Immunotherapy for primary squamous cell carcinoma of the liver: A case report

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Received December 14, 2024; Accepted March 21, 2025

DOI: 10.3892/ol.2025.15025

Abstract. The present study reports an exceedingly rare case of primary squamous cell carcinoma of the liver (PSCCL), a malignancy that has been documented in only ~30 cases worldwide, with both diagnosis and treatment presenting significant challenges. A 72-year-old man presented with right upper abdominal discomfort was admitted to Shaanxi Provincial Cancer Hospital (Xi'an, China). Computed tomography (CT) imaging revealed a space-occupying lesion in the liver. A subsequent percutaneous liver biopsy confirmed a diagnosis of PSCCL. Positron emission tomography/CT was performed to exclude metastasis from other primary sites and confirmed the diagnosis of PSCCL. The patient received combination therapy of envafolimab and albumin-paclitaxel plus cisplatin. Telephone follow-up continued until December 2024 (a total of 18 months), during which the patient achieved and maintained a sustained partial response. The uniqueness of the present case lies in the patient's receipt of an innovative therapeutic regimen combining envafolimab with albumin-paclitaxel and cisplatin, achieving a sustained partial response over an 18-month follow-up period. This outcome not only offers novel insights for the clinical management of PSCCL but also underscores the importance of multidisciplinary comprehensive treatment in rare tumors.

Introduction

Primary squamous cell carcinoma of the liver (PSCCL) is an exceedingly rare malignancy, with only ~30 cases reported worldwide according to the available literature (1). Unlike hepatocellular carcinoma (HCC), PSCCL lacks specific laboratory tests and imaging characteristics, making diagnosis challenging. It is important to exclude metastatic SCC from other sites in the differential diagnosis, and histopathological examination remains the gold standard for diagnosis (2).

PSCCL occurs in the liver, which lacks squamous epithelium, and its pathogenesis is not fully understood. Research suggests that chronic inflammation and liver injury (e.g., chronic cholangitis, congenital biliary cysts, hepatic cysts, infections and stones) may be primary causes (3). Histopathologically, PSCCL features keratin pearls, polygonal cancer cells with abundant cytoplasm and prominent nucleoli, intercellular bridges, and positive cytokeratin (CK)5/6 and tumor protein p63 (p63) staining. These features help distinguish PSCCL from other liver tumors and exclude metastatic SCCs. The present case is unique as the patient received an innovative treatment combining envafolimab, albumin-paclitaxel and cisplatin, achieving sustained remission over 18 months. This provides new insights for PSCCL diagnosis and treatment.

Case report

A 72-year-old man was admitted to Shaanxi Provincial Cancer Hospital (Xi'an, China) in July 2023 with a diagnosis of a hepatic space-occupying lesion. The patient had previously experienced pain in the liver region and underwent an upper abdominal computed tomography (CT) scan at a local hospital. The CT scan revealed an intrahepatic lamellar shadow of slightly reduced density, indicative of a space-occupying lesion. Slight dilatation of the common bile duct was also observed, along with a left renal cyst. Tumor marker evaluations performed at Shaanxi Provincial Cancer Hospital showed significantly elevated levels of carcinoembryonic antigen (CEA) at 40.10 ng/ml (reference range, 0-5.5 ng/ml), carbohydrate antigen 199 (CA19-9) at 335.2 IU/ml (reference range, 0-28 IU/ml) and ferritin at 1,184.10 ng/ml (reference range, 25-350 ng/ml). The patient also reported recent weight loss of ~5 kg over a period of ~10 days. The patient had a history of gallstones diagnosed 10 years prior and underwent a cholecystectomy in 2019.

On admission in July 2023, the Eastern Cooperative Oncology Group (ECOG; https://ecog-acrin.

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Key words: cancer, primary squamous cell carcinoma of the liver, case report, envafolimab

org/resources/ecog-performance-status/) performance status score was 1 and the Numerical Rating Scale (NRS; with 0 indicating no pain and 10 indicating the most severe pain) score for pain was 1. A physical examination revealed an enlarged liver palpable in the right upper abdomen, with positive percussion tenderness. Laboratory findings upon admission showed elevated tumor markers, including CEA at 40.10 ng/ml, CA-50 at 223.5 IU/ml (reference value, 0-20 IU/ml), CA19-9 at 335.2 IU/ml and CA24-2 at >200 IU/ml (reference value, 0-20 IU/ml). Liver function tests showed decreased albumin at 36.9 g/l (reference value, 40-55 g/l) and elevated aspartate transferase (AST) at 73 U/l (reference value, 7-50 U/l).

CT imaging showed multiple low-density nodules and masses beneath the capsule of the right hepatic lobe and within the right lobe of the liver, raising suspicion for potential hepatocellular carcinoma or intrahepatic cholangiocarcinoma with subperitoneal and intrahepatic multiple metastases (Fig. 1A). Thrombus formation was noted in the lumen of the right branch of the portal vein (Fig. 1B). The gallbladder was not clearly visualized. The kidneys showed multiple cysts. Multiple enlarged lymph nodes were identified in the posterior mediastinal paraspinal region, hepatic hilum and retroperitoneum, some of which were partially fused, suggestive of metastatic disease (Fig. 1C).

A liver biopsy was performed 3 days after admission. Histopathological examination revealed an invasive, poorly differentiated carcinoma of the liver, with histopathological features suggestive of a poorly differentiated SCC (Fig. 2A and B). Immunohistochemical results showed Ki-67 positivity in 80% of cells (Fig. 2C), a lack of synaptophysin expression (Fig. 2D), partial positivity for p63 (Fig. 2E), p40 (Fig. 2F), partial positivity for CK5/6 (Fig. 2G) and positivity for pan cytokeratin (CKpan) (Fig. 2H). Other positive immunohistochemical markers included CK7 (Fig. 2I), CK20 (Fig. 2J), villin (Fig. 2K), hepatocyte paraffin 1 (Fig. 2L), glypican-3 (Fig. 2M), CK19, GATA binding protein 3, caudal type homeobox transcription factor 2, uroplakin III, nuclear protein in testis, thyroid transcription factor 1, SWI/SNF related matrix-associated actin dependent regulator of chromatin subfamily a member 4/Brahma-related gene 1, and INI1 protein (data not shown). Programmed death-ligand 1 (PD-L1) expression detected using the 22C3 antibody showed a combined positive score (CPS) of 5 [(number of PD-L1-positive tumor cells + number of PD-L1-positive immune cells)/total number of tumor cells x100; Fig. 2N and O].

Given the rarity of hepatic SCC, a positron emission tomography (PET)/CT scan was performed to exclude the possibility of metastases from other primary sites. The PET/CT findings were as follows: An irregular mass was observed in the right lobe of the liver (Fig. 3A). Multiple low-density nodules were identified within the liver, as well as multiple enlarged lymph nodes in the hepatic hilum, posterior to both diaphragmatic crura, around the abdominal aorta in the retroperitoneum, and at the root of the mesentery (Fig. 3B). Additional enlarged lymph nodes were noted in the upper abdominal peritoneal area, posterior mediastinum, around the esophagus, the right axillary area (Fig. 3C) and the left clavicular area (Fig. 3D). Bone destruction was observed in the left transverse process of the sixth cervical vertebra (Fig. 3E), and in the left 10th and 11th posterior ribs (Fig. 3F), suggestive of metastases.

The increased glucose metabolism observed in these regions suggested a primary malignant hepatic lesion, possibly intrahepatic cholangiocarcinoma, with intrahepatic metastasis, multiple lymph node metastases and bone metastases. No other primary tumors were detected. Based on the pathology and imaging findings, a final diagnosis of PSCCL was made.

After multidisciplinary discussion, the patient was treated with envafolimab (200 mg subcutaneously once weekly) in combination with albumin-paclitaxel (200 mg on day 1 and 100 mg on day 5) plus cisplatin (30 mg on days 1-3). After two cycles (each cycle lasting 21 days), the efficacy evaluation indicated a partial response (PR) (Fig. 4A and B), which was sustained on subsequent evaluation (Fig. 4C). The tumor, initially shown on CT in July 2023 as multiple low-density nodules and a mass in the subcapsular region of the right lobe of the liver, with the largest measuring ~8.2x7.8 cm, had shrunk to 5.4x5.1 cm upon re-examination in September 2023, and further reduced to 3.3x3.0 cm when reviewed at Shaanxi Provincial Cancer Hospital in 2024. Following treatment, the patient's pain was significantly alleviated, physical strength was gradually recovered and mental status was improved. The various symptoms subsided, indicating a marked treatment effect. The multiple metastases were effectively controlled, the tumors significantly reduced in size, the tumor marker levels continued to decline (Fig. 5) and the patient's condition tended to be stable. With the improvement of physical condition, the patient's quality of life was also greatly enhanced, with normal mobility and diet. Telephone follow-up continued until December 2024 (a total of 18 months), during which time the patient maintained a sustained PR. Tumor marker levels continue to fall.

Tissue staining methods. Tissues were fixed in 10% neutral formalin for 6-24 h. The tissues were sectioned to a 3- to 4-μm thickness. For hematoxylin and eosin staining, hematoxylin was added for 3-5 min, followed by eosin for 2-10 sec, all at room temperature. Staining was evaluated using a light microscope. For immunohistochemical analysis, the EnVision two-step method was used. The primary and secondary antibodies used were ready-to-use antibodies, all purchased from Fuzhou Maixin Biotechnology Development Co., Ltd. The PD-L1 (clone 22C3) antibody was also ready-to-use and purchase from Dako; Agilent Technologies, Inc. All staining was performed using an automated immunohistochemical staining machine and performed according to the manufacturer's instructions.

Discussion

PSCCL is an extremely rare malignant tumor, with only ~30 cases reported in the literature worldwide. Squamous epithelial tissue is commonly found in areas such as the esophagus, trachea, pharynx, skin and vulva. Since the liver lacks squamous epithelial tissue, metastasis from other SCCs must be excluded when diagnosing PSCCL. The etiology of PSCCL remains unclear, with potential associations suggested with solitary non-parasitic liver cysts, developmental liver cysts (4-6), intrahepatic bile duct stones (7), gallstones, chronic cholangitis, hepatic teratoma, liver cirrhosis (8), and other related diseases.

Several theories have been proposed regarding the pathogenesis of PSCCL. Chronic inflammation from conditions such as chronic cholangitis, congenital biliary cysts or hepatic

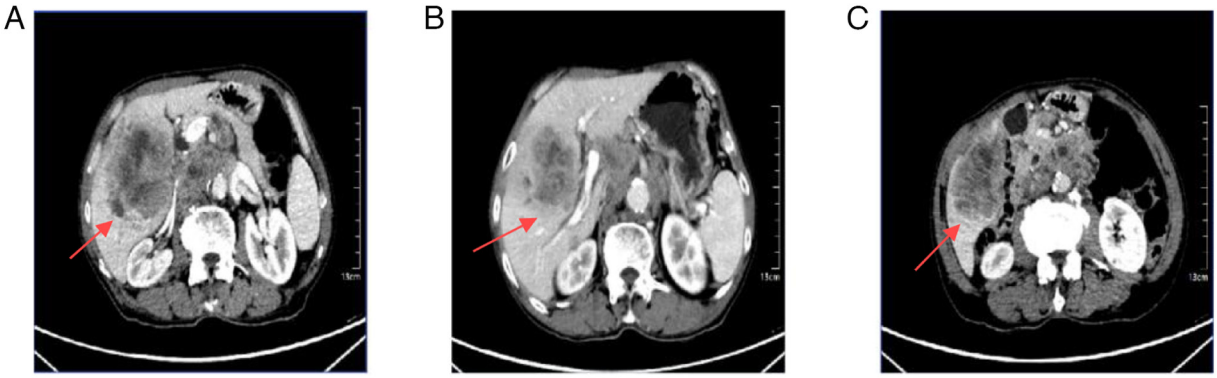


Figure 1. Abdominal computed tomography images at the patient's initial consultation. (A) Multiple intrahepatic metastases (arrow). (B) Thrombus formation within the right branch of the portal vein (arrow). (C) Multiple enlarged lymph nodes in the retroperitoneal paraspinal region, hepatic hilum and retroperitoneum (arrow).

cysts combined with infections and stones are considered the main etiological factors. Hepatic pluripotent stem cells can be transformed into cancerous tissue containing squamous cells, hepatocytes and biliary epithelial cells in response to various oncogenic factors, eventually developing into SCC. The development of most SCCs is considered to be associated with squamous metaplasia and progressive carcinoma of the epithelial cells of the biliary tract or cyst wall stimulated by chronic inflammation, leading to malignant transformation (9).

Clinically, PSCCL lacks specific symptoms and laboratory markers, making it difficult to distinguish from other hepatic malignancies. Liver function tests may show abnormalities similar to those seen in HCC, such as elevated alanine aminotransferase (10), AST (11) and bilirubin (12) levels. Tumor markers such as α-fetoprotein (13,14), SCC antigen and CA19-9 (15,16) may be elevated, but are not specific to PSCCL. SCC antigen has diagnostic value in SCC, but is mainly used for the diagnosis and monitoring of lung (17), head and neck (18), and cervical (19) cancer. To date, there remains a lack of specific serum markers for diagnosing PSCCL. In the present case, laboratory tests demonstrated significant elevations of CEA and CA19-9, consistent with the characteristics of gastrointestinal tract tumors, but other indices were normal.

CT imaging of PSCCL typically shows mild hypodense shadows, occasionally with cystic components. Persistent enhancement is observed in both the portal and delayed phases. Enhanced imaging demonstrates enhanced lesion margins in the arterial phase with lobulated features. Mild enhancement is observed in the center of the lesion, with persistent enhancement in the delayed phase (20). A CT scan alone is insufficient to diagnose PSCCL. For example, in some patients, no discernible hepatic mass is exhibited on CT, and only hepatic cysts or intrahepatic stones are observed, but the postoperative pathology indicates SCC. In the present case, the initial CT of the patient suggested a hepatic space-occupying lesion. To the best of our knowledge, limited literature exists on the use of PET/CT in diagnosing PSCCL. The PET/CT images of the present patient showed an irregular mass in the right lobe of the liver, multiple intrahepatic hypodense nodules, multiple lymph node metastases and bone metastases, helping to exclude metastasis from other systems. Based on these findings, a final diagnosis of PSCCL was made.

Histopathological examination remains the gold standard for diagnosing PSCCL. Key pathological features include keratinized cell clusters forming keratin pearls, polygonal cancer cells with abundant cytoplasm and prominent nucleoli, evident intercellular bridges, and positive immunohistochemical staining for markers such as CK5/6 and p63. Metastasis from other SCCs must be rigorously excluded (21).

In the present case, histopathological examination of the biopsy tissue showed cancer cells arranged in sheets forming nests, with polygonal cells, abundant cytoplasm, large nuclei, nuclear pleomorphism, prominent nucleoli and numerous mitotic figures. Keratinization was observed in the center of the nests, arranged concentrically to form cancer beads. The tumor parenchyma and stroma were clearly demarcated. Immunohistochemistry showed positive results for CK5/6, CKpan and p63. No lesions were seen on chest CT, leading to a final diagnosis of PSCCL.

Treatment options for PSCCL include surgery, chemotherapy, radiotherapy and immunotherapy. Okuda *et al* (22) reported that early stage PSCCL can be surgically resected with no recurrence for >1.5 years postoperatively. Zhang *et al* (23) reported that among 19 surgically resected cases, 8 survived for >12 months, while 11 died within a year. Within this study, 1 patient experienced tumor recurrence and died from metastatic disease 18 months after radical surgery (23). Surgical resection is the mainstay for early stage disease and can result in prolonged survival times. However, most patients are diagnosed at advanced stages when surgery is not feasible. Lee *et al* reported that patients who refused surgery and were treated with chemotherapy using carboplatin combined with 5-fluorouracil had an overall survival time of >8 months (24). Regarding radiotherapy, it was reported that patients with PSCCL who were physically unable to undergo chemotherapy were treated with local radiotherapy and died 1 month after hospital discharge (25). Immunotherapy has shown efficacy in esophageal (26), lung (27), head and neck (28), and skin (29) SCC.

At the time of presentation, the current patient had multiple metastases and an advanced malignant tumor, making surgical resection impossible. Since basic research has found that SCCs are immunogenic, immune checkpoint inhibitors have become the standard first-line treatment option for these tumor types. The patient also had SCC, but PSCCL is a rare

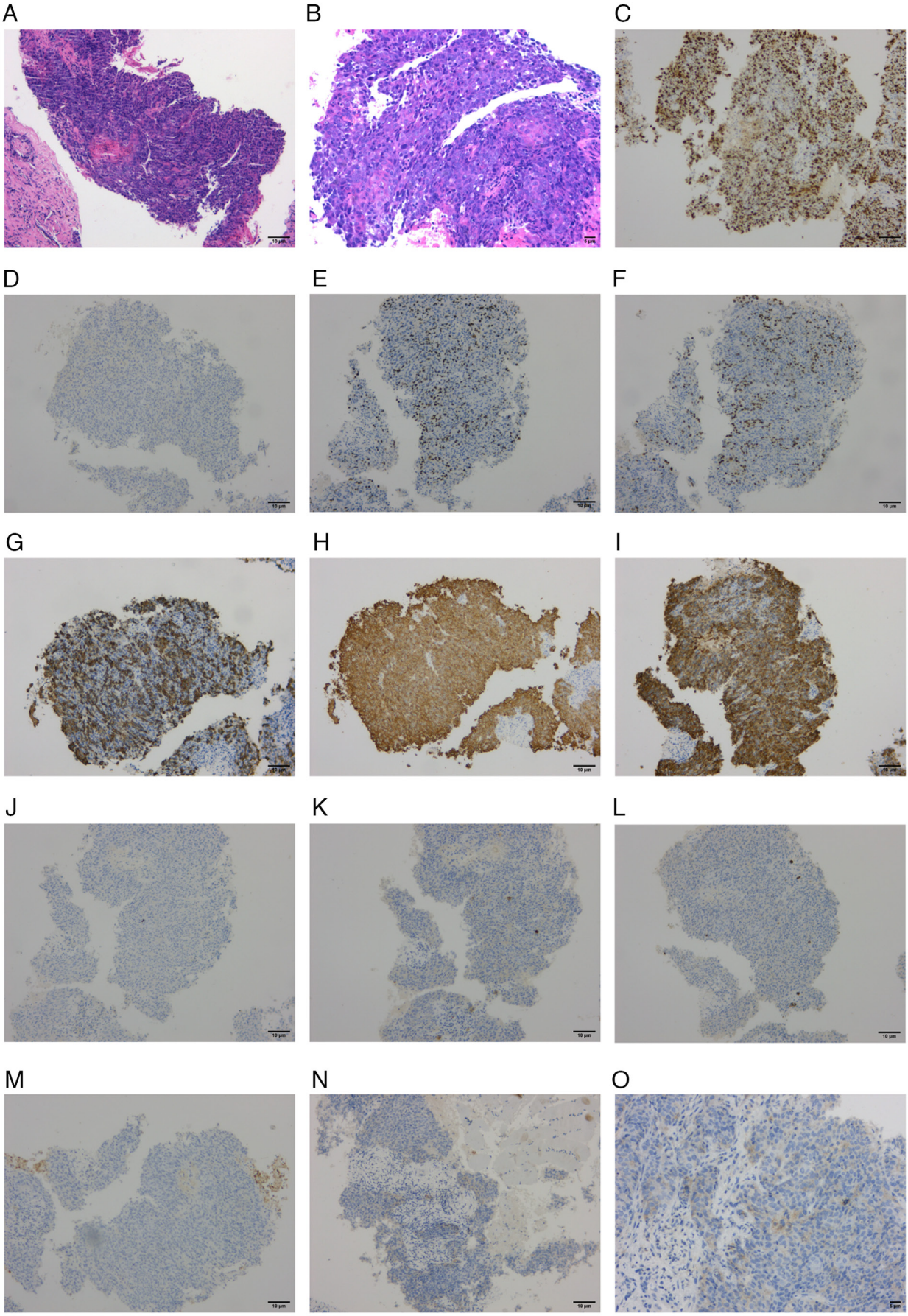


Figure 2. Histopathological and immunohistochemical results indicating squamous cell carcinoma. (A) H&E staining, x100 magnification. (B) H&E staining, x200 magnification. (C-M) Immunohistochemical staining at x100 magnification for (C) Ki-67, (D) synaptophysin, (E) tumor protein p63, (F) tumor protein p40, (G) CK5/6, (H) pan CK, (I) CK7, (J) CK20, (K) villin, (L) hepatocyte paraffin 1 and (M) glypican-3. (N and O) Immunohistochemical staining for programmed death-ligand 1 at (N) x100 magnification and (O) x200 magnification. H&E, hematoxylin and eosin; CK, cytokeratin.

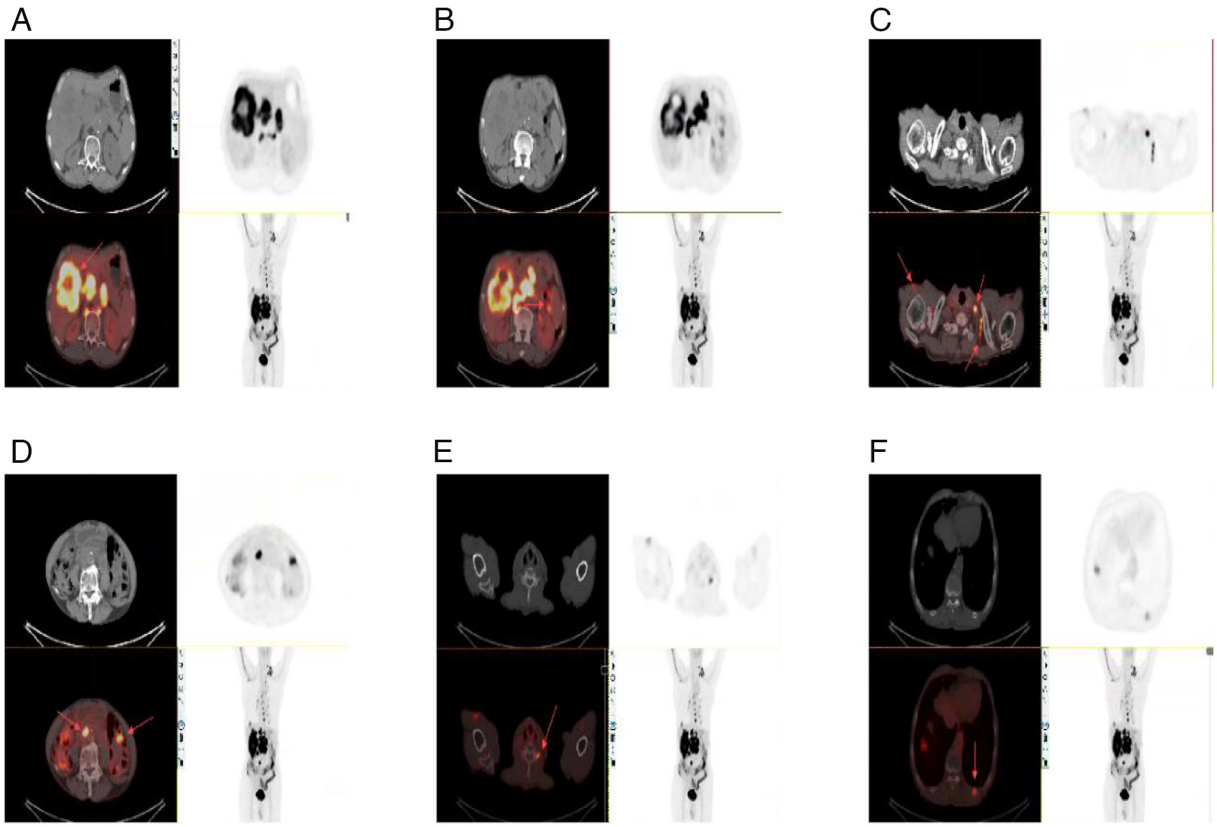


Figure 3. Positron emission tomography/computed tomography images demonstrating disease progression. (A) Irregular mass in the right lobe of the liver suggesting a primary hepatic lesion (SUV_{max}, 14.0) (B) Bilateral enlarged lymph nodes posterior to the diaphragmatic crura, around the abdominal aorta in the retroperitoneum and at the mesenteric root (SUV_{max}, 14.9). (C) Multiple enlarged lymph nodes in the left clavicular region and right axilla (SUV_{max}, 4.5-12.4). (D) Lymph node metastases in the upper abdominal peritoneal region and around the thoracic aorta (SUV_{max}, 4.21-15.36). (E) Bone metastasis involving the left transverse process of the sixth cervical vertebra. (F) Bone destruction of the left 10th and 11th posterior ribs indicative of bone metastasis (SUV_{max}, 6.1). SUV_{max}, maximum standardized uptake value.

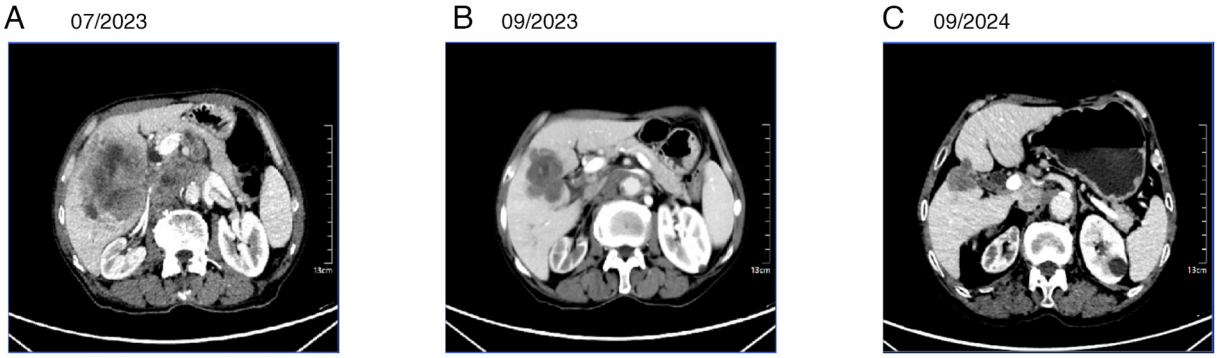
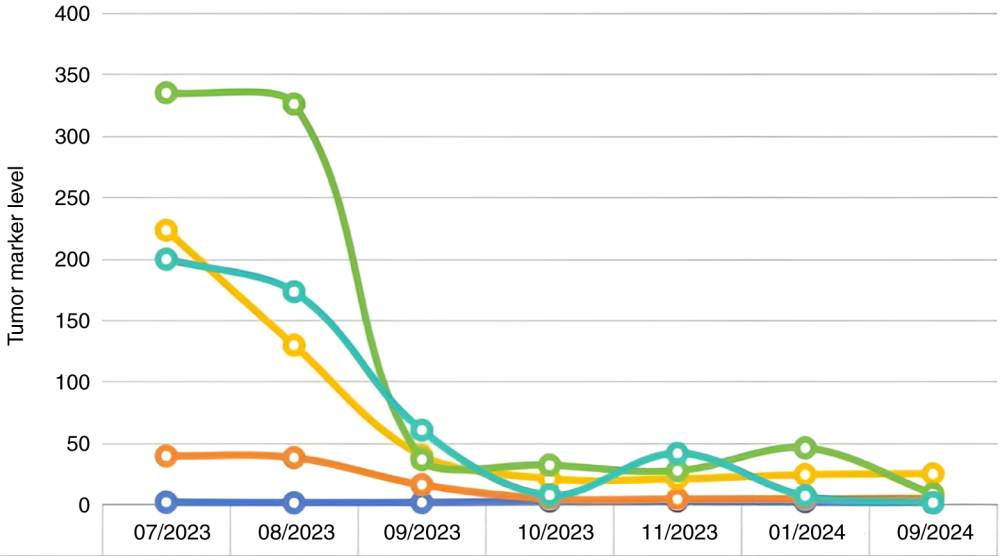


Figure 4. Abdominal CT images before and after treatment. (A) Initial abdominal CT at diagnosis. (B) Abdominal CT after two cycles of treatment showing a reduction in tumor size. (C) More recent follow-up abdominal CT demonstrating a sustained partial response. CT, computed tomography.

tumor, and there is a lack of large-scale clinical research data for reference. Therefore, the treatment selection was mainly based on the histopathological type and referencing of other tumors, using immune checkpoint inhibitors combined with paclitaxel and platinum drugs commonly used in SCC (30-34). Other studies suggest that immunotherapy combined with chemotherapy can improve progression-free survival and overall survival (OS); for example, gemcitabine combined with cisplatin and doxorubicin extended the OS time from 11.5 to 12.8 months, showing a statistically significant difference compared with conventional treatment (chemotherapy, radiotherapy and surgery) (35). After considering the current patient's age, physical condition and potential adverse effects, and after communicating with the patient's family, the safer (milder and more manageable side effects) PD-L1 inhibitor envafolimab (36) combined with albumin-bound paclitaxel plus cisplatin regimen was selected for treatment.

The final regimen was envafolimab (200 mg subcutaneously once a week) combined with albumin-paclitaxel (200 mg on day 1 and 100 mg on day 5) plus cisplatin (30 mg on days



	07/2023	08/2023	09/2023	10/2023	11/2023	01/2024	09/2024
AFP (IU/ml)	2.55	2.07	2.28	3.24	3.29	2.82	1.95
CEA (ng/ml)	40.1	38.67	16.68	5.35	4.99	5.33	5.76
CA-50 (IU/ml)	223.5	130.1	40.49	21.54	21.47	24.86	25.54
CA19-9 (IU/ml)	335.2	326.1	37.21	32.65	28.11	46.63	9.33
CA24-2 (IU/ml)	200	173.5	61.08	8.36	42.25	7.77	2.11

Figure 5. Tumor marker levels over time. The patient's tumor markers show a continuously decreasing trend during the treatment process. AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

1-3). Albumin-bound paclitaxel promotes the polymerization of tubulin, inhibits mitosis of tumor cells and leads to cell apoptosis. Cisplatin binds to DNA, interfering with replication and transcription, exerting cytotoxic effects. The combination enhances the antitumor effect and improves the objective response rate and disease control rate. Envafolimab is a monoclonal antibody targeting PD-L1; it binds to human PD-L1 protein, blocking its interaction with the receptor programmed cell death protein 1 (PD-1). This mechanism can relieve the suppression of T cells by tumors through the PD-1/PD-L1 pathway, mobilize the antitumor activity of the immune system and thereby kill tumor cells (37,38). During two treatment cycles, efficacy was assessed as a PR. Follow-up to December 2024 (a total of 18 months) showed a sustained PR.

It has been demonstrated that patients with digestive system tumors exhibiting one or more of the following characteristics respond better to immunotherapy: Positive PD-L1 expression, high microsatellite instability (MSI-H) and defective mismatch repair (dMMR) (39). These patients are expected to achieve longer survival times with immunotherapy. The present patient had a CPS of 5, which may be advantageous in immunotherapy. If financial conditions permit, comprehensive genome sequencing of tumor samples using genetic testing and next-generation sequencing (NGS) can identify specific mutations associated with the tumor, aiding in the early diagnosis of rare tumors and identifying patients with high tumor mutational burden (TMB-H) (40) who will benefit from immunotherapy. Therefore, some scholars have proposed that rare tumors should undergo NGS testing (41). For example, data from a domestic phase II pivotal clinical trial demonstrated that envafolimab had favorable therapeutic efficacy in patients with MSI-H/dMMR advanced solid tumors (42). Clinical trials investigating the efficacy of immunotherapy in patients with advanced solid tumors and TMB-H have demonstrated that patients with TMB-H (TMB ≥20 mutations/Mb) may derive greater benefit from this approach, compared with those with TMB-L (43,44).

In conclusion, PSCCL is an extremely rare malignant tumor of the liver with an unclear pathogenesis. The majority of patients have a poor prognosis, often with survival times <1 year, typically ranging from 4 to 6 months (45). The clinical symptoms and laboratory tests for PSCCL lack specificity, and imaging examinations such as CT help in the preliminary diagnosis. However, a definitive diagnosis relies on histopathology and immunohistochemistry, making PSCCL challenging to diagnose. Additionally, clinicians often lack sufficient awareness of the disease, leading to late diagnoses and a lack of treatment guidelines, further complicating prognosis. Currently, the main treatment modality for PSCCL is surgery, supplemented by radiotherapy and immunotherapy. However, given the considerable variability in the treatment approaches among patients, there is an urgent need to further explore and optimize therapeutic strategies for PSCCL, including chemo-immunotherapy and immunotherapy alone. If financial conditions allow, genetic testing and NGS can provide more precise guidance for the treatment of PSCCL, offering additional information for the selection of clinical drugs.

Acknowledgements

Not applicable.

Funding

This study was supported by the Wu Jieping Medical Foundation Clinical Research Special Grant Fund (Project Name: Application of T-Cell Subsets Combined with Dynamic Monitoring of Blood ctDNA in Predicting the Efficacy of Immunotherapy in Advanced NSCLC Patients; grant no. 320.6750.2023-17-23) and the Xi'an Science and Technology Program (Construction of a Prediction Model for Immunotherapy in Advanced NSCLC Based on ctDNA and Peripheral Blood T-cell Subsets; grant no. 2024JH-YLYB-0176).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JJ was responsible for manuscript writing, data organization and data analysis. SL, JB, JM, and ZZ provided critical writing guidance and made revisions to the manuscript. Contributions included input on the study design, data analysis and interpretation, and ensuring the accuracy and integrity of the content. GD and JH were responsible for data collection and analysis, and the provision of medical images (PET/CT and CT scans). HG was responsible for immunohistochemical image analysis, data extraction and interpretation, result verification, anomaly investigation and manuscript revision. ZZ was responsible for the final review, overall supervision and funding acquisition. All authors have read and approved the final manuscript. SL and ZZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted in accordance with ethical standards.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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