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Case Report

Successful treatment of alpha-fetoprotein-producing gastric cancer with synchronous liver metastasis: a case report and literature review

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Abstract:

We present a rare case of synchronous liver metastatic alpha-fetoprotein (AFP)-producing gastric cancer (AFPGC) with an elevated serum AFP level of 9610 ng/mL. The patient who was non-responsive to chemotherapy achieved an unexpected complete remission (CR) in fourth-line treatment with immune checkpoint inhibitors (ICIs) (camrelizumab, an anti-PD-1 agent) and anti-angiogenic drugs (apatinib, a highly selective inhibitor of vascular endothelial growth factor receptor-2 [VEGFR-2]). The serum AFP level declined to the normal range for almost four years, and the patient remained disease-free for three years after radical gastrectomy until June 2024, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0. Our results demonstrated that using ICIs in combination with anti-angiogenic drugs could improve prognosis in such cases.

Keywords: alpha-fetoprotein; gastric cancer; liver metastasis; immune checkpoint inhibitors; anti-angiogenic drugs

Introduction

The first case of alpha-fetoprotein (AFP)-producing gastric cancer (AFPGC) with liver metastasis was reported by Bourreille et al. in 1970[1]. AFPGC is a relatively rare and unique subtype of gastric cancer (GC), accounting for 2.3%–7.1% of all GC cases in China [2]. AFPGC demonstrates a more aggressive biological behavior than common GC, and it can metastasize to the liver and lymph nodes with a poor therapeutic response and prognosis [3]. Currently, no specific treatment strategy is available for this type of GC, and treatment approaches are primarily based on the principles of common GC. Common chemotherapeutic regimens for GC, including platinum, taxane, irinotecan, and fluoropyrimidines, have demonstrated poor efficacy against AFPGC.

Recently, immune checkpoint inhibitors (ICIs) and anti-angiogenic targeted therapies have been demonstrated to improve the survival of patients with various cancers, including GC. The KEYNOTE-059[4] and ATTRACTION-2[5] trials confirmed that PD-1 monoclonal antibody treatment improves survival and safety in patients with advanced, recurrent, or metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma. Based on the results of the phase III Checkmate-649 trial [6], nivolumab was approved by the Food and Drug Administration in April 2021 as a first-line treatment for patients with advanced or metastatic GC combined with chemotherapy.

Angiogenesis is a vital process under physiological and pathophysiological conditions and is one of the hallmarks of cancer progression and metastasis [7]. The vascular endothelial growth factor (VEGF)/VEGF receptor-2 (VEGFR-2) signaling pathway is critical in promoting angiogenesis. Therefore, several VEGFR-2 inhibitors have been clinically tested and/or approved for treating angiogenesis-related diseases. Ramucirumab, an anti-VEGFR-2 monoclonal antibody, is second-line therapy for advanced gastric adenocarcinoma [8]. Apatinib, a small molecule tyrosine kinase inhibitor targeting VEGFR-2, has been recommended as a third-line treatment for metastatic GC patients in China [9]. Although the development of ICIs and anti-angiogenic targeted therapy has improved the prognosis of common advanced GC, standardized treatment for AFPGC remains elusive.

Herein, we report a unique case of a chemotherapy-resistant advanced AFPGC patient who received camrelizumab combined with apatinib and achieved complete remission (CR) with disease-free survival (DFS) of over four years.

Case report:

In January 2017, a 69-year-old male with upper abdominal bloating was diagnosed with multiple liver lesions via imaging. The patient had no history of hepatitis or cancer-related family history. Endoscopic examination revealed a Borrmann II-like tumor in the distal stomach (Figure 1).

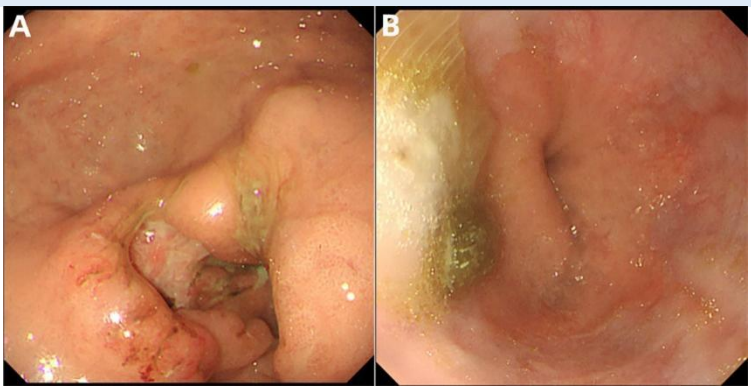

Figure 1: Gastric sinus: Mucosal congestion and edema, small curvature in the anterior pyloric area, and the surrounding mucosal bulge are visible.

A biopsy revealed high-grade intraepithelial neoplasia and invasive cancerization (Figure 2).

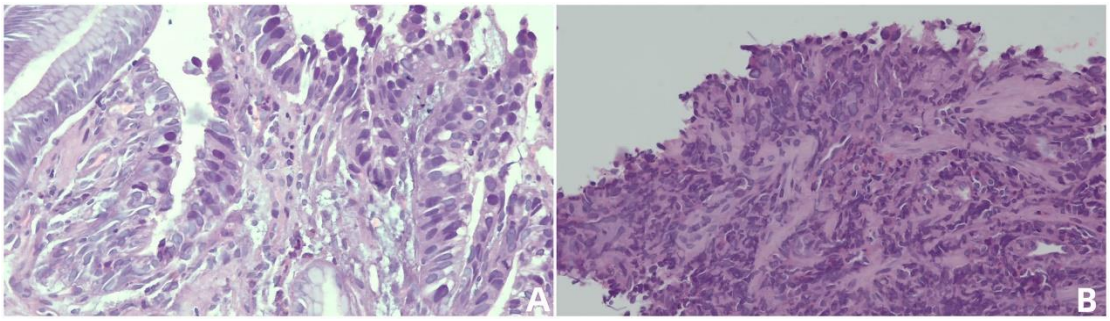

Figure 2: High magnification images of two biopsies from the antrum (H&E stain, ×400).

H&E = hematoxylin and eosin

One month after diagnosis, the patient received four cycles of SOX (oxaliplatin 130 mg/m2/day intravenously on day 1 + S-1 80 mg/m2/day on days 1–14, every three weeks) as first-line palliative chemotherapy. After two courses of chemotherapy, the serum AFP level decreased from 7932 to 2615 ng/mL. However, after four courses of chemotherapy, the serum AFP level spiked to 9610 ng/mL, with abdominal contrast-enhanced computed tomography (CECT) revealing liver metastasis. According to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, progressive disease (PD) was identified.

Four months after the diagnosis, the patient received second-line palliative chemotherapy with five cycles of the TP regimen (paclitaxel 135 mg/m2/day intravenously on day 1 and cisplatin 40 mg/m2/day on days 1–2, every three weeks). After five cycles of chemotherapy, serum AFP levels decreased significantly to 13.23 ng/mL, and abdominal CECT revealed a significant reduction in liver metastasis, indicating partial remission (PR). The patient discontinued chemotherapy after experiencing significant anorexia and started using traditional Chinese medicine (TCM) with irregular outpatient follow-up.

At 28 months post-diagnosis, the serum AFP level increased to 594 ng/mL, and abdominal CECT revealed a significantly enlarged antrum mass. The patient received five cycles of albumin-paclitaxel combined with nedaplatin chemotherapy (albumin-paclitaxel 260 mg/m2/day and nedaplatin 80 mg/m2/day intravenously on day 1, every three weeks). Subsequent abdominal CECT revealed no significant reduction in antrum mass, indicating stable disease (SD). Serum AFP levels decreased slightly to 529.1 ng/mL. Due to the COVID-19 pandemic, the patient discontinued chemotherapy with irregular outpatient follow-up.

At 38 months post-diagnosis, the patient developed cachexia and upper gastrointestinal bleeding, with a hemoglobin level of 34 g/L, and the serum AFP levels increased to 2365 ng/mL. Abdominal CECT revealed a significant antrum mass enlargement and liver metastasis. After a blood transfusion and supportive care, the patient underwent laparoscopy and gastrointestinal bypass surgery, revealing significant tumour invasion of the serous membrane, liver, and pancreas.

At 39 months post-diagnosis, the patient received camrelizumab and apatinib as fourth-line therapy (camrelizumab 200 mg/day intravenously on day 1 and apatinib 250 mg/day orally on days 1–14, every two weeks). The serum AFP level decreased significantly to 64.21 ng/mL after one cycle of treatment, which decreased to 4 ng/mL after four cycles. The patient's general condition improved significantly with better appetite and weight gain. Abdominal CECT revealed a significant reduction in the antrum mass and multiple liver metastases, indicating PR.

At 52 months post-diagnosis, the serum AFP levels reduced to less than 0.61 ng/mL. A positron emission tomography-computed tomography scan conducted in May 2021 (Fig. 3B) revealed that the gastric wall of the antrum was thicker than it was in January 2017 (Fig. 3A). Fluorodeoxyglucose (FDG) uptake in the liver and antrum was normal, indicating CR (Fig. 3).

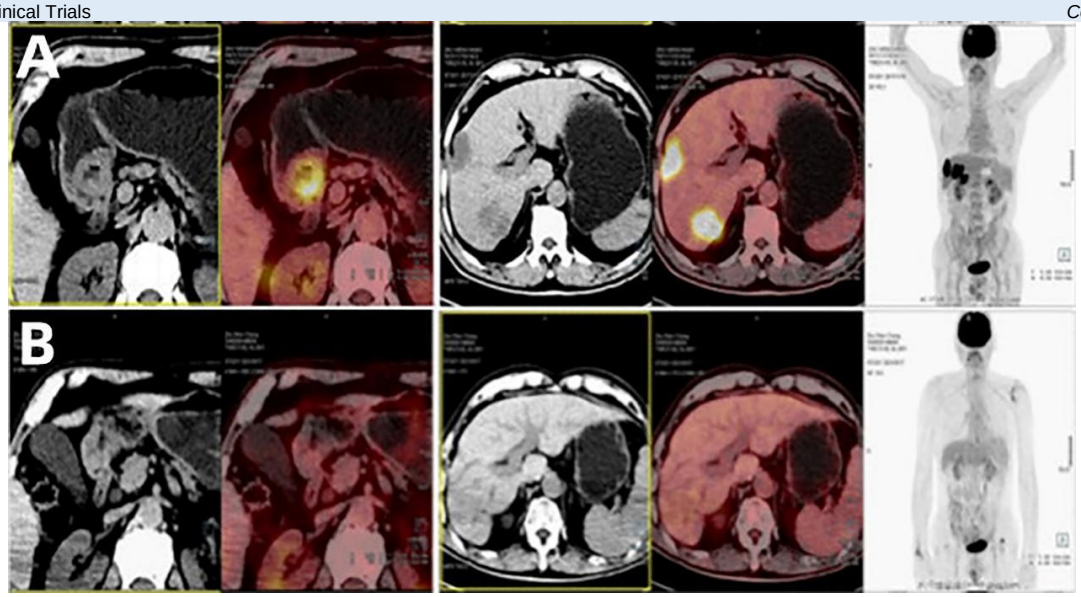

Figure 3: (A) PETCT results from January 2017 indicating increased FDG uptake in the antrum and liver. (B) PETCT results in May 2021 indicate normal FDG uptake in the gastric antrum and the liver.

PETCT = Positron Emission Tomography-Computed Tomography

FDG = Fluorodeoxyglucose

At 54 months post-diagnosis (one month after apatinib discontinuation), radical gastrectomy was performed with esophagojejunal Roux-en-Y anastomosis and retroperitoneal lymph node dissection. A pathological complete response (pCR) was confirmed through postoperative pathology with negative lymph nodes (0/20). Camrelizumab and apatinib were administered postoperatively for two years. The patient was followed up carefully. No evidence of recurrence or liver metastasis was detected on abdominal CECT scans every six months. Tumor biomarkers were used to monitor changes in serum AFP levels, which remained within the normal range for almost four years until June 2024 (Figure 4).

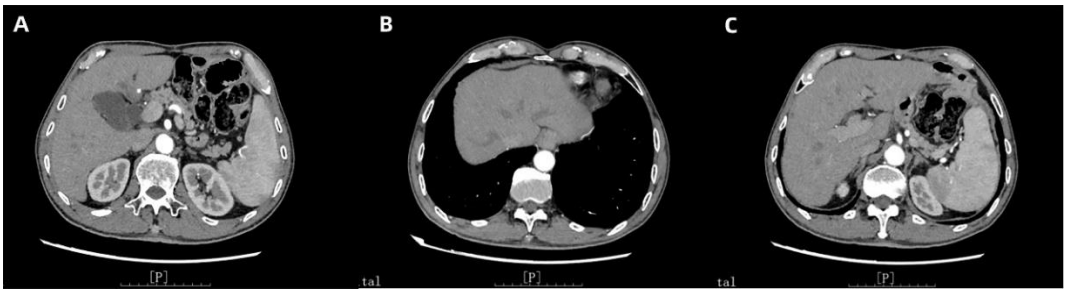

Figure 4: Recent abdominal CECT, indicating no evidence of disease

CECT = Contrast-enhanced computed tomography

The overall survival (OS) exceeded six years until June 2024, with a DFS of more than four years and a performance status of 0.

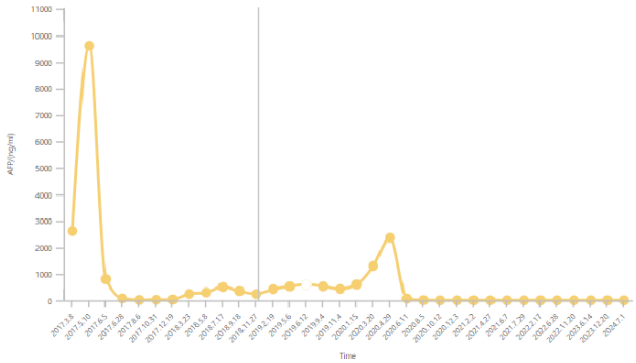

Figure 5: Changes in AFP levels from January 2017 to June 2024.

AFP = Alpha-fetoprotein

Discussion

Globally, GC ranks fifth in incidence and fourth in mortality, with the highest incidence rate in Eastern Asia [10]. AFPGC is a unique type of GC, accounting for 2.3%–7.1% of all gastric cancers in China [2]. AFPGC is usually identified as primary GC with a serum AFP level > 20 ng/mL or AFP-positive immunohistochemical staining [11].

Previous studies have demonstrated that the poor prognosis of AFPGC compared to common gastric adenocarcinoma is due to its biological aggressiveness, high incidence rate of liver and lymph node metastasis, and rapid progression [12]. The long-term follow-up results of 104 patients with AFPGC demonstrated that the incidence of liver metastasis was 60.6%, with a median time of 7.4 months from surgery to the appearance of liver metastases, significantly shorter than the 20.6 months for AFP-negative GC [3]. Current research on AFPGC mainly includes case studies or reviews of clinicopathological features with limited treatment data in the literature. Currently, the efficacy of common chemotherapy regimens for GC, including platinum, paclitaxel, irinotecan, and fluoropyrimidines, is inadequate for AFPGC [13, 14].

With the advent of immunotherapy, ICIs have been approved for a variety of solid tumors, including carcinomas of the lungs, liver, esophagus, kidneys, and stomach. Recently, combination therapies of ICIs with radiotherapy, chemotherapy, or targeted therapy have become prospective strategies for improving GC treatment options [15]. The results from CheckMate 649 revealed that the combination of nivolumab and chemotherapy improved OS and progression-free survival (PFS) in advanced GC patients with a PD-L1 CPS ≥ 5 compared with chemotherapy alone [6]. However, the use of ICIs in AFPGC has rarely been reported. Wei Li et al. [16] investigated the efficacy of immunotherapy combined with chemotherapy in patients with AFPGC, wherein seven patients received anti-PD-1 antibody (nivolumab) + XELOX (capecitabine and oxaliplatin) chemotherapy regimen and 14 patients (control) received chemotherapy with or without Herceptin/Apatinib. The overall response rate (ORR) was 85.7% in the immunotherapy group and 21.4% in the control group. The median PFS was 5.0 months for first-line treatment, 4.3 months in the control group, and 22.0 months in the immunotherapy group, indicating that immunotherapy and chemotherapy could be a viable treatment option for AFPGC [16].

AFPGC exhibits increased VEGF expression and abundant angiogenesis compared to non-AFP-producing GC [17]. VEGF is highly expressed in AFPGC compared to non-AFP-producing GC [18]. The introduction of anti-angiogenic drugs has expanded the therapeutic options for AFPGC. Doi Y et al. reported a case in which the patient receiving systemic chemotherapy with paclitaxel/ramucirumab achieved CR, indicating the efficacy of ramucirumab [19].

Ramucirumab inhibits VEGF-A, VEGF-C, and VEGF-D by blocking VEGFR-2 expression. Apatinib is an oral tyrosine kinase inhibitor that selectively targets VEGFR-2 using a similar mechanism to ramucirumab. The National Medical Products Administration (NMPA) approved the agent in 2014 as a third-line therapy for advanced GC [20]. The analysis included 21 patients diagnosed with AFPGC from an open-label, prospective, multicenter, non-interventional study (AHEAD-G202) on apatinib for metastatic GC [21]. The ORR was 10%, and the disease control rate was 70%, with a median PFS of 3.5 months and a median OS of 4.5 months. In the subgroup analysis, the median OS of AFPGC patients without carcinoembryonic antigen elevation was 30.8 months. These results indicate that apatinib demonstrated promising efficacy in patients with advanced AFPGC. Anti-angiogenic therapy might be an effective strategy for AFPGC treatment.

A randomized, open-label, multicenter, single-arm phase II study involving 36 adult patients with clinical stage III-IV unresectable, recurrent, or metastatic alpha-fetoprotein-producing gastric/gastroesophageal junction (G/GEJ) adenocarcinoma was conducted. All patients received four cycles of camrelizumab + apatinib + SOX treatment. The median follow-up time was 6.4 months, with two patients achieving CR and 22 achieving PR. The confirmed ORR was 55.6% (95% confidence interval 38.1–72.1), and the disease control rate (DCR) was 86.1%. The 12-month PFS and OS rates were 42.1% (20.9, 62.1) and 63.7% (41.0, 79.6), respectively [22]. A single-arm, multicenter phase II clinical study (NCT04098796) investigated the efficacy and safety of anti-PD-1 antibody (sintilimab) in combination with chemotherapy (XELOX) as the first-line treatment for patients with unresectable, locally advanced recurrent, or metastatic AFPGC. The other open-label, single-arm, multicenter phase II study (NCT04006821) investigated the efficacy of camrelizumab combined with apatinib as a second-line treatment for AFPGC. Additionally, trials assess the ORR of camrelizumab + apatinib and SOX in AFPGC patients who have failed ≥ 1 line of previous treatment (NCT04609176).

With the development of next-generation sequencing and other genomic technologies, gastric cancers, including AFPGC, are now being comprehensively studied at the molecular level [23]. miR 122 5p, which inhibits apoptosis and facilitates tumor progression by targeting forkhead box protein O3 (FOXO3), was identified as a potential biomarker for early detection and disease monitoring, as well as a potential therapeutic target in AFPGC [24] [25]. Further research is urgently required to elucidate the pathogenesis and genetic characteristics of AFPGC, identify potential molecular targets, and optimize therapeutic approaches to improve the prognosis of patients with AFPGC.

Conclusion:

Although treatment remains the biggest challenge for AFPGC, immunotherapy combined with targeted therapy has significant potential in the future. This report is the first to propose the possible clinical applications of camrelizumab in combination with apatinib for treating AFPGC. More clinical trials are required to elucidate the efficacy of ICIs and anti-angiogenic therapies for AFPGC treatment.

Author Contributions

Conceptualization: K H, D.L M; writing-original draft: R.R S, H.L Z; writing-review & editing: H.L Z, C T, K H.

Limitation analysis

This study is a case report and the results are accidental. It is necessary to collect such cases as much as possible for clinical research to make the results more convincing.

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