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CASE REPORT

A Rare Case of Chemotherapy Combined with Immunotherapy for Dual Primary AFP-Positive Gastric Cancer and Synchronous Small Cell Lung Cancer

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Background: Alpha-fetoprotein-positive gastric cancer (AFPGC) is a rare subtype of gastric cancer characterized by high invasiveness and extremely poor prognosis. According to relevant studies, the median overall survival of such patients is significantly shorter than that of AFP-negative gastric cancer patients (14 months vs 40 months). Small cell lung cancer (SCLC), the most malignant type of lung cancer, has a median survival time of only 8–12 months in patients with extensive disease. To date, there have been no reported cases of dual primary cancers involving both AFPGC and SCLC, and the therapeutic role of immunotherapy in such dual primary tumors remains unclear.

Case Presentation: This paper reports a case of a 72-year-old male patient who was diagnosed via imaging and pathology as having concurrent AFPGC (moderately to poorly differentiated adenocarcinoma, PD-L1 positive, Tumor mutation burden(TMB) 10.03Muts/Mb, PD-L1 Combined Positive Score (CPS)<1) combined with primary extensive-stage SCLC. The patient received CAPEOX regimen (capecitabine plus oxaliplatin) combined with tislelizumab therapy. After 4 cycles, partial response (PR) was observed in the gastric lymph nodes, and stable disease (SD) was noted in the pulmonary lesions. Following pathological confirmation of dual primary cancers, treatment continued with the original regimen, followed by maintenance therapy with tegafur gimeracil oteracil potassium capsule (teysuno) plus tislelizumab. During treatment, serum AFP levels decreased from baseline 502 μg/L to 1.56 μg/L. Both primary tumor lesions remained stably controlled for over 33 months, and the patient currently tolerates treatment well with an Eastern Cooperative Oncology Group (ECOG) performance status of 0.

Conclusion: Through the long-term treatment course of this case, we validated the therapeutic efficacy of chemotherapy combined with immunotherapy (CAPEOX plus tislelizumab) for the rare aggressive dual primary tumors AFPGC and SCLC, demonstrating significant long-term maintenance benefits from the immunotherapy. Concurrently, this case confirmed the efficacy and safety of tislelizumab during the maintenance therapy phase for both tumors, offering a new treatment option for managing such complex clinical presentations.

Keywords: AFPGC, SCLC, case report, immunotherapy, tislelizumab

Introduction

Gastric cancer (GC) is one of the most common and deadly digestive system cancers worldwide, and its heterogeneity significantly impacts clinical decision-making. Among these, alpha-fetoprotein-producing gastric cancer (AFPGC) is a rare, aggressive subtype defined as gastric cancer with serum AFP≥20μg/L or AFP-positive immunohistochemistry.[1] Epidemiological data indicate that AFPGC accounts for 1.3%–15% of all gastric cancer cases worldwide.[2] This subtype exhibits unique clinical characteristics, including high aggressiveness, a tendency to metastasize to the liver, lymph nodes, and peritoneum, and often advanced staging at diagnosis. According to relevant studies, the median overall survival (mOS) and 5-year survival rate were significantly shorter in patients with AFP-positive gastric cancer compared to AFP-negative patients (mOS: 14 months vs 40 months; 5-year survival rate: 19.8% vs 36.8%).[3,4] Based on the latest results from the CAP 06 study, the combination of SOX with camrelizumab/apatinib has been recommended in the CSCO guidelines, becoming the only

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standard treatment regimen for AFPGC.[5] Previous studies have shown that chemotherapy combined with immunotherapy yields beneficial outcomes in AFPGC patients; however, clinical trial data on this combination therapy remain limited. Therefore, the combined application of chemotherapy and immunotherapy may continue to be an area of ongoing exploration in treatment strategies.

Small cell lung cancer (SCLC) accounts for approximately 15–20% of all lung cancer cases and is more malignant than other types of lung cancer. It progresses rapidly, has a high risk of early metastasis, and has a 5-year survival rate of less than 7% in patients with extensive disease.[6] Currently, immune checkpoint inhibitors, particularly PD-1/PD-L1 inhibitors, have shown promising results in patients with high tumor mutational burden or PD-L1-positive GC or SCLC as a single tumor type. However, their role in patients with concurrent AFPGC and SCLC has not been explored. Such cases not only face the risk of synergistic deterioration from two highly aggressive tumors but also require treatment strategies that address drug interactions and cumulative toxicity issues. This study reports the first case of a patient with concurrent AFPGC and primary SCLC, exploring the potential clinical value of chemotherapy combined with immunotherapy, and providing new insights for the comprehensive management of rare concurrent primary cancers.

Case Presentation

The patient is a 72-year-old male, underwent a physical examination on June 9, 2022, which revealed elevated tumor markers: AFP (Alpha-fetoprotein) 430 μg/L. A chest computed tomography (CT) scan at the local hospital showed a 2.5 cm mass in the lower lobe of the right lung. A PET-CT scan revealed multiple solid nodules in both lungs, the largest of which was located in the right lower lobe (2.3×2.2 cm, SUVmax 4.2), thickening of the greater curvature wall of the stomach (SUVmax 6.3), thickening of the gastric fundus (SUVmax 3.2), and associated lymph node metastasis (2.0×1.7 cm). Multiple nodular shadows in the hepatic portal and portal-venous regions, the largest measuring 0.6×1.7 cm, SUVmax 2.0, cannot rule out metastasis (Figure 1). On June 27, 2022, tumor markers were rechecked at the West Lake Hospital of the China Academy of Traditional Chinese Medicine: AFP 502 μg/L. On July 4, 2022, a gastroscopy biopsy was performed at Peking University Third Hospital: Moderately to poorly differentiated adenocarcinoma, Lauren intestinal type. Immunohistochemistry: Syn (Diffuse+), CD56 (-),TTF-1 (-), Cmet (-), EGFR (1+), HER2 (0), pan-TRK (-), EBER (-), PD-L1 (+), Proficient mismatch repair (pMMR). Genetic testing: MicroSatellite Stable (MSS), TP53 mutation, Tumor mutation burden (TMB) 10.03Muts/Mb, PD-L1 Combined Positive Score (CPS)<1. The patient has a 40-year history of hypertension, currently managed with telmisartan, with blood pressure control adequate. There is a family history of cancer: the father had gastric cancer, and the mother had esophageal cancer. However, the patient and their family explicitly declined to undergo germline mutation testing and other related genetic tests due to concerns about the high financial costs. On admission, the patient had an Eastern Cooperative Oncology Group (ECOG) score of 0, body surface area of 2.05 m^2, and no obvious positive findings. Based on the patient's relevant test results, the Western medical diagnosis was gastric malignant tumor (moderately to poorly differentiated adenocarcinoma, AFPGC), lymph node metastasis around the stomach, and a space-occupying lesion in the right lower lobe of the lung. Since the patient explicitly refused lung biopsy, our department

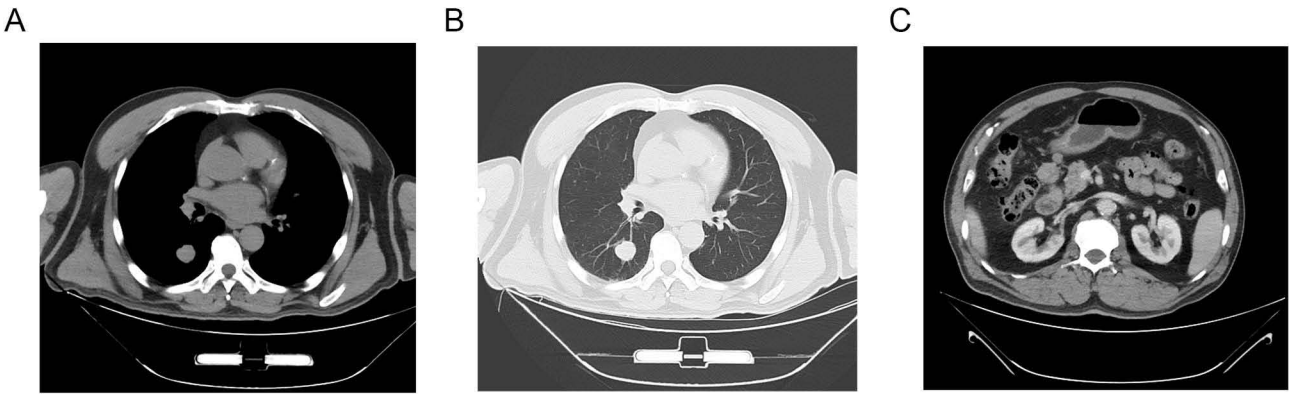

Figure 1 The baseline CT scan results of the patient's chest and abdomen (July 15, 2022). (**A**) The patient's chest CT mediastinal window reveals multiple solid nodules in both lungs, with the largest located in the right lower lobe (2.3×2.2 cm). (**B**) Patient's chest CT image in lung window. (**C**) The abdominal CT scan reveals thickening of the greater curvature wall of the stomach, thickening of the gastric fundus, and metastatic lymph nodes around the stomach (2.0×1.7 cm).

discussed in July 2022: The diagnosis was advanced gastric cancer, with the nature of the pulmonary lesions undetermined and metastasis not ruled out. It was proposed to follow the first-line treatment protocol for advanced gastric cancer. If the pulmonary lesions showed synchronous shrinkage in response to treatment, the patient would transition to maintenance therapy after completing the original treatment protocol. If the pulmonary lesions did not respond synchronously with the primary tumor, another lung biopsy would be recommended to guide the treatment plan.

The patient underwent four cycles of CAPEOX plus tislelizumab chemotherapy combined with immunotherapy in our department on July 15, August 10, August 30, and September 20, 2022. Specific regimen: Capecitabine 2 g bid on days 1–14 + Oxaliplatin 200 mg on day 1 + Tislelizumab 200 mg on day 1. Follow-up chest and abdominal CT scan on August 31, 2022: Multiple small nodules in both lungs, with the lesion in the right lower lobe slightly enlarged compared to previous scans; thickening of the gastric antrum wall, with multiple enlarged lymph nodes in the surrounding area. Compared with baseline imaging (July 15, 2022), the lymph nodes around the gastric antrum have decreased in size. Tumor marker tests on September 20, 2022: CEA 5.14μg/L, AFP 7.23μg/L, CA199 0.69 U/mL. The patient discontinued treatment due to personal reasons. Follow-up chest and abdominal CT scan on February 11, 2023: Compared with the CT scan on August 31, 2022, the nodule in the lower lobe of the right lung has slightly increased in size (2.3×2.6 cm), the gastric antrum wall is slightly thickened, and the lymph nodes around the gastric antrum have decreased in size. Response assessment: stable disease (SD) for the enlarged lesion in the lung, partial response (PR) for the lymph nodes around the stomach. The patient agreed to undergo a lung biopsy, and on February 21, 2023, a pathological consultation was conducted at Peking University Cancer Hospital (PUCCH): Immunophenotyping suggested small cell carcinoma. Immunohistochemistry: CK7 (–), CK5/6 (–), CK20 (–), CgA (+), Syn (+). ProGRP: 440.90 pg/mL. Based on these results, PUC conducted a multidisciplinary discussion (MDT) and concluded that the possibility of dual primary tumors could not be ruled out, and surgery was not recommended at this time. Considering the patient's response to CAPEOX plus tislelizumab therapy, the original treatment regimen was repeated for two cycles in April 2023 (same dosage as before).Following a follow-up chest and abdominal CT scan in May 2023, the response was assessed as persistent PR for gastric lymph nodes and SD for the right lung lesion (Figure 2). From May 2023 to February 2024, the patient underwent 14 cycles of first-line maintenance therapy, specifically with tegafur gimeracil oteracil potassium capsule (teysuno) (60 mg bid) plus tislelizumab (200 mg on day 1). Regular follow-up evaluations showed the same results as before. The patient experienced progressive worsening of gastric discomfort due to the use of teysuno capsules, so teysuno was discontinued. From March 2024 to March 2025, the patient underwent 15–28 cycles of immunotherapy maintenance treatment with tislelizumab (200 mg on day 1). After follow-up in March 2025, the evaluation results were as follows: Peripheral lymph nodes maintained PR, right lung lesion SD (Figure 3). Alpha-fetoprotein (AFP) isoform measurement: AFP 1.56μg/L; AFP isoform ratio: < 5% (reference range 0–10.00) (Figure 4). The patient was in good condition at the time of the last admission, with no significant discomfort. Physical examination revealed an ECOG score of 0, with no significant positive findings. It is proposed that the patient will continue subsequent maintenance therapy at this hospital. The timeline of cancer history is graphically displayed in Figure 5.

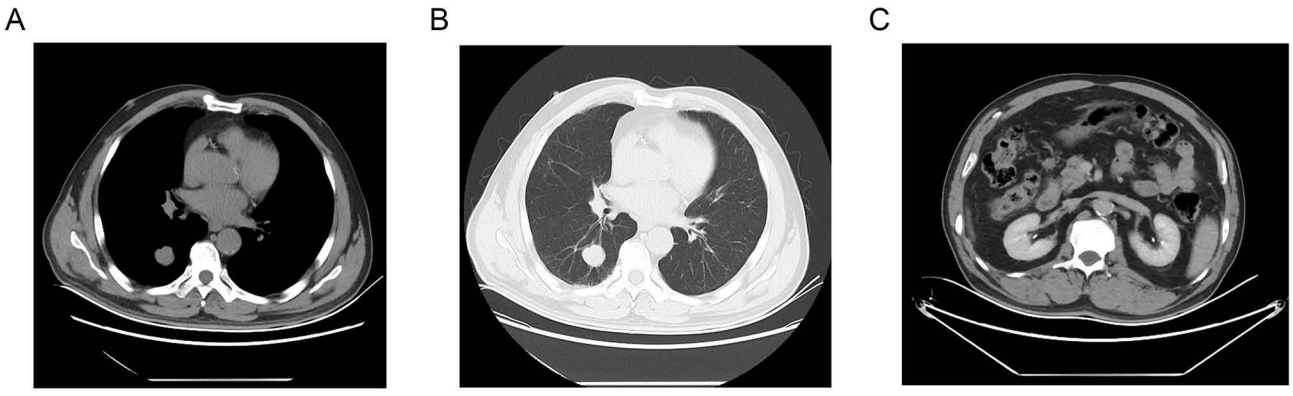

Figure 2 Chest and abdominal CT scan results prior to the patient entering the maintenance therapy phase (May 25, 2023). (**A**) The patient's chest CT mediastinal window reveals multiple solid nodules in both lungs. The largest nodule is located in the right lower lobe and remains stable compared to previous findings (2.5×2.4 cm). (**B**) Patient's chest CT image in lung window. (**C**) Abdominal CT reveals thickening of the greater curvature wall and gastric fundus, with perigastric lymph nodes showing reduced size compared to previous imaging (1.4×1.5 cm).

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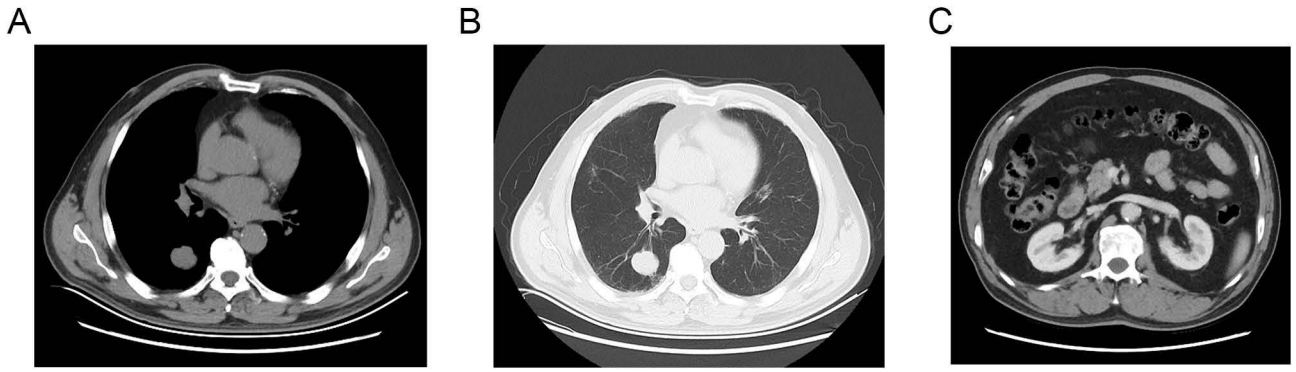

Figure 3 Chest and abdominal CT scan results prior to the patient's last hospitalization (March 25, 2025). (**A**) The patient's chest CT mediastinal window reveals multiple solid nodules in both lungs. The largest nodule is located in the right lower lobe and remains stable compared to previous findings (2.9×2.6 cm). (**B**) Patient's chest CT image in lung window. (**C**) Abdominal CT scan reveals thickening of the greater curvature of the stomach and thickening of the gastric fundus, with perigastric lymph nodes showing reduced size compared to previous findings (1.1×1.4 cm).

Discussion

This study reports the first case of simultaneous occurrence of AFPGC and SCLC, two highly aggressive primary tumors. Since Bourreille first reported AFPGC liver metastasis in 1970, researchers have gradually recognized that various cancers, including gastric cancer, colorectal cancer, gallbladder cancer, and lung cancer, can produce AFP to varying degrees, with gastric cancer having the highest probability of AFP production.[7] An analysis of the results from 11 clinical studies in China revealed that AFPGC patients have larger tumor volumes, poorer cellular differentiation, worse histopathological types, deeper serosal invasion, more lymph node and liver metastases, poorer staging, shorter survival times, and significantly higher positive expression of vascular endothelial growth factor compared to non-AFPGC patients,[8] resulting in overall poor prognosis.

Based on National Comprehensive Cancer Network (NCCN) guideline recommendations and multiple high-quality clinical studies, the efficacy of tislelizumab in GC and SCLC has been established. Therefore, we selected this immunotherapy for the treatment of this patient with dual primary tumors. The RATIONALE-305 study[9] demonstrated that in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, regardless of PD-L1 expression status, tislelizumab plus chemotherapy compared with placebo plus chemotherapy resulted in a statistically significant improvement in overall survival (OS) in patients with a PD-L1 TAP score ≥5% (median 17.2 months vs 12.6 months) across all randomized subgroups (median 15.0 months vs 12.9 months; P=0.001). The RATIONALE-312 study[10] demonstrated a statistically significant OS benefit for tislelizumab plus chemotherapy versus placebo plus chemotherapy in patients with extensive-stage SCLC receiving first-line treatment (p=0.0040; 15.5 vs 13.5 months), with a significant improvement in progression-free survival (PFS) ($p < 0.0001$; 4.7 vs 4.3 months). The patient in this case demonstrated clear long-term benefit from immune maintenance therapy, further validating the efficacy and safety of tislelizumab in both maintenance treatment phases for these tumors.

In recent years, immune checkpoint inhibitors such as pembrolizumab, nivolumab, and tislelizumab (as reported in the RATIONALE 305 study) have been successively approved for inclusion in gastric cancer treatment guidelines. There are also relevant clinical reports regarding the treatment of AFPGC. Studies have shown that the combination of sepalimab with lenvatinib and chemotherapy in a chemotherapeutic, targeted, and immunotherapy regimen can effectively improve survival in AFPGC patients. In this study, the objective response rate (ORR) reached 33.3%, with median progression-free survival (mPFS) and overall survival (OS) of 7.67 months (95% CI 4.07–11.27) and 13.17 months (95% CI 2.78–23.56), respectively.[11] In a study comparing nivolumab combined with chemotherapy to trastuzumab/apatinib combined with or without chemotherapy, after 28 months of follow-up, the mPFS was 22 months versus 4.3 months in the control group, with the mOS in the control group being 16 months, while the mOS for patients receiving nivolumab immunotherapy had not yet been reached.[12] Related case reports indicate that tislelizumab combined with the SOX chemotherapy regimen[13] and atezolizumab combined with irinotecan and sorafenib capsules[14] both demonstrated corresponding clinical benefits. However, overall, the survival outcomes of APFGC treatment remain limited, and

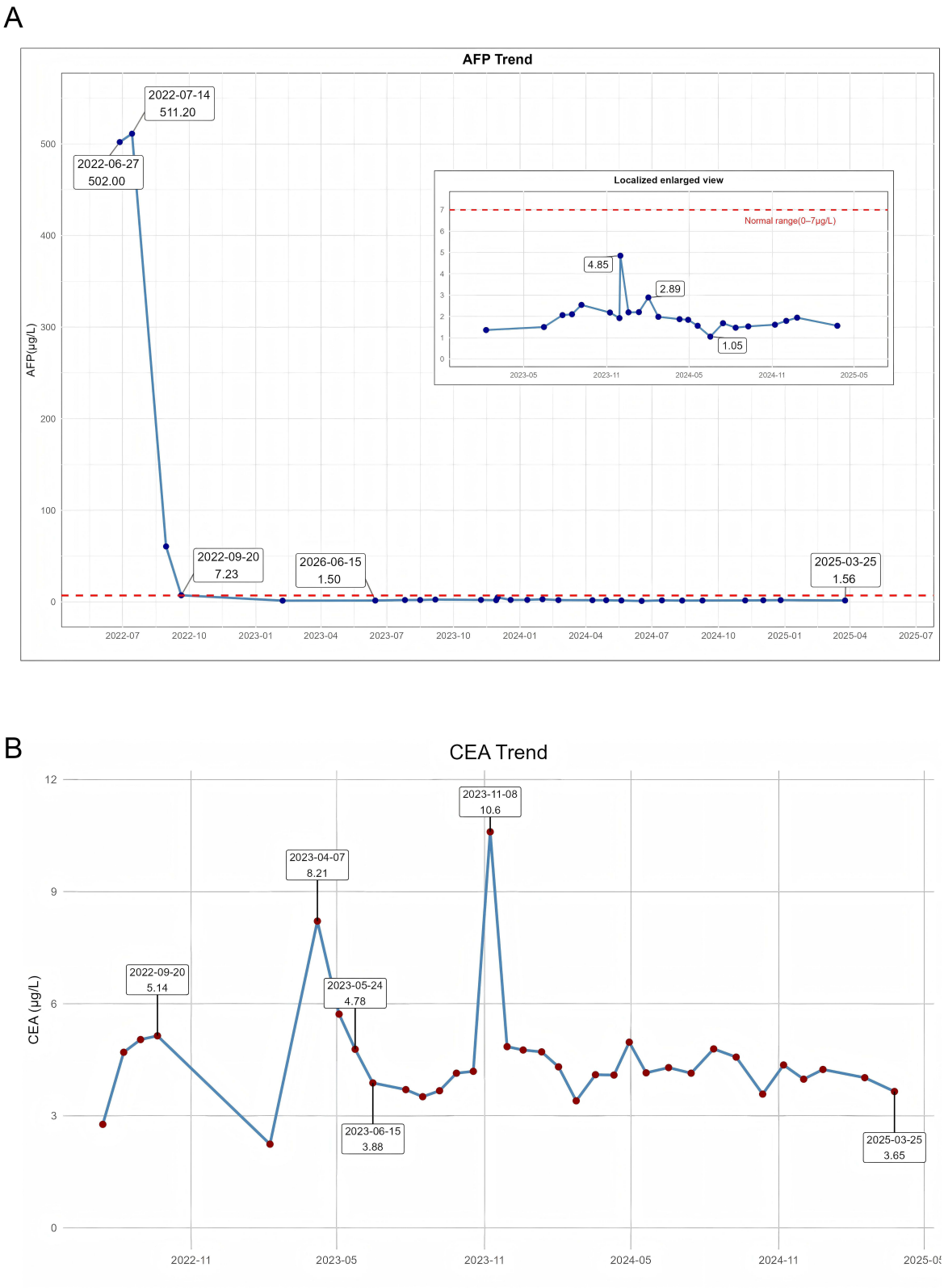

Figure 4 Biomarker change curve graph (**A**) Curve graph of changes in the patient's Alpha-fetoprotein index (Reference value 0.00–7.00μg/L) (**B**) Curve graph of changes in the patient's Carcinoembryonic antigen index (Reference value: Non-smokers: <5.00μg/L).

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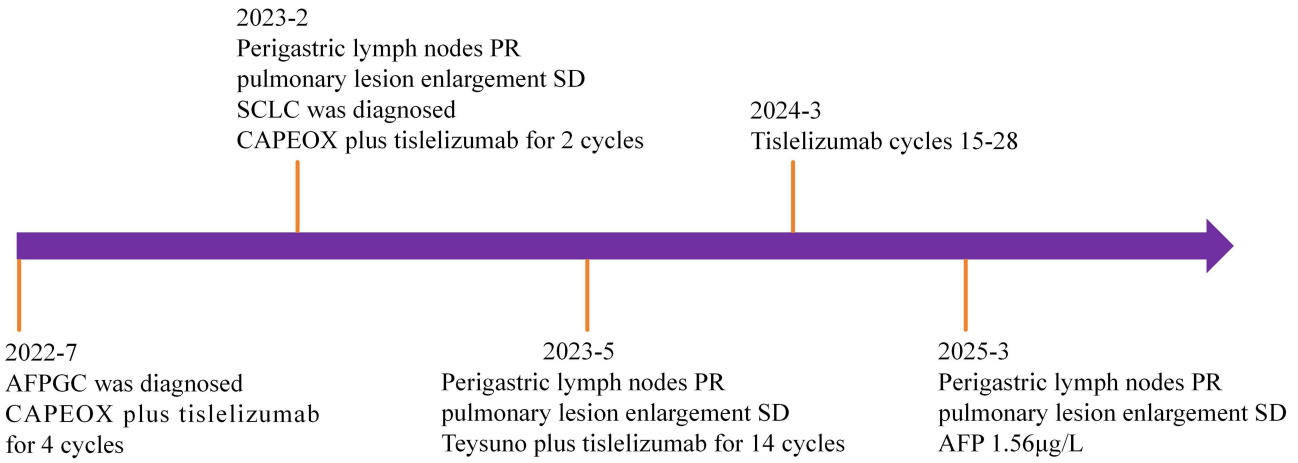

Figure 5 Timeline of disease treatment.

there are no large-scale clinical studies on the associated immunotherapy. Further clinical data accumulation and randomized controlled trial analyses are needed to determine the optimal treatment regimen.

In the treatment of extensive-stage small cell lung cancer, immunotherapy also plays a significant role. Studies such as CASPIAN have demonstrated that[15] the combination of PD-L1 inhibitors with chemotherapy can increase the 3-year survival rate for extensive-stage SCLC to 17.6%. Immunotherapy regimens combining immune checkpoint inhibitors such as atezolizumab, durvalumab, toripalimab, and tislelizumab with chemotherapy have become the core treatment strategy for extensive-stage SCLC.

In summary, there are currently no large-scale clinical studies on APFGC-related immunotherapy to provide more reliable evidence-based medical evidence. Although multiple standard treatment options are available for extensive-stage SCLC, the median survival period is only 8–12 months,[16] and only 10% of patients have a total survival period exceeding two years, indicating a high degree of tumor malignancy. There are currently no reported cases of concurrent or sequential coexistence of AFPGC and SCLC in the literature. In this case, the patient was diagnosed with AFPGC based on significantly elevated AFP levels detected during a physical examination and imaging studies. The patient underwent CAPEOX chemotherapy combined with immuno-therapy using tislelizumab. Subsequently, while the gastric lesions responded to treatment, the pulmonary lesions progressed to SD. After a pathological biopsy, concurrent SCLC was confirmed, and it was classified as extensive stage. Considering the efficacy of the previous regimen, the original regimen was continued, and the patient entered maintenance therapy. During this period, regular follow-up evaluations showed that both lesions were stable and controlled. The patient is currently undergoing maintenance immunotherapy with tislelizumab and is undergoing regular follow-up. In this case report, the patient presented with two primary malignant tumors simultaneously. After appropriate treatment, the patient's first-line PFS has now exceeded 33 months, with significant prolongation of survival benefit, demonstrating feasibility and potentially providing a viable treatment option for similar patients in future clinical practice.

Conclusion

In this first-reported case of long-term treatment, we validated the therapeutic efficacy of chemotherapy combined with immunotherapy (CAPEOX plus tislelizumab) for the rare aggressive dual primary tumors AFPGC and SCLC. The long-term maintenance immunotherapy demonstrated significant benefits, markedly prolonging the patient's progression-free survival. Concurrently, this case demonstrates the efficacy and safety of tislelizumab during maintenance therapy for both tumors, offering a novel therapeutic option for managing such complex clinical presentations.

Informed Consent

The patient has consented for the publication of identifiable details, which can include photograph(s) and/or videos and/or case history and/or details within the text ("Material") to be published in the Journal and Article. Publication of case details does not require institutional approval.

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Disclosure

Th authors report no conflicts of interest in this work.

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