OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

CASE REPORT

Long-Term Follow-Up of Combination Therapy with Sintilimab and Anlotinib in Gallbladder Follicular Dendritic Cell Sarcoma: A Rare Case Report

Jieping Yan[1,2], Xue Zhang[3], Lili Yu[4], Meihua Ye[4], Yun Chen[5]

[1]Clinical Pharmacy Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, 310014, People's Republic of China; [2]Key Laboratory of Endocrine Gland Diseases of Zhejiang Province, Hangzhou, 310014, People's Republic of China; [3]Department of Pharmacy, Kunming Yan'an Hospital, Yan'an Affiliated Hospital of Kunming Medical University, Kunming, Yunnan, 650051, People's Republic of China; [4]Department of Pathology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, 310014, People's Republic of China; [5]Cancer Center, Department of Oncology, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, 310014, People's Republic of China

Correspondence: Jieping Yan, Clinical Pharmacy Center, Department of Pharmacy, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, 158 Shangtang Road, Hangzhou, 310014, People's Republic of China, Tel +86 571 85893117, Email yanjieping@hmc.edu.cn; Yun Chen, Department of Oncology, Zhejiang Provincial People's Hospital, People's Hospital of Hangzhou Medical College, 158 Shangtang Road, Hangzhou, 310014, People's Republic of China, Tel +86 571 85893609, Email chenyun@hmc.edu.cn

Abstract: Follicular dendritic cell sarcoma (FDCS) is a rare malignant neoplasm for which a standardized treatment approach has yet to be established. The prevailing therapeutic strategy typically involves resection followed by adjuvant chemotherapy or radiation. This case report details the long-term follow-up of a 59-year-old Chinese male diagnosed with gallbladder FDCS and liver metastases. The patient received a combination therapy of sintilimab and anlotinib, resulting in a substantial partial response (PR) lasting for a noteworthy duration of 30 months. Notably, this is the first documented instance of gallbladder FDCS with liver metastases being treated with PD-1 antibody and antiangiogenic agents as first-line therapy. These findings suggest that this treatment regimen may offer a potential therapeutic option for patients with gallbladder FDCS and liver metastases, with a duration of PR lasting up to 30 months.

Keywords: gallbladder follicular dendritic cell sarcoma, long-term follow-up, PD-1 antibody, antiangiogenic agents, first-line therapy, partial response

Introduction

Follicular dendritic cell sarcoma (FDCS) is an exceedingly uncommon malignant cancer that was classified as a neoplasm of histiocytic and dendritic cells. The crude incidence rate for FDCS is 1 case per 200,000 individuals annually.[1] Predominantly, FDCS manifests in extranodal sites (79.4%), with lymph nodes being implicated in only approximately 15% of cases.[2] The malignancy commonly affects extranodal sites such as the spleen, liver, gastrointestinal tract, skin, lungs, mediastinum and soft tissues.[3–7] The occurrence of extra-nodal origin in the gallbladder is exceedingly uncommon, with no reported cases thus far.

Due to the rarity of this malignant neoplasm, there is presently no established standard treatment for instances of inoperable and metastatic FDCS, prompting the utilization of alternative therapies, typically encompassing comprehensive approaches involving radiotherapy and chemotherapy. Nevertheless, these interventions are primarily palliative in nature and have demonstrated limited efficacy in attaining favorable treatment outcomes. The coadministration of PD-1 antibody and antiangiogenic therapy has demonstrated favorable outcomes in the regression of tumors across diverse solid malignancies, such as hepatocellular carcinoma, lung carcinoma and renal cell cancer.[8–10] Nonetheless, there is a dearth of case reports documenting extended progression-free survival (PFS) in patients with gallbladder FDCS who

Received: 7 December 2023
Accepted: 22 March 2024
Published: 3 April 2024

underwent treatment with PD-1 antibody and antiangiogenic agents. In this study, we present a case of gallbladder FDCS accompanied with liver metastases, wherein the patient was administered a first-line treatment comprising sintilimab in conjunction with anlotinib. The aforementioned patient exhibited a 30-month PR, thereby substantiating the effectiveness of this therapeutic intervention for gallbladder FDCS and underscoring potential therapeutic alternatives.

Case Report

A 59-year-old Chinese male was admitted to Zhejiang Provincial People's Hospital due to recurrent paroxysmal upper abdominal pain persisting for one month on December 31, 2020. The patient had a medical history of hypertension spanning over five years, which was effectively managed through regular administration of amlodipine besylate. The admissions examination revealed the lack of yellow discoloration in the skin and sclera, the absence of swollen superficial lymph nodes and the absence of any abnormalities in the heart and lungs. The abdomen exhibited a flat and soft appearance, without tenderness or rebound pain, and no evident masses. The liver and spleen were located under the ribs with negative shifting dullness. There was no edema observed in both lower extremities, and the neurological examination yielded normal results. The comprehensive laboratory blood work-up indicated an elevated enolase level of 30.7 ng/mL (within the normal range of 0–20 ng/mL). Tumor markers, including AFP, CEA, CA125 and CA199, were all found to be negative. Liver function was found to be impaired, as indicated by elevated levels of ALT (182 U/L), AST (74 U/L), γ-GTP (654 U/L), and ALP (234 U/L). The PET/CT scan revealed abnormal morphology of the gallbladder, characterized by the presence of a soft tissue mass exhibiting abnormally high fluorodeoxyglucose (FDG) metabolism. Additionally, multiple low-density liver lesions, enlarged lymph nodes adjacent to major blood vessels, and increased FDG metabolism in the hepatic hilar area, gallbladder vicinity, pancreatic head vicinity, and left iliac region were observed (Figure 1A). In light of the aforementioned malignant lesions, the origin of the gallbladder may be substantial. Subsequent to a liver mass needle biopsy, the presence of spindle cell proliferation accompanied by infiltration of lymphoid and plasma cells was observed, along with partial cholestasis of the liver cells. Notably, endothelial or dendritic cells were found to possess enlarged nuclei (Figure 2). Immunohistochemistry analysis revealed the following results: CD23 (-), CK (pan) (±), CD21 (+), CD30 (-), Ki-67 (80%+), EBER (-), CD34 (-), ALK (-), s100 (-), HMB45 (-), CD3 (-), CD20 (-), EMA (-) (Figure 3). In conjunction with the findings from pathological examination and immunohistochemical staining, the diagnosis conclusively indicated the presence of gallbladder FDCS with liver metastases.

Prior to treatment, the total tumor diameter of the target lesions measured 161.7 mm (Figure 4A1–A3, Table 1). The Positron Emission Tomography (PET)/Computed Tomography (CT) results obtained in January 2021 revealed abnormal gallbladder morphology, characterized by the presence of a soft tissue mass accompanied by an abnormal elevation in FDG metabolism (SUVmax=23.2). Additionally, multiple intrahepatic low-density lesions were observed, exhibiting increased FDG metabolism (SUVmax=20.9). Increased FDG metabolism was observed in multiple lymphatic enlargements in various locations, including the portal area, around the gallbladder, around the head of the pancreas (SUVmax=25.9) and near the left common iliac blood vessel (SUVmax=2.9) (Figure 1A).

The patient underwent six cycles of combined therapy (sintilimab 200 mg D1, anlotinib 8 mg qd D1-D14 and paclitaxel albumin 125 mg/m^2 D1, D8 every 3 weeks) from January 2021 to March 2021. After two cycles of combined therapy, the patient achieved partial response (PR) based on CT evaluation, with a sharp decrease in total tumor diameter to 76.3 mm (Figure 4B1–B3, Table 1). After undergoing two additional treatment cycles, the size of the mass lesion continued to decrease, resulting in a reduction of total tumor diameter to 56.5 mm in April 2021 (Figure 4C1–C3). There were no instances of severe nonhematological or delayed toxicities during the therapy. Subsequently, the patient successfully completed 35 cycles of combined therapy, consisting of sintilimab 200 mg on Day 1 and anlotinib 8 mg once daily from Day 1 to Day 14, repeated every 3 weeks as a sequential treatment. After undergoing a combined therapeutic regimen consisting of 10 cycles, the PET/CT results obtained in September 2021 indicated that the gallbladder exhibited no significant enlargement, the wall of the sac did not display uniform thickening, and there was a slight increase in FDG metabolism (SUVmax=1.2). Additionally, the slightly low-density nodules were either lower or comparable to the liver (SUVmax=3.0). Notably, no enlarged lymph nodes or abnormal elevation in FDG metabolism were observed in the hepatic portal area, peripancreatic head, and retroperitoneum (Figure 1B). Total tumor diameter of the target lesions continued to decrease (Table 1), reaching a measurement of 21.8 mm in July 2023 (Figure 4O1–O3).

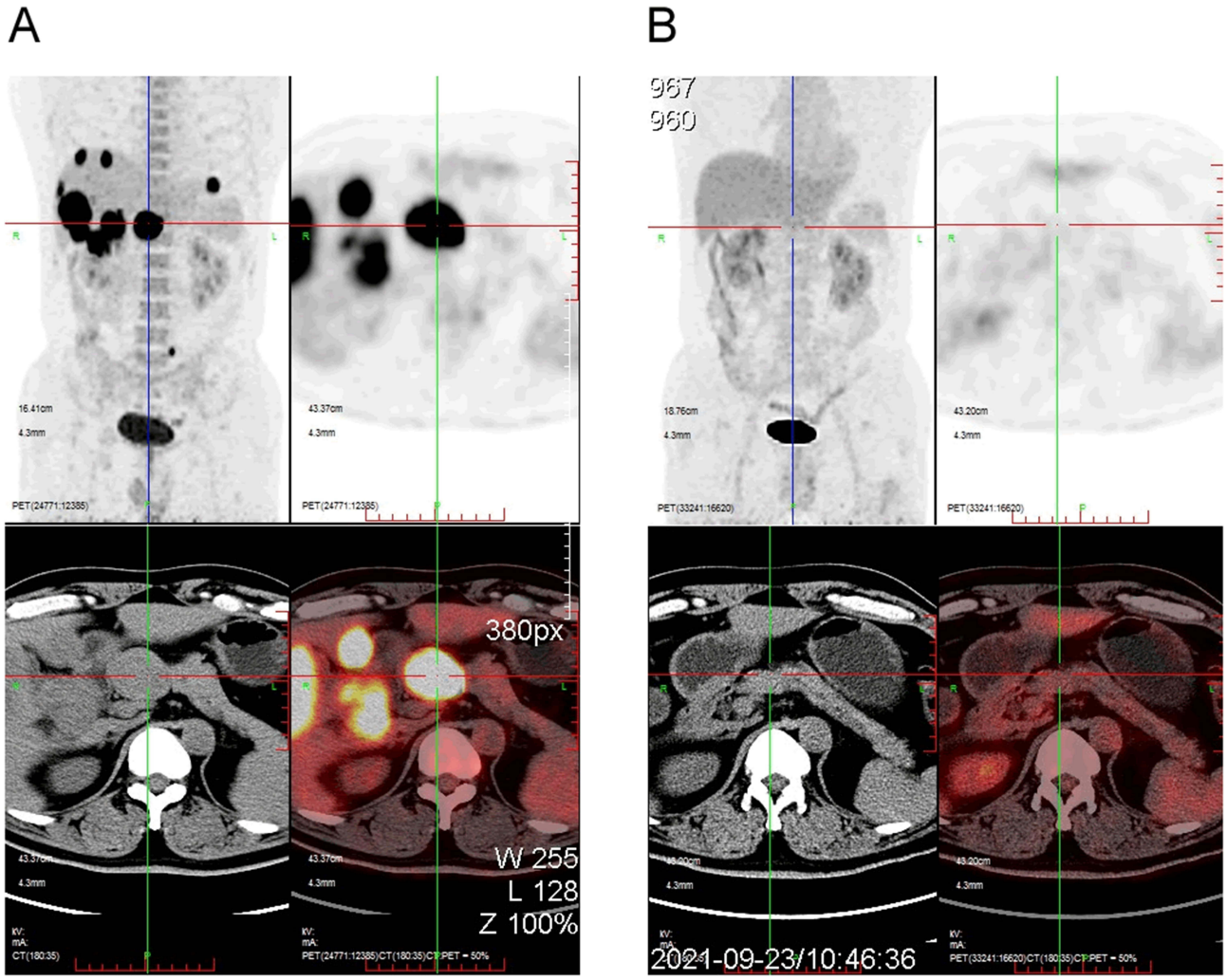

Figure 1 PET/CT revealed focal hypermetabolism in the lesions corresponding to the nodules observed in the CT scans before and after the combined treatment. The PET/CT scans conducted in January 5, 2021 (**A**) and September 23, 2021 (**B**).

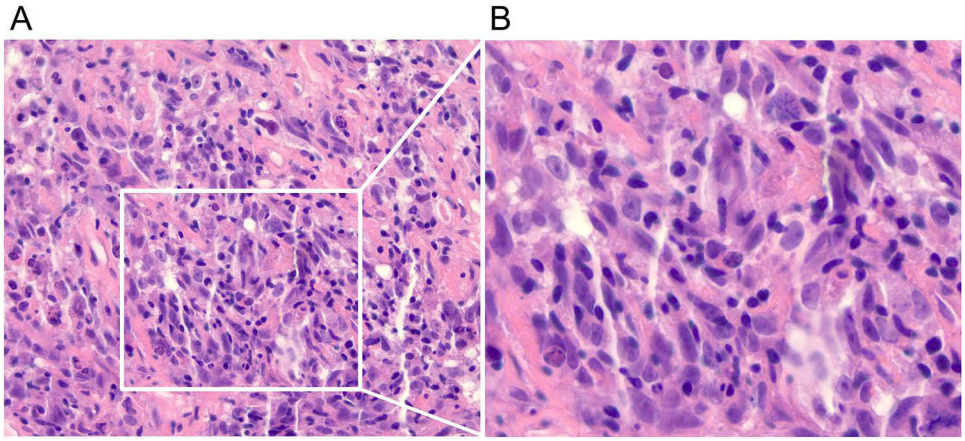

Figure 2 The results of hematoxylin-eosin staining on primary tumors. The liver mass aspiration biopsy revealed partial hepatocytes stasis, red-stained amorphous necrotic foci, and spindle cell hyperplasia fibrous tissue with lymphoid and plasma cell infiltration. The original magnification of the image is 100×. 100×(**A**) and 200×(**B**).

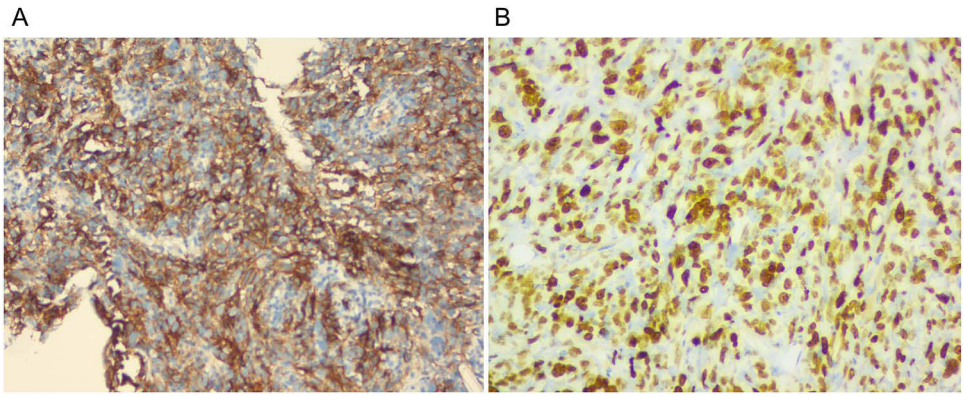

Figure 3 The presents representative immunohistochemical staining images of tissues. The cells exhibited positivity for CD21 (**A**) and Ki-67 (**B**). The original magnification of the image is 100×.

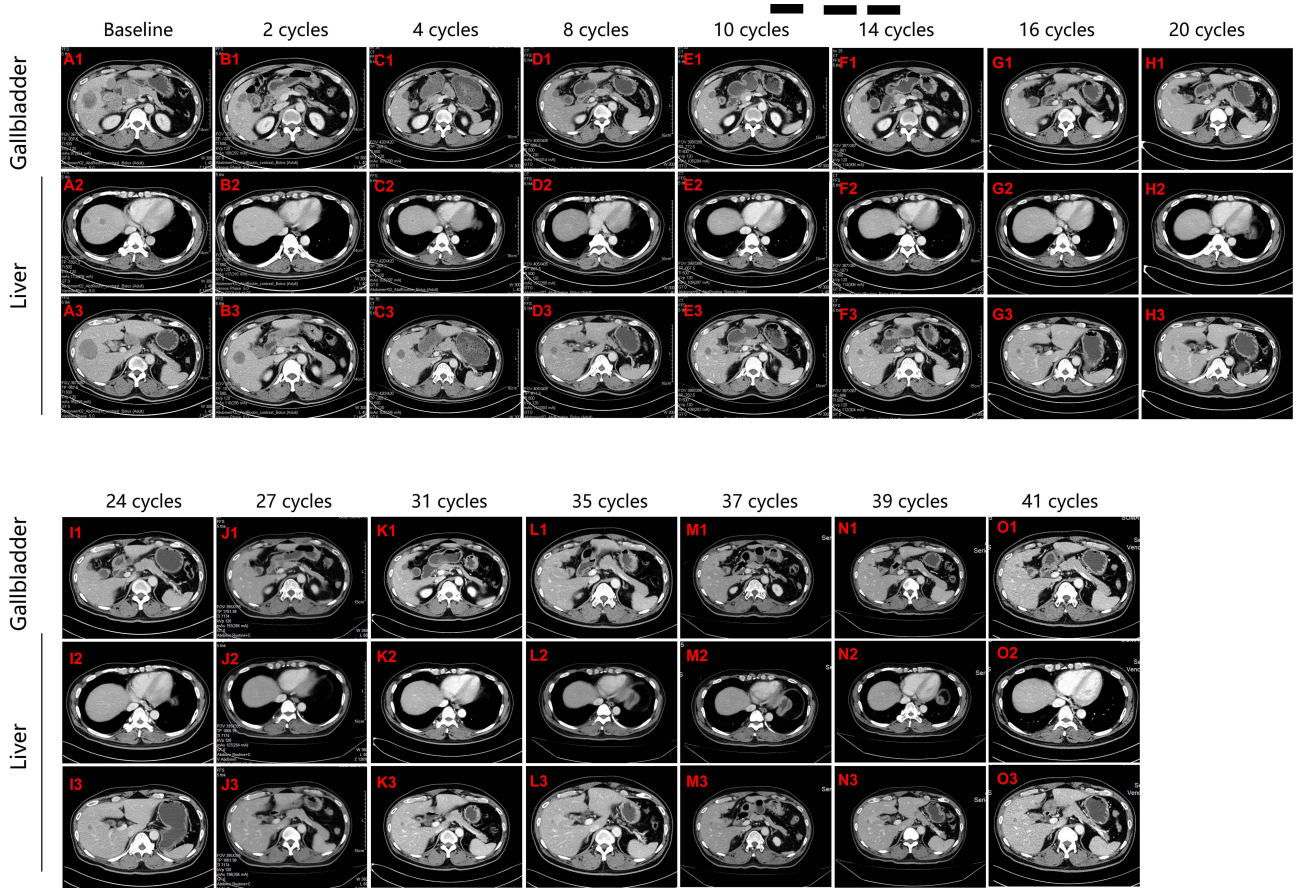

Figure 4 The lesions achieved partial response after 41 cycles of treatment in gallbladder FDCS patient by CT scan.

Throughout the administration of sintilimab in conjunction with anlotinib, the patients exhibited favorable tolerance towards the combined therapeutic strategy. In the first two cycles, the patient had a mild rash that was treated with loratadine. After 12 months, the patient developed hypertension, managed with amlodipine. Around 15 months into treatment, the patient had subclinical hypothyroidism, which improved with levothyroxine therapy. These side effects were grade II according to CTCAE 5.0. The patient did not have any serious immune-related side effects. PR was observed for a duration of up to 30 months subsequent to the administration of sintilimab and anlotinib (Figure 5).

Table 1 The Course of Treatment and Relevant Efficacy

Cycles	Treatment	Tumor Diameters of Target Lesions (mm)				Total Tumor Diameters (mm)	Clinical Efficacy Evaluation
		Gallbladder Lesion	Liver Lesion Area A	Liver Lesion Area B	Pancreas Lesion		
Baseline	Sintilimab + anlotinib + paclitaxel albumin	44.4	52.5	17.7	47.1	161.7	N/A
2 cycles		15.1	33.6	7.9	19.7	76.3	PR
4 cycles		10.5	25.3	6.2	14.5	56.5	PR
8 cycles	Sintilimab + anlotinib	11.8	23.4	0	13.8	49.0	PR
10 cycles		11	21.5	0	12.3	44.8	PR
14 cycles		9.2	18.2	0	11.4	38.8	PR
16 cycles		8.6	17.7	0	0	26.3	PR
20 cycles		8.3	14.5	0	0	22.8	PR
24 cycles		9.4	12.3	0	0	21.7	PR
27 cycles		10.1	13.1	0	0	23.2	PR
31 cycles		10.5	13.0	0	0	23.5	PR
35 cycles		14.8	12.1	0	0	26.9	PR
37 cycles		12.3	10.8	0	0	23.1	PR
39 cycles		12.7	10.4	0	0	23.1	PR
41 cycles		11.7	10.1	0	0	21.8	PR

Notes: Sintilimab + anlotinib + paclitaxel albumin, sintilimab 200 mg D1 + anlotinib 8 mg qd D1-D14 + paclitaxel albumin 125 mg/m^2 D1, D8; Sintilimab + anlotinib, sintilimab 200 mg D1 + anlotinib 8 mg qd D1-D14.

Discussion

To the best of our knowledge, this is the first documented instance of a patient with primary gallbladder FDCS with liver metastases, and also offers a long-term follow-up of the effectiveness and safety of combining PD-1 antibody and angiogenic agents (Figure 5).

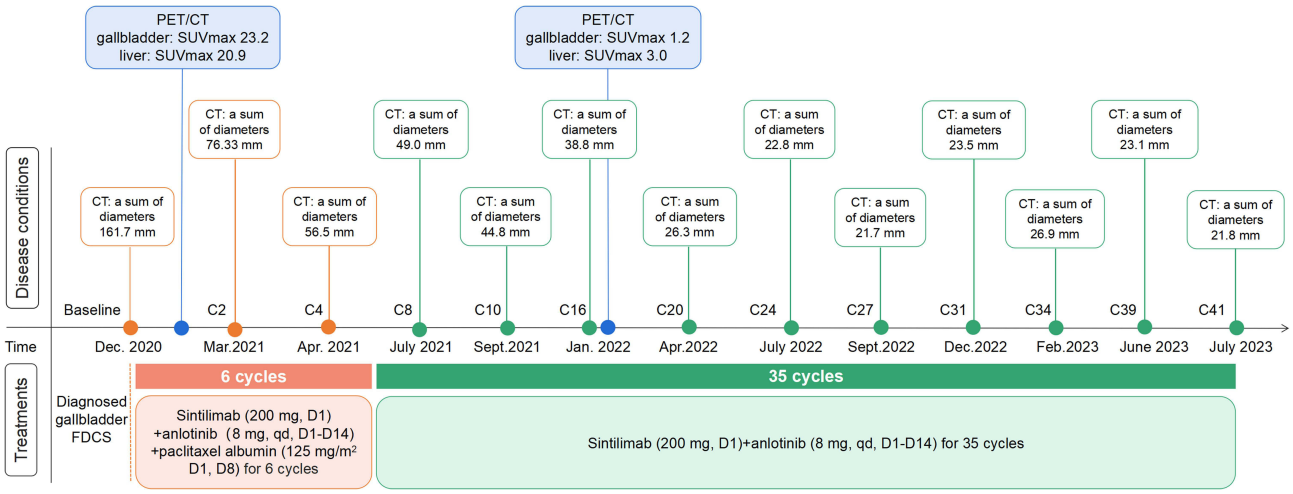

Figure 5 Timeline scheme depicted the major clinical events experienced by the patient since initial diagnosis.

FDCS is an infrequent malignancy characterized by follicular dendritic cell differentiation, initially documented and designated in 1986.[1] The distinction can be made on the basis of both cytomorphology and immunophenotype for the differential diagnosis of gallbladder cancer and gallbladder FDCS. Most gallbladder adenocarcinomas of epithelial origin have an ulcerated or cauliflower-like appearance. Microscopically, malignant glands are diffuse in a dense fibroproliferative stroma, and synaptophysin- and chromogranin-positive neuroendocrine cells are common in adenocarcinomas. Positive expression of CK7, MUC1, CEA, CA19-9 and CK20 are typical immunohistochemical findings in gallbladder cancer of epithelial origin.[11] The typical pathological characteristics of FDCS are spindle- or oval-shaped cells arranged in storiform, whorl-like, or fascicular patterns, individual tumor cells exhibit pale eosinophilic and fibrillar cytoplasm, and some lymphocytes infiltrate the tumor. The nuclei are hyperchromatic and spindle- or oval-shaped with clear nucleoplasm. Typically, the diagnosis of FDCS necessitates the immunohistochemical staining of one or more FDC markers, namely CD21, CD23 and CD35. These markers are commonly found to be immunohistochemically positive in the majority of FDCS specimens.[12] Additionally, CXCL13 is often positive but lacks complete specificity and exhibits a higher Ki-67 proliferation index.[13,14] However, it is important to note that the diffuse-positive diffusion of FDCS markers CD21, CD23 and CD35 may not always be observable. In our specific case, immunohistochemical staining of FDCS patient specimens revealed positivity for CD21 and negativity for CD23 and CD35, along with a Ki-67 proliferation index of 80%. It is worth noting that primary gallbladder FDCS cases have not been previously documented.

The absence of a treatment protocol for FDCS is attributed to its low occurrence rate. In cases of localized FDCS, the prevailing approach involves surgical removal, potentially accompanied by adjuvant chemotherapy and/or radiation therapy.[12] However, due to the patient's extensive metastasis affecting the intraabdominal lymph nodes and liver, radical surgery is deemed inappropriate. In recent times, the advent of novel pharmaceuticals has significantly transformed the established treatment paradigm for various malignancies, including targeted therapy and immunotherapy.

Immune checkpoint inhibitors (ICIs) block inhibitory signals, thereby stimulating T cell activation and enhancing anti-tumor immune responses, has resulted in sustained clinical improvements and potential cures for a significant portion of patients.[15] PD-1 is a kind of T cell inhibitory molecule that interact with its ligands PD-L1 and PD-L2. Clinical trials have demonstrated the efficacy of PD-1/PD-L1 antibodies in the treatment of various of tumors, including melanoma, renal cell carcinoma (RCC), and non-small cell lung carcinoma (NSCLC). Furthermore, PD-1 antibodies have shown promise in treating tumors characterized by high microsatellite instability (MSI), mismatch repair (MMR) deficiency, and high tumor mutation burden (TMB).[15] This groundbreaking approach has transformed the landscape of cancer immunotherapy, establishing it as an integral component of cancer management in conjunction with traditional modalities such as surgery, chemotherapy and radiation therapy.

PD-L1 staining has been found to exhibit positivity in a range of 50–80% of FDCS cases, thus providing a rationale for the utilization of immunotherapy in patients with FDCS. A study involving 54 assessable cases revealed that 13% displayed positive PD-L1 expression.[16] Furthermore, three FDCS patients examined exhibited overexpression of PD-L1.[17] These investigations collectively suggest that immunotherapy may serve as a viable treatment option for FDCS. Additionally, Another study documented the successful treatment of two FDCS patients who received nivolumab and ipilimumab, while two other patients experienced symptom stability and significant improvement within 8–12 weeks of initiating treatment.[18] Furthermore, it should be noted that a patient diagnosed with primary small bowel FDCS received sintilimab and gallonvatinib as a third-line therapy, resulting in a PFS of 7 months.[9] However, it is important to acknowledge that there is currently less evidences supporting the efficacy and safety of PD-1/PD-L1 antibody as a first-line treatment for FDCS. Recently, primary spleen FDCS with multiple peritoneal metastases was treated with sintilimab plus chemotherapy as first-line treatment achieving PR and a relatively long PFS of 17 months.[19]

Combination therapy has been shown to be more effective in treating a variety of tumors. For instance, IMPOWER150 demonstrated that a combination of chemotherapy, anti-angiogenic targeted therapy, and ICIs produced positive outcomes in advanced lung cancer with liver metastasis.[20] Several studies have shown that the combination of anti-angiogenic targeted drugs and ICIs can achieve a synergistic effect, significantly prolonging the survival time of patients with primary liver cancer.[20] Angiogenesis plays a significant role in the pathogenesis of tumors, facilitating tumor proliferation and metastasis. Consequently, antiangiogenic drugs have demonstrated clinical efficacy in diverse solid cancers, including colorectal cancer, hepatocellular carcinoma and renal cell carcinoma.[21–24] Nonetheless, the

effectiveness of these drugs as monotherapy remains constrained. Research indicates that anti-angiogenic drugs exhibit a synergistic effect when combined with PD-1/PD-L1 antibodies. The findings from the IMBrave150[20] and KEYNOTE 426[25] trials indicate that the utilization of this combination therapy can confer a survival benefit and ensure safety, consequently altering the selection of initial treatment. This particular combination therapy possesses the ability to augment the recruitment of T cells through the normalization of tumor blood vessels.[26–28] Therefore, the implementation of combination therapies has demonstrated notable efficacy against various tumor types.

Considering the unfavorable characteristics of our FDCS patient, such as a significant tumor burden, impaired liver function, low PS score and limited options for initial treatment, the approval of sintilimab in China for the management of relapsed or refractory classical Hodgkin lymphoma patients provides a potential therapeutic option.[29] Anlotinib has been authorized for the treatment of patients diagnosed with acinar soft tissue sarcoma, clear cell sarcoma, and other recurrent advanced soft tissue sarcomas.[30,31] After fully informing the patient of their condition, the patient received a combination of sintilimab, anlotinib and paclitaxel albumin every 3 weeks as the initial therapeutic approach following comprehensive discussion and evaluation. Following two cycles of this treatment regimen, the patient's abdominal CT scan revealed a reduction in liver lesions, as well as significant shrinkage in gallbladder lesions and lymph nodes compared to previous scans. After six cycles of treatment, a subsequent abdominal CT scan demonstrated further reduction in gallbladder lesions, lymph nodes, and liver lesions compared to previous scans, with no presence of focal hypermetabolism (Figure 4). The patient discontinued the use of paclitaxel albumin and instead received maintenance therapy with sintilimab plus anlotinib. Throughout the treatment, the patient's condition was regularly assessed. Abdominal CT scans did not reveal any focal hypermetabolism, indicating that the disease did not advance. Moreover, the patient achieved a relatively long PR lasting 30 months. Our report highlights the potential of this treatment approach for patients with gallbladder FDCS, and it is worth noting that our patients did not report any significant discomfort while following this protocol.

Since the molecular aspects of this rare disease remain largely unknown, there is a lack of studies on the mechanism of targeted or immunotherapy on FDCS. The infiltration and functional activity of immune cells within the tumor microenvironment are significant prognostic indicators for predicting treatment response.[32–35] Further efforts are still required to translate whose markers into the clinical setting and to more accurately identify patients who will benefit from immunotherapy. The patient pathologic manifestations showed lymphocytic infiltration, which may have contributed to the improved efficacy of the PD-L1 antibody in this case. Consensus predictors of immunotherapy efficacy include PD-L1 expression levels, TMB and MSI status.

There are several limitations to this case study. However, this lack of evidence is further compounded by the limited number of reports on combination therapies involving FDCS, insufficient data on treatment efficacy, and the absence of next-generation sequencing (NGS) in this particular case. Tumor-related markers mainly included TMB, MSI and MMR.[15] Generally, high-MSI is correlated with a stronger immune response and patients with high-TMB are more likely to benefit from ICIs.[15] High-TMB assessed by targeted NGS was significantly associated with improved benefit from anti-PD-1/PD-L1 therapies among patients with cancers.[36] In this case, the reason for not performing the test was due to specimen limitations and the additional financial burden that NGS for TMB testing would impose on patients. The integration of NGS methodologies has the potential to facilitate the identification of efficacious therapeutic interventions in the future. It remains uncertain whether the high levels of PD-L1 expression and NGS in FDCS are essential for the response to these drugs.

Conclusion

To the best of our knowledge, this is the first documented instance of a patient with primary gallbladder FDCS with liver metastases, and also offers an assessment of the effectiveness and safety of combining PD-1 antibody and angiogenic agents. Notably, the patient exhibited a relatively prolonged PR lasting up to 30 months during the longitudinal follow-up. This case introduces a novel treatment option that warrants further investigation and validation through additional clinical trials.

Abbreviations

FDCS, follicular dendritic cell sarcoma; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; ICIs, immune checkpoint inhibitors; PR, partial response; FDG, fluorodeoxyglucose; NGS, next-generation sequencing; TMB, mutation tumors burden; MSI, microsatellite instability; PFS, progression-free survival.

Data Sharing Statement

All inquiries can be directed to the corresponding authors.

Ethics

The patient provided informed consent to publish their case details and any accompanying images. The studies involving human participants were reviewed and approved by the Institutional Review Board review (Approval number QT2023279) at Zhejiang Provincial People's Hospital in Hangzhou, China. The patient provided their written informed consent to participate in this study.

Acknowledgments

The authors thank the patient and his family for their support.

Funding

This work was supported by Medical and Health Science and Technology Research Program of Zhejiang Province (2022KY061), Zhejiang Province Traditional Chinese Medicine Science and Technology Project (2023ZA015).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer*. 2011;47(17):2493–2511. doi:10.1016/j.ejca.2011.08.008
2. Facchetti F, Simbeni M, Lorenzi L. Follicular dendritic cell sarcoma. *Pathologica*. 2021;113:316–329. doi:10.32074/1591-951X-331
3. Wang E, Zhang L, Wang Y, Zhang M. Epstein–Barr virus-negative inflammatory pseudotumor-like variant of follicular dendritic cell sarcoma of the liver: a case report. *Asian J Surg*. 2023;46(4):1846–1847. doi:10.1016/j.asjsur.2022.10.054
4. Shacklette AH, Chen S, DeWitt JM, Patel KS, Saeed OA. Fine needle aspiration cytology of follicular dendritic cell sarcoma of the stomach masquerading as gastrointestinal stromal tumor: a case report of a unique entity with emphasis on cytomorphology. *Diagn Cytopathol*. 2023;51(7):E214–E218. doi:10.1002/dc.25132
5. Lim JY, Hong SK, Huang WF. Splenic pseudotumor-like follicular dendritic cell sarcoma. *J Gastrointest Surg*. 2023;27(7):1486–1488. doi:10.1007/s11605-023-05630-y
6. Lu X, Wu Y, Gong J, Yu X, Zhang Y, Yang C. Pancreatic follicular dendritic cell sarcoma: one case report and literature review. *J Int Med Res*. 2022;50(12):3000605221142401. doi:10.1177/03000605221142401
7. Hu A, Chen T, Dong J. Promising clinical outcome after body gamma knife radiotherapy for mediastinal follicular dendritic cell sarcoma with thoracic spine invasion and iliac metastasis: a case report and literature review. *Front Oncol*. 2022;2022:12919644.
8. Yang X, Wang D, Lin J, et al. Atezolizumab plus bevacizumab for unresectable hepatocellular carcinoma. *Lancet Oncol*. 2020;21(9):e412. doi:10.1016/S1470-2045(20)30430-7
9. Lei Y, Zhao S, Jiang M. Unexpected favorable outcome to PD-1 antibody plus lenvatinib in a patient with recurrent intestinal follicular dendritic cell sarcoma: a case report and literature review. *Front Immunol*. 2021;12:653319. doi:10.3389/fimmu.2021.653319
10. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *New Engl J Med*. 2019;380(12):1116–1127. doi:10.1056/NEJMoa1816714
11. Nagtegaal ID, Odze RD, Klimstra D, et al. WHO classification of tumours editorial board. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182–188. doi:10.1111/his.13975
12. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703–1719. doi:10.1038/s41375-022-01613-1
13. Swerdlow S, Campo E, Harris NL, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (Revised 4th Edition)*. Vol. 421. Lyon: IARC; 2017:476.
14. Asiry S, Khader SN, Villanueva-Siles E, et al. Follicular dendritic cell sarcoma: cytomorphologic features and diagnostic challenges. *Diagn Cytopathol*. 2021;49(3):457–461. doi:10.1002/dc.24691
15. Sharma P, Goswami S, Raychaudhuri D, et al. Immune checkpoint therapy—current perspectives and future directions. *Cell*. 2023;186(8):1652–1669. doi:10.1016/j.cell.2023.03.006

16. Agaimy A, Michal M, Hadravsky L, Michal M. Follicular dendritic cell sarcoma: clinicopathologic study of 15 cases with emphasis on novel expression of MDM2, somatostatin receptor 2A, and PD-L1. *Ann Diagn Pathol*. 2016;23:21–28. doi:10.1016/j.anndiagpath.2016.05.003
17. Gatalica Z, Bilalovic N, Palazzo JP, et al. Disseminated histiocytoses biomarkers beyond BRAFV600E: frequent expression of PD-L1. *Oncotarget*. 2015;6:19819. doi:10.18632/oncotarget.4378
18. Lee M-Y, Bernabe-Ramirez C, Ramirez DC, Maki RG. Follicular dendritic cell sarcoma and its response to immune checkpoint inhibitors nivolumab and ipilimumab. *BMJ Case Rep*. 2020;13:e234363. doi:10.1136/bcr-2020-234363
19. Li J, Ren M, Bi F, et al. Favorable response to PD-1 inhibitor plus chemotherapy as first-line treatment for metastatic follicular dendritic cell sarcoma of the spleen: a case report. *Front Immunol*. 2023;14:1228653. doi:10.3389/fimmu.2023.1228653
20. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo controlled, Phase 3 trial. *Lancet*. 2013;381(9863):303–312. doi:10.1016/S0140-6736(12)61900-X
21. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56–66. doi:10.1016/S0140-6736(16)32453-9
22. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *New Engl J Med*. 2015;373 (19):1814–1823. doi:10.1056/NEJMoa1510016
23. Motzer RJ, Hutson TE, Glen H, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, Phase 2, open-label, multicentre trial. *Lancet Oncol*. 2015;16(15):1473–1482. doi:10.1016/S1470-2045(15)00290-9
24. Galle PR, Finn RS, Qin S, et al. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(7):991–1001. doi:10.1016/S1470-2045(21)00151-0
25. Powles T, Plimack E, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2020;21(12):1563–1573. doi:10.1016/S1470-2045(20)30436-8
26. 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):325–340. doi:10.1038/nrclinonc.2018.29
27. Kudo M. Scientific rationale for combined immunotherapy with PD-1/PD-L1 antibodies and VEGF inhibitors in advanced hepatocellular carcinoma. *Cancers*. 2020;12(5):1089. doi:10.3390/cancers12051089
28. Furukawa K, Nagano T, Tachihara M, Yamamoto M, Nishimura Y. Interaction between immunotherapy and antiangiogenic therapy for cancer. *Molecules*. 2020;25(17):3900. doi:10.3390/molecules25173900
29. Hoy SM. Sintilimab: first global approval. *Drugs*. 2019;79(3):341–346. doi:10.1007/s40265-019-1066-z
30. Jin S, Zhao R, Zhou C, et al. Feasibility and tolerability of sintilimab plus anlotinib as the second-line therapy for patients with advanced biliary tract cancers: an open-label, single-arm, Phase II clinical trial. *Int J Cancer*. 2022;152(8):1648–1658. doi:10.1002/ijc.34372
31. Liu J, Gao T, Tan Z, et al. Phase II study of TQB2450, a novel PD-L1 antibody, in combination with anlotinib in patients with locally advanced or metastatic soft tissue sarcoma. *Clin Cancer Res*. 2022;28(16):3473–3479. doi:10.1158/1078-0432.CCR-22-1785
32. Zhang Y, Vu T, Palmer DC, et al. A T cell resilience model associated with response to immunotherapy in multiple tumor types. *Nat Med*. 2022;28 (7):1421–1431. doi:10.1038/s41591-022-01799-y
33. Laumont CM, Banville AC, Gilardi M, Hollern DP, Nelson BH. Tumour-infiltrating B cells: immunological mechanisms, clinical impact and therapeutic opportunities. *Nat Rev Cancer*. 2022;22(7):414–430. doi:10.1038/s41568-022-00466-1
34. Dolton G, Rius C, Wall A, et al. Targeting of multiple tumor-associated antigens by individual T cell receptors during successful cancer immunotherapy. *Cell*. 2023;186(16):3333–3349. doi:10.1016/j.cell.2023.06.020
35. Tay C, Tanaka A, Sakaguchi S. Tumor-infiltrating regulatory T cells as targets of cancer immunotherapy. *Cancer Cell*. 2023;41(3):450–465. doi:10.1016/j.ccell.2023.02.014
36. Rizvi H, Sanchez-Vega F, La K, et al. Molecular determinants of response to anti-programmed cell death (PD)-1 and anti-programmed death-ligand 1 (PD-L1) blockade in patients with non-small-cell lung cancer profiled with targeted next-generation sequencing. *J Clin Oncol*. 2018;36 (7):633–641. doi:10.1200/JCO.2017.75.3384