic/nuclear pool mediates transcriptional regulation of the Wnt pathway^[15]. During transdifferentiation of gastric epithelium toward a hepatocyte-like phenotype, epithelial phenotype reprogramming occurs with downregulation of CK7/CK20, accompanied by a parallel decrease in membranous β -catenin. The double-negative CK7/CK20 immunophenotype in this case is consistent with this regulatory pattern. Importantly, reduced membranous β -catenin does not equate to global suppression of the Wnt pathway, as nuclear signaling activity can exist independently.

Second, non-classical bidirectional regulation between AFP and the Wnt pathway may be involved. A positive feedback loop between AFP and Wnt signaling has been described in AFPGC: Wnt pathway activation upregulates AFP transcription, and AFP in turn stabilizes cytoplasmic β -catenin by inhibiting GSK3 β and downregulating Axin1, thereby driving tumor proliferation and hepatoid differentiation. However, this transcriptional activation is not necessarily accompanied by β -catenin nuclear translocation, and may present as pathway activation without obvious nuclear accumulation^[1].

Third, superimposed effects of EBV infection and *ARID1A* mutation may contribute to this phenotype. EBV-encoded viral microRNAs can activate the canonical Wnt pathway, enhance the nuclear transcriptional activity of β -catenin and promote tumor invasion and metastasis^[16]. Meanwhile, EBV can silence E-cadherin by inducing hypermethylation of the *CDH1* promoter, directly reducing membranous β -catenin levels^[15]. In addition, functional studies using human gastric organoids have demonstrated that *ARID1A* deficiency leads to genome-wide enhancer reprogramming, which redirects the downstream target gene transcription program of the Wnt/ β -catenin pathway. Although *ARID1A* loss basally suppresses canonical Wnt activity, the pathway retains responsiveness to upstream stimuli, resulting in non-classical transcriptional outputs related to differentiation^[17]. The activating effect of EBV on the Wnt pathway may counteract the basal suppression caused by *ARID1A* deficiency, and their combination may ultimately shape this unique expression pattern. Recent evidence also shows that ligand-dependent Wnt

pathway activation promotes gastric cancer metastasis by remodeling hyaluronan metabolism in the tumor microenvironment^[18], which may also underlie the high invasive potential of this hepatoid AFPGC case.

This finding suggests that β -catenin nuclear translocation alone should not be used as the sole criterion for Wnt pathway activation in AFPGC; comprehensive evaluation should be performed in combination with histological subtype and molecular background. Further functional studies are required to validate the exact regulatory mechanisms.

4.3 Therapeutic and diagnostic implications

The deep and rapid response observed in this case results from the synergistic action of three therapeutic mechanisms: trastuzumab blocks the core HER2-driven pathway, PD-1 inhibitors break the EBV-associated immunosuppressive balance, and chemotherapy directly reduces tumor burden and induces immunogenic cell death^[19]. The KEYNOTE-811 trial has confirmed that the combination of PD-1 inhibitor, trastuzumab and chemotherapy significantly improves response rates in advanced HER2-positive gastric cancer^[20], providing evidence-based support for the regimen used in this case.

The strategy of "short-course intensive induction followed by individualized de-escalated maintenance" has clinical reference value for elderly patients. Elderly patients can rarely tolerate long-term intensive combination therapy. For tumors with well-defined drivers and high treatment sensitivity, short-course combination therapy can rapidly reduce tumor burden and achieve deep remission, followed by maintenance with low-toxicity agents to balance disease control and quality of life. In addition, dynamic monitoring of serum AFP and EBV titer can reflect treatment response earlier than imaging and guide regimen adjustment^[2,21].

From the perspective of pathological diagnosis, standardized histological subtyping is the premise of precise management for hepatoid AFPGC. The updated classification criteria for hepatoid adenocarcinoma can help unify diagnostic thresholds, reduce missed diagnosis of rare morphological variants, and lay the foundation for subsequent targeted molecular testing^[22]. For this highly aggressive subtype, comprehensive genomic profiling is recommended at initial diagnosis to fully screen clinically actionable molecular targets. Large-cohort genomic studies of hepatoid gastric adenocarcinoma have confirmed that the enrichment rate of actionable alterations is higher than that of conventional gastric adenocarcinoma, which supports the clinical value of routine multi-gene panel testing^[23]. Clinically, for patients with significantly elevated serum AFP, differential diagnosis should be performed in combination with endoscopic manifestations and pathological immunophenotypes to distinguish from primary liver cancer, germ cell tumors and other AFP-elevated diseases, so as to avoid misdiagnosis and delayed treatment^[24].

For HER2-positive AFPGC, special attention should be paid to the potential spatiotemporal heterogeneity of HER2 during the course of disease. Previous studies have confirmed that HER2 heterogeneity is

common in AFP-producing gastric cancer, which may lead to false-negative detection or secondary drug resistance during treatment. Dynamic molecular re-testing at disease progression can help adjust targeted strategies in time, which is a key measure to achieve long-term disease control^[25]. For patients carrying *ARID1A* loss-of-function mutations, synthetic lethality therapies represented by EZH2 inhibitors have shown definite anti-tumor activity in multiple solid tumors, bringing new precision treatment options for patients with this molecular subtype^[26-27]. On the whole, this case further supplements the practical evidence for the pathway-driven precision treatment paradigm of gastric cancer, and enriches the molecular phenotype spectrum of EBV-positive gastric adenocarcinoma, providing reference for the formulation of diagnosis and treatment strategies for similar rare cases^[28].

4.4 Study limitations

This is a single-case molecular pathological study. First, the generalizability of the molecular phenotype and treatment paradigm requires validation in larger multicenter cohorts. Second, the follow-up duration is relatively short, and long-term survival outcomes remain to be accumulated. Third, serial tissue samples before and after treatment are unavailable, so direct validation of clonal evolution and resistance mechanisms is not feasible. Fourth, the mechanistic discussion of aberrant β -catenin expression is inferred based on previously published literature and the molecular characteristics of this case. Direct functional validation of Wnt pathway activity and downstream target gene expression is lacking due to the limitation of biopsy specimens, and the exact mechanism remains to be confirmed by further experiments.

5. Conclusion

This study comprehensively characterizes a rare case of hepatoid AFPGC with concurrent EBV positivity, HER2 amplification, *ARID1A* mutation and *PIK3CA* mutation, representing a unique molecular subset of the EBV-positive subtype with superimposed chromosomal instability features. The downregulated membranous β -catenin expression potentially results from the combined effects of hepatoid transdifferentiation, non-classical Wnt pathway regulation, EBV infection and *ARID1A* deficiency. The strategy of short-course intensive induction followed by de-escalated maintenance therapy achieves favorable efficacy. This work provides important original evidence for the pathological diagnosis and precision management of this rare gastric cancer subtype.

Declarations

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Availability of data and materials

All data generated or analysed during this study are included in this published article. Additional raw pathological and molecular data are not publicly available to protect patient privacy, but are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This study was approved by the Institutional Ethics Committee of PLA Rocket Force Characteristic Medical Center (No. LC2016102) and conducted in accordance with the Declaration of Helsinki. Written

informed consent was obtained from the patient for publication of the clinical data and pathological images.

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Figures

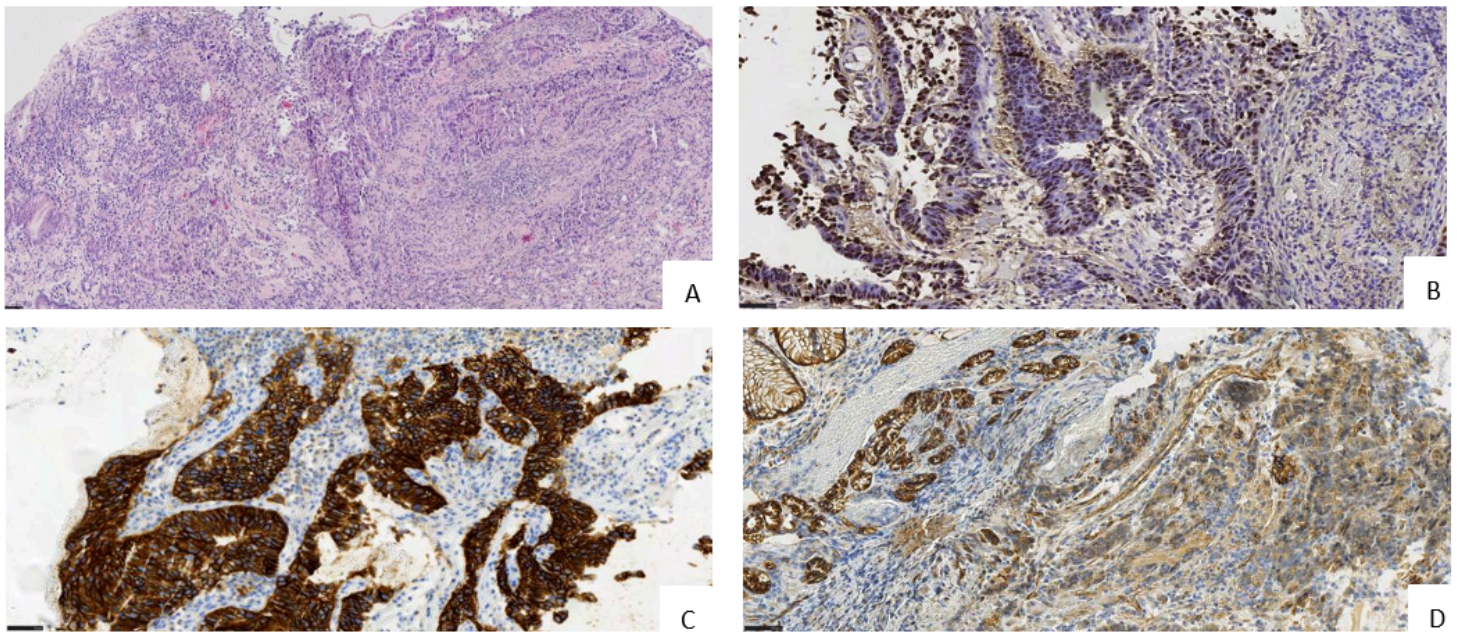


Figure 1

Histopathological and immunohistochemical features of the tumor. (A) HE staining showing typical hepatoid differentiation with abundant eosinophilic cytoplasm and prominent lymphoid stroma (original magnification $\times 100$); (B) EBER in situ hybridization showing diffuse nuclear positivity in tumor cells (original magnification $\times 200$); (C) HER2 immunohistochemistry showing 3+ strong complete membranous staining in 90% of tumor cells (original magnification $\times 200$); (D) β -catenin immunohistochemistry showing markedly reduced membranous expression in tumor cells, with no obvious nuclear or cytoplasmic translocation (original magnification $\times 200$).

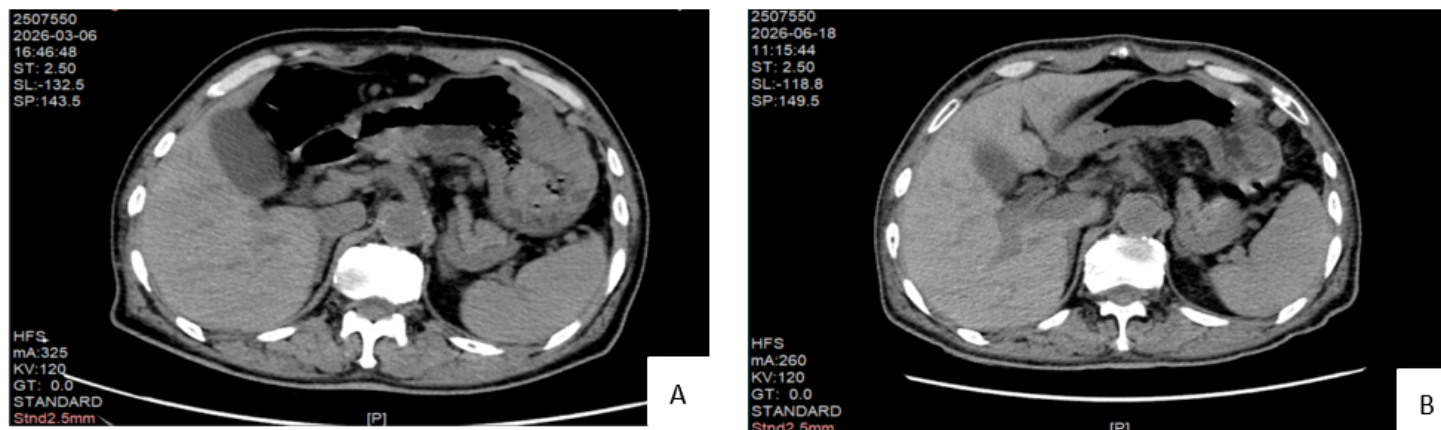


Figure 2

Contrast-enhanced abdominal CT images at baseline and after treatment. (A) Baseline CT showing irregular thickening of the gastric body wall with regional lymph node enlargement; (B) Post-treatment CT showing significant shrinkage of the primary lesion and metastatic lymph nodes, evaluated as partial response according to RECIST v1.1 criteria.