The combination of Tislelizumab and apatinib obtained complete remission for alpha-fetoprotein-producing gastric cancer with microsatellite stability: case report

Jinyu Xiang (kiwi2010@163.com)
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital https://orcid.org/0000-0003-4698-5717

CongCong Wang
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital

Wenjing Gong
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital

Aina Liu
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital

Ping Sun
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital

Research Article

Keywords: alpha-fetoprotein-producing gastric cancer（AFPGC), Tislelizumab, apatinib, anti-angiogenesis, immune checkpoint inhibitor (ICI)

Posted Date: September 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-853241/v1

Abstract

Background

Alpha-fetoprotein (AFP)-producing gastric cancer (AFPGC) is a rare type of gastric cancer with high metastasis rate and poor prognosis. Despite substantial progress in the treatment of many solid tumors, there are no reports of the safety and effectiveness of immune checkpoint inhibitor (ICI) in combination with anti-angiogenesis in AFPGC patients with microsatellite stability (MSS).

Case presentation

This is a case of a 69-year-old man who was diagnosed with metastatic AFPGC. After the progression of resistance to chemotherapy, Tislelizumab combined with apatinib was attempted, although the patient was microsatellite stable. With 3 cycles of combination therapy, a partial remission (PR, shrunk by 56%) was obtained, and the quality of life improved significantly. Surprisingly, after more than one year of continuous application of the above treatment regimen, both the primary and metastatic tumors in this patient eventually disappeared, which achieved complete remission (CR) without surgery. Following the combined treatment, the patient had a progression-free survival of more than 16 months and now is still in continue to benefit.

Conclusions

This is the first report that we are aware of on the effective treatment of AFPGC with Tislelizumab in combination with Apatinib. This provides a highly effective and tolerable therapeutic strategy for microsatellite-stabilized AFPGC.

Introduction

Alpha-fetoprotein-producing gastric cancer (AFPGC) is a relatively rare disease, accounting for 1.3–15% cases of gastric cancer(1). AFPGC is usually identified as primary gastric cancer with serum AFP level more than 20 ng/ml or showed AFP positive staining by immunohistochemistry. Compared to non-AFP gastric cancer, AFPGC is associated with poor prognosis because of high rates of liver and lymph node metastases(2). At present, the conventional treatment for gastric cancer includes surgery, chemotherapy, targeted therapy and immunotherapy. In the treatment of gastric cancer, immunotherapy is mainly based on biomarkers, such as the expression of PD-L1, microsatellite status, TMB, etc. Tislelizumab (BeiGene, Beijing, China) is a monoclonal antibody with high affinity and specificity for PD-1 that was designed to prevent antibody-dependent phagocytosis, a putative mechanism of T-cell clearance and resistance to anti-PD-1 treatment, by minimizing Fc□R binding to macrophages(3). In Rationale 205 study (NCT03469557), Tislelizumab plus chemotherapy demonstrated durable responses with manageable tolerability as first-line treatment in patients with advanced ESCC(esophageal squamous cell carcinoma) or G/GEJ (gastric/gastroesophageal junction) adenocarcinoma)(4) A worldwide multicenter phase III trial, Rationale 305 ((NCT03777657), Tislelizumab with chemotherapy versus placebo plus chemotherapy as

first-line treatment in patients with gastric or gastroesophageal junction cancer), is currently in progress(5).

Apatinib (Hengrui, Jiangsu, China) is a small molecule anti-angiogenic targeted drug with significant anti-angiogenic and anti-tumor effects anti-angiogenic and anti-tumor effects(6). The CFDA has authorized apatinib as a third-line treatment for individuals with advanced gastric cancer. In patients with progressing Hepatocellular Carcinoma, a trial using anti-PD-1 anti-body SHR-1210 in combination with apatinib (VEGFR2 TKI) demonstrated encouraging therapeutic efficacy(7). Low-dose apatinib improved the tumor microenvironment (TME) and boosted the anti-tumor impact of PD-1/PD-L1 blockage in lung cancer, according to another study(8).

Combining immune checkpoint inhibitor (ICI) and anti-angiogenesis drugs has been shown to have a synergistic effect while retaining a good safety profile(9). Inhibition of VEGF not only causes tumor vascular normalization, but also promotes tumor CD8 + T lymphocyte infiltration and improves tumor immunotherapy, according to latest research(10). PD-1/PD-L1 inhibitors, on the other hand, can regulate tumor blood vessels by activating effector T cells and upregulating interferon-γ (IFN-γ) production, therefore increasing the efficacy of anti-angiogenic medicines and improving effector T cell infiltration and killing(11). Consequently, PD-1/PD-L1 inhibitors coupled with antiangiogenic medicines can create a positive feedback loop that is mutually beneficial.

This is a case report of a 69-year-old man with AFPGC with numerous metastases who responded to therapy with Tislelizumab plus apatinib and achieved CR. After twenty-two treatment cycles, follow-up imaging indicated that both the original tumor and metastatic lesions had shrunk and finally vanished. The patient's vital signs were stable, and he had a better quality of life.

Case Presentation

A 69-year-old man presented to Yantai Yuhuangding Hospital with upper abdominal pain in August 2019. He had type 2 diabetes before. No family history was identified. His Eastern Cooperative Oncology Group (ECOG) score was 1. The laboratory findings reported that the hemoglobin was 72g/L and the erythrocyte count was 2.91×10^{12}. Serum cancer embryonic antigen (CEA) 117.2 ng/ mL, alpha fetoprotein (AFP) 131.6 ng/ mL, other tumor markers were generally normal. On August 29, 2019, enhanced abdominal and pelvic computed tomography scan (CT) showed gastric cancer with multiple lymph node enlargement in perigastric, mesenteric travel region and retroperitoneal region. Endoscopy shows gastric antrum ulcer, nature to be determined (Fig. 1A). Gastroscopic pathology (Fig. 1B, August 30, 2019) :(gastric antrum) adenocarcinoma, part of which showed signet ring cell carcinoma differentiation. According to Serological and histopathological findings, the tumor was diagnosed as AFPGC rather than hepatoid adenocarcinoma of stomach (HAS). The immunohistochemistry indicated that HER2 (0), Ki67 (+ 90%), MSH2 (+), MSH6 (+), PMS2 (+), MLH1 (+). PD-L1 (22C3): Combined positive score (CPS) = 3(mainly tumor cells), positive control (DAKO0905 +), negative control (-). In situ hybridization: Eber (-). PET/CT (Fig. 1E) showed Non-uniform thickening of gastric wall in antrum area, coarse serous surface, increased

FDG metabolism in thickened gastric wall, consistent with PET/CT findings of gastric cancer. And multiple enlarged lymph nodes in the left supraclavicular fossa, lesser omentum sac area, retroperitoneum, mesenteric root, and left iliac vessels, with increased FDG metabolism, lymph node metastasis should be considered.

He was definitely diagnosed as AFP-producing gastric cancer (stage IV) with multiple lymph node metastases in the left supraclavicular fossa, lesser omentum sac, retroperitoneal, mesenteric root, and left iliac artery. After the anemia was improved, the hemoglobin rose to 95g/L. After 4 cycles of standard first-line chemotherapy of oxaliplatin (230mg d1) combined with S-1 (60mg bid d1-14/21d), the efficacy was evaluated as stable disease (SD) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Since the efficacy was unsatisfactory, albumin paclitaxel was added in the fifth cycle in combination with oxaliplatin and oxaliplatin, due to anemia, treatment fell off on the 8th day. From January 12, 2020 to February 26, 2020, the 6th, 7th, and 8th cycle of chemotherapy were given: albumin-bound paclitaxel 200mg d1,8 + S-1 60mg bid d1-14/21d. After 6 cycles, the lesion remained SD. However, the tumor progressed significantly after 8 cycles. On March 20, 2020, Re-examination of abdominal and pelvic cavity with enhanced CT (Fig. 2) indicated that the gastric antrum wall was thicker than before, and multiple enlarged lymph nodes in the abdominal cavity and retroperitoneum were more and more enlarged than before. And the right renal pelvis, the right upper segment of the ureter and its surrounding changes, metastatic tumor invasion of the ureter, the right renal vein and the inferior vena cava. There were hydronephrosis in the right kidney, hydrops around the ureter in the renal sinus and upper segment, hydrops around the testicular sheath, and subcutaneous soft tissue edema in the abdominal pelvis wall, suggesting progressive diseases (PD). The level of serum CEA and AFP increased to 113.1ng/ml and 236.9U/ml after 8 cycles (Fig. 3). On March 23, 2020, due to urinary tract obstruction caused by the compression of metastatic tumor, the patient received "catheter drainage for right renal hydronephrosis" under local anesthesia. Given the rapidly disease progression, limited efficacy of chemotherapy, Tislelizumab (once, every 3 weeks) plus oral apatinib (250 mg, once daily) was administered in our hospital since March 31, 2020.

After 3 cycles' treatment, CT examination (Fig. 2, June 5, 2020 vs. March 20, 2020) revealed the thickening of gastric antrum wall was better than before, and the multiple enlarged lymph nodes in abdominal cavity and retroperitoneal area were reduced. And the metastatic tumor of the right renal pelvis and the upper part of the right ureter was smaller than before, the peripheral exudation and effusion were better than before, the right renal vein and inferior vena cava were clearer than before, pelvic effusion and testicular hydrocele were basically absorbed than before. Bladder wall thickening and abdominal pelvis wall edema were better than before. The carcinoembryonic antigen decreased to 8.17ng/ml, AFP decreased to 8.73U/ml (Fig. 3). After 3 cycles, response evaluation achieved a large partial response (PR), which shrunk by 56%. In December 2020, the patient's right hydronephrosis completely disappeared and the right kidney drainage tube was removed. At the last review of the patient, at the end of April 2021, it was surprising to find that the gastric tumor and intraperitoneal metastasis had disappeared under endoscopy and that the patient had achieved complete remission (CR) (Fig. 1C, 1D, Fig. 2). The patient achieved 16 months of progression-free survival (PFS) with the combination

treatment, which significantly improved the quality of life. During the treatment, he experienced grade 2 treatment-related hypertension according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0, which was relieved after symptomatic treatment. He continued the above treatment and is still in follow-up.

Discussion

In this case, gastric cancer of this patient progressed after first-line standard chemotherapy, and the metastatic tumor caused obstruction in right urinary tract. The rapid progression of the disease reflects the grade malignancy of this AFPGC. The patient finally achieved complete remission (CR) to tislelizumab plus apatinib following progression on chemotherapy. At present, PFS is more than 16 months, and the patient is well tolerated.

AFPGC is defined as gastric cancer with elevated serum AFP (≥20 ng/mL) It has been reported that AFP-producing gastric cancer has high proliferative activity, weak apoptotic activity, and rich neovascularization compared with AFP-negative gastric cancer(12). AFPGC is found to have a poor response to chemotherapy and basic research indicated that AFP-producing cell lines were be less sensitive to many drugs including platinum and fluoropyrimidines(13). However, it has also been reported that triplet regimen as first-line chemotherapy can improve prognosis of AFPGC with liver metastasis(14). Up to now, three articles have reported that apatinib has a good effect on AFPGC(15, 16), which suggested that antiangiogenic treatment may also be an option. It is consistent with previous case reports on the efficacy of antiangiogenic therapy in AFPGC(17). One study suggested PD-1 checkpoint inhibitor plus chemotherapy could be benefit for AFPGC(15). AFPGC patients respond to immunotherapy, possibly associated with their specific genetic features. Recent studies(18) suggest that most TCGA tumors with elevated AFP expression were categorized as CIN subtypes. Loss of heterozygosity (LOH) occurs frequently in gastric cancer, resulting in chromosomal instability and loss of tumor suppressor genes. Pathological results of this patient showed that the microsatellite was stable (MSI-L, microsatellite instability-Low), but the PD-L1 expression level by CPS was 3. In accordance with the NCCN and CSCO guidelines, the patient should be treated with apatinib or immunotherapy monotherapy or other drugs. Following the pattern of REGONIVO, we found that administering immunotherapy combined with antiangiogenic therapy was surprisingly effective. We hypothesized that ICI combined with anti-angiogenesis had a 1 + 1 > 2 effect on this AFPGC.

Because anti-angiogenesis and immune checkpoint inhibition both target the tumor microenvironment, combining ICI with anti-angiogenic drugs might have a synergistic anti-tumor effect(19). Blocking both the VEGF and the PD-1/PD-L1 axis has demonstrated to be beneficial in a variety of cancers, and it is developing as a potential combo therapy. ICIs have been demonstrated to be complimentary to antiangiogenic treatment in a number of preclinical and clinical investigations. Anti-angiogenesis, on the one hand, reduces the expression of several immunological checkpoints and increases the percentage of anti-tumor/pro-tumor immune cells, therefore blocking inhibitory immune signals. On the other hand, ICIs treatment can restore the microenvironment of immune support and promote vascular normalization,

which is conducive to drug delivery, reduce the dosage of ICIS and reduce the risk of adverse events(20).The use of VEGFR TKIs in combination with ICIs has been linked to improved outcomes in RCC, HCC, NSCLC, mucosal melanoma, endometrial carcinoma, esophageal carcinoma, triple-negative breast cancer, microsatellite stability (MSS) gastric carcinoma (GC) and CRC, head and neck squamous cell carcinoma, urothelial carcinoma, osteosarcoma, and other malignant tumors(21). The combination therapies of anti-PD-1/PD-L1 treatments with antiangiogenic agents in the REGONIVO study have demonstrated activation of immune checkpoints that result in more potent antitumor activity than anti-PD-1 monotherapy(7),[8]. Thus, we believe further work is still needed to elucidate the underlying mechanism for the modulation of PD-L1 expression via antiangiogenesis in AFPGC.

Conclusion

In AFPGC patients, combining anti-angiogenic therapy with an immune checkpoint inhibitor looks to be a potential approach for treating this type of tumor. According to the available preclinical and clinical evidence, combining ICI with a VEGF targeting drug may enhance the overall result. The findings of continuing studies' mature survival outcomes are eagerly expected. We reported herein that a patient with AFPGC achieved durable complete remission from the combined treatment of the PD-1 inhibitor Tislelizumab and the anti-angiogenic agent apatinib with mild toxicity. We believe that an anti-angiogenic agent combined with immunotherapy will be a promising treatment choice for patients with AFPGC. The regimen is worth further investigation in clinical trials.

Abbreviations

AFP: alpha-fetoprotein; GC: Gastric cancer; AFPGC: alpha-fetoprotein-producing gastric cancer; ICI: immune checkpoint inhibitor; MSS: microsatellite stability; TME: tumor microenvironment; VEGF: Vascular Endothelial Growth Factor; PD-1: Programmed cell death 1; RCC: Renal Cell Carcinoma; HCC: Hepatocellular Carcinoma; CRC: Colorectal Cancer; NSCLC: Non-Small Cell Lung Cancer; PD-L1: Programmed Cell Death Ligand 1; CR: complete remission; ECOG: Eastern Cooperative Oncology Group; CEA: cancer embryonic antigen.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from the patient for publication of this study and any accompanying images. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013).

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding: This work was supported by the Youth Foundation of Yantai Yuhuangding under Grant 201903.

Authors' contributions

Ping Sun and Aina Liu: conception and design and study supervision. Jinyu Xiang: analysis and interpretation of data and writing, review, and revision of the manuscript. Congcong Wang collected laboratory and imaging data and followed up the patients. Wenjing Gong helped perform the analysis with constructive discussions. All authors contributed to the article and approved the submitted version.

Acknowledgements

Not applicable

References

1. Kono K, Amemiya H, Sekikawa T, Iizuka H, Takahashi A, Fujii H, et al. Clinicopathologic features of gastric cancers producing alpha-fetoprotein. Dig Surg. 2002;19(5):359–65. discussion 65.
2. He R, Yang Q, Dong X, Wang Y, Zhang W, Shen L, et al. Clinicopathologic and prognostic characteristics of alpha-fetoprotein-producing gastric cancer. Oncotarget. 2017;8(14):23817–30.
3. Zhang T, Song X, Xu L, Ma J, Zhang Y, Gong W, et al. The binding of an anti-PD-1 antibody to FcgammaRIota has a profound impact on its biological functions. Cancer Immunol Immunother. 2018;67(7):1079–90.
4. Xu J, Bai Y, Xu N, Li E, Wang B, Wang J, et al. Tislelizumab Plus Chemotherapy as First-line Treatment for Advanced Esophageal Squamous Cell Carcinoma and Gastric/Gastroesophageal Junction Adenocarcinoma. Clin Cancer Res. 2020;26(17):4542–50.
5. Xu R, Arkenau T, Bang Y, Denlinger C, Kato K, Tabernero J, et al. P-26 RATIONALE 305: Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line therapy in patients with gastric or gastroesophageal junction adenocarcinoma. Ann Oncol. 2020;31:97-S8.
6. Scott LJ. Apatinib. A Review in Advanced Gastric Cancer and Other Advanced Cancers. Drugs. 2018;78(7):747–58.
7. Xu J, Zhang Y, Jia R, Yue C, Chang L, Liu R, et al. Anti-PD-1 Antibody SHR-1210 Combined with Apatinib for Advanced Hepatocellular Carcinoma, Gastric, or Esophagogastric Junction Cancer: An Open-label, Dose Escalation and Expansion Study. Clin Cancer Res. 2019;25(2):515–23.

8. Zhao S, Ren S, Jiang T, Zhu B, Li X, Zhao C, et al. Low-Dose Apatinib Optimizes Tumor Microenvironment and Potentiates Antitumor Effect of PD-1/PD-L1 Blockade in Lung Cancer. Cancer Immunol Res. 2019;7(4):630–43.
9. Li J, Qin S, Xu J, Xiong J, Wu C, Bai Y, et al. Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Apatinib in Patients With Chemotherapy-Refractory Advanced or Metastatic Adenocarcinoma of the Stomach or Gastroesophageal Junction. J Clin Oncol. 2016;34(13):1448–54.
10. Huang Y, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A. 2012;109(43):17561–6.
11. Huang Y, Kim BYS, Chan CK, Hahn SM, Weissman IL, Jiang W. Improving immune-vascular crosstalk for cancer immunotherapy. Nat Rev Immunol. 2018;18(3):195–203.
12. Koide N, Nishio A, Igarashi J, Kajikawa S, Adachi W, Amano J. Alpha-fetoprotein-producing gastric cancer: histochemical analysis of cell proliferation, apoptosis, and angiogenesis. Am J Gastroenterol. 1999;94(6):1658–63.
13. Chang YC, Nagasue N, Kohno H, Ohiwa K, Yamanoi A, Nakamura T. Xenotransplantation of alpha-fetoprotein-producing gastric cancers into nude mice. Characteristics and responses to chemotherapy. Cancer. 1992;69(4):872–7.
14. Wang Y, Shen L, Lu M, Ji Z, Zhang X. Multimodality Treatment Including Triplet Regimen as First-Line Chemotherapy May Improve Prognosis of Serum AFP-Elevated Gastric Cancer with Liver Metastasis. Gastroenterol Res Pract. 2017;2017:5080361.
15. Li N, Bai C, Zhang R, Ma L, Ren X, Zhang J, et al. Efficacy and safety of apatinib for the treatment of AFP-producing gastric cancer. Transl Oncol. 2021;14(2):101004.
16. Wang N, Chen S, Liu D, Guo J, Sun Y, Zhang J, et al. Therapeutic effect of small molecule targeting drug apatinib on gastric cancer and its role in prognosis and anti-infection mechanism. Saudi J Biol Sci. 2020;27(2):606–10.
17. Arakawa Y, Tamura M, Aiba K, Morikawa K, Aizawa D, Ikegami M, et al. Significant response to ramucirumab monotherapy in chemotherapy-resistant recurrent alpha-fetoprotein-producing gastric cancer: A case report. Oncol Lett. 2017;14(3):3039–42.
18. Arora K, Bal M, Shih A, Moy A, Zukerberg L, Brown I, et al. Fetal-type gastrointestinal adenocarcinoma: a morphologically distinct entity with unfavourable prognosis. J Clin Pathol. 2018;71(3):221–7.
19. Georganaki M, van Hooren L, Dimberg A. Vascular Targeting to Increase the Efficiency of Immune Checkpoint Blockade in Cancer. Front Immunol. 2018;9:3081.
20. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. Nat Rev Clin Oncol. 2018;15(5):325–40.
21. Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, et al. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. J Clin Oncol. 2020;38(11):1154–63.

Figures

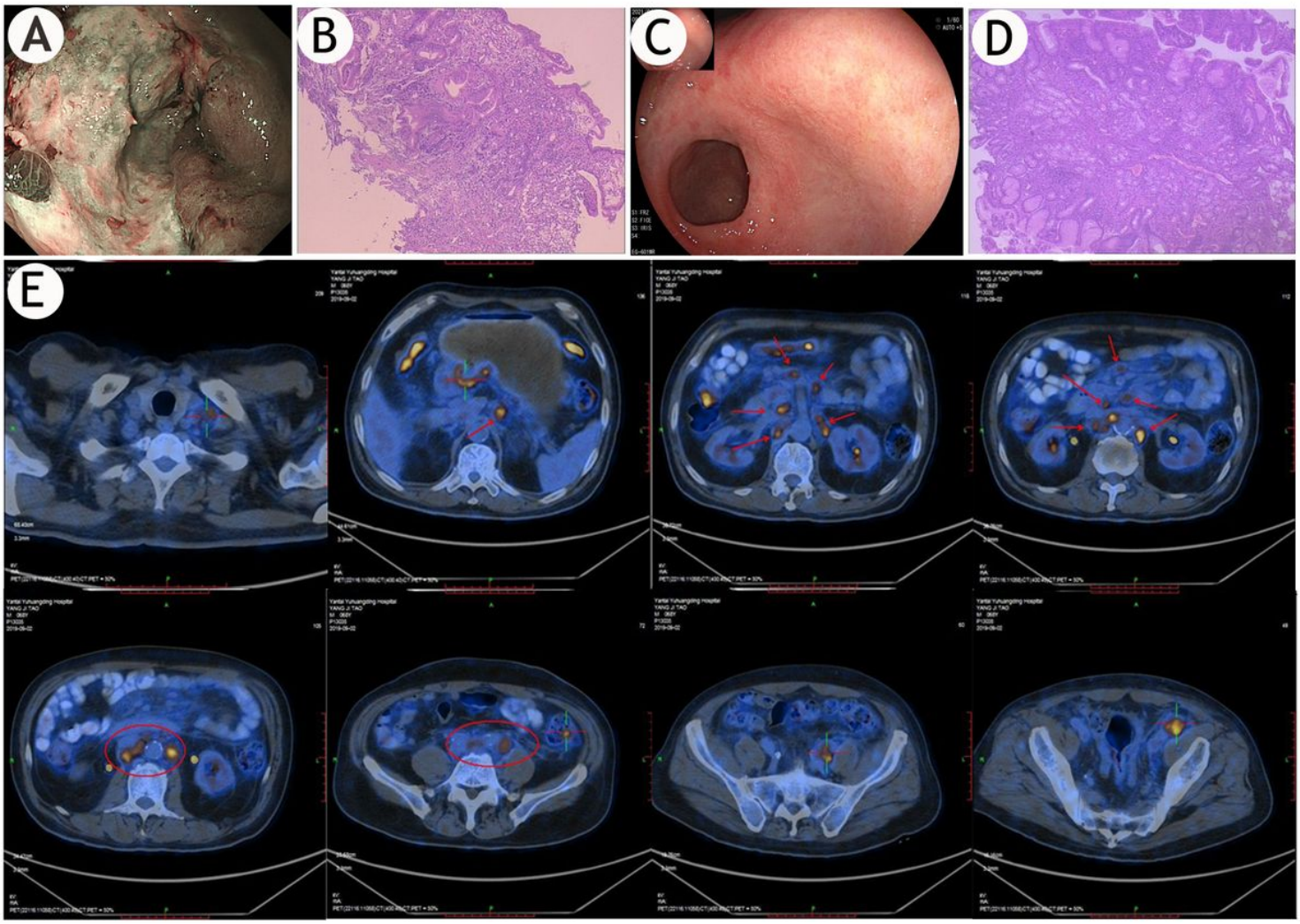

Figure 1

Figure 1A. gastric ulcer was found during gastroscopy. Figure 1B. Pathological findings (gastric antrum) adenocarcinoma, part of which showed signet ring cell carcinoma differentiation. Figure 1C. In 2021-4, after over a year of treatment, the gastric ulcer lesions(cancer) disappeared. Figure 1D. The antrum mucosal tissue is inflammatory, and the glandular epithelium presents mild intestinal metaplasia Figure 1E. PET/CT showed gastric cancer with multiple lymph node metastases in the left supraclavicular fossa, lesser omentum sac, retroperitoneal, mesenteric root, and left iliac artery

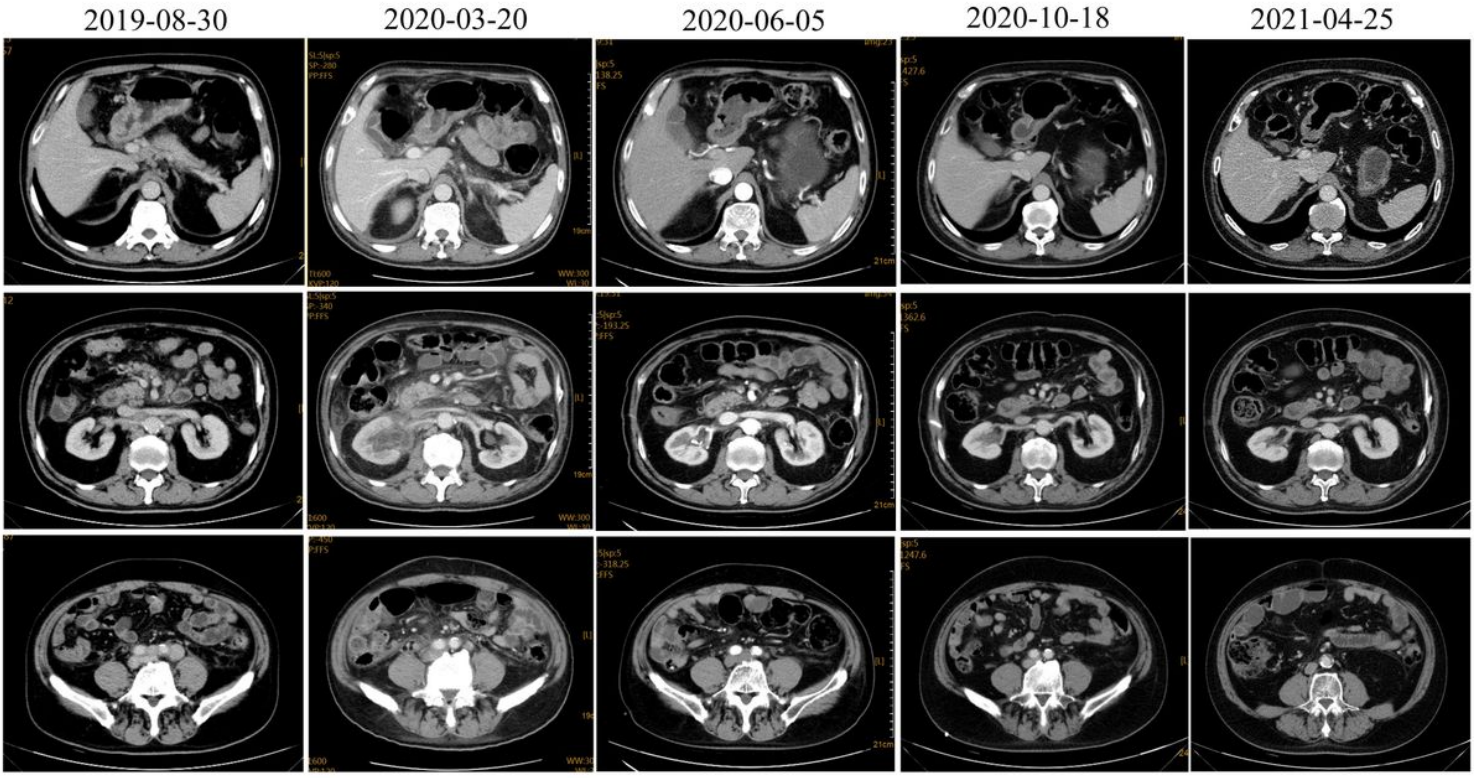

Figure 2

Through regular CT scan, it was found that with the progress of treatment, cancer in gastric antrum and metastases in other parts were significantly smaller than before. Eventually, the tumor disappeared completely.

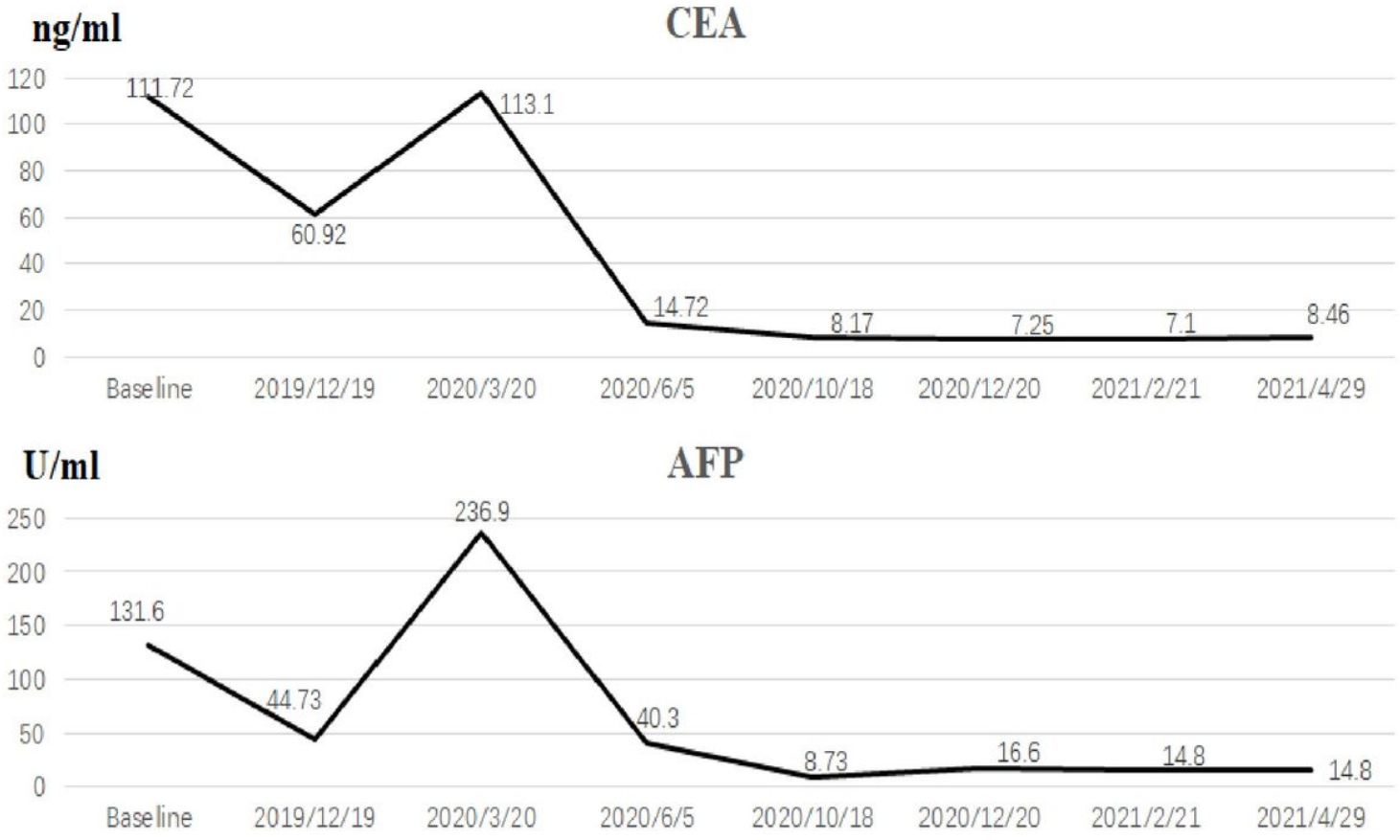

Figure 3

Changes in the levels of the tumor marker carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP).