Received: 14 January 2022 | Revised: 7 March 2022 | Accepted: 12 March 2022

DOI: 10.1111/cas.15339

Cancer Science WILEY

CASE REPORT

High PD-L1 level of advanced hepatic lymphoepithelioma-like carcinoma response favorably to lenvatinib plus toripalimab

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Funding information
None

Abstract

Lymphoepithelioma-like carcinoma (LELC) is an uncommon subtype of primary liver cancer with predominant lymphocyte infiltration and a relatively favorable outcome. However, no standard treatment for advanced hepatic LELC has been established. Here, we give a first report of a 60-year-old man with advanced hepatic LELC who had a high expression of PD-L1 in tumor cells and a high level of tumor-infiltrating leukocytes (TILs) in the tumor microenvironment (TME). After receiving six cycles of multiple receptor tyrosine kinase inhibitor (rTKI) with lenvatinib plus PD-1 inhibitor toripalimab treatment, the patient achieved persistent partial response (PR). Our report indicates that advanced hepatic LELC with high expression of PD-L1 may benefit from the combination of rTKI and PD-L1/PD-1 blockade. Therefore, this potential strategy should be considered when treating those rare liver cancers.

KEYWORDS
immune checkpoint inhibitor, liver cancer, lymphoepithelioma-like carcinoma, PD-L1, receptor tyrosine kinase inhibitor, tumor microenvironment

1 | INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) is characterized by undifferentiated epithelial cells composed of predominant lymphoid infiltration, which was initially described in the nasopharynx by Applebaum et al.[1] In the 2010 World Health Organization (WHO) classification, LELC of the liver was acknowledged as a distinctive variant of liver cancer.[2] Similar to conventional liver cancer, hepatic

Abbreviations: CPS, combined positive score; ICI, immune checkpoint inhibition; LEL-HCC, lymphoepithelioma-like hepatocellular carcinoma; LELC, lymphoepithelioma-like carcinoma; LEL-CC, lymphoepithelioma-like cholangiocarcinoma; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; rTKI, receptor tyrosine kinase inhibitor; TILs, tumor-infiltrating leukocytes; TME, tumor microenvironment; TPS, tumor proportion score.

Yueting Zhu and Zhuyi Dang contributed equally to this work.

LELC can be classified as lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) and lymphoepithelioma-like cholangiocarcinoma (LEL-CC).[3] In 2019, the WHO updated the vital diagnostic criteria of LELC, which is the amount of infiltrating lymphocytes–overwhelmed tumor cells in most fields on H&E staining.[4] Lymphoepithelioma-like carcinoma in the liver is associated with lower recurrence rates after resection and better outcomes than classical primary liver cancer.[3,5] However, no recognized effective treatment for advanced hepatic LELC has been established. Here, for the first time we present a case of advanced hepatic LELC that received lenvatinib plus toripalimab as first-line therapy and achieved a favorable response.

2 | CASE INTRODUCTION

A 60-year-old man with a history of chronic hepatitis B virus infection was referred to our hospital in November 2019 with a liver-occupying lesion through a routine medical examination. Abdominal contrast-enhanced computed tomography (CT) scan revealed a 17 mm × 16 mm enhancing mass in the right liver. The tumor markers of AFP, CEA, CA125, and CA19-9 were all negative. Then the patient underwent right hepatectomy, cholecystectomy, and portal vein repair. Histological diagnosis was hepatic LELC, along with cirrhosis. Immunohistochemical analyses revealed that the neoplastic cells were positive for EMA, P63, CK8/18 (partial), and Ki-67 (80%), and negative for hepatocyte, GPC-3, CK7, CK19, ARG, and ERBR1/2-ISH (Figure 1). Without further treatment, the patient underwent surveillance with regular CT scans and blood measurement of tumor markers in the last 2 years.

The patient conducted a periodic CT scan in March 2021, which revealed multiple enlarged lymph nodes in the hepatic hilar, hepatogastric ligament, and para-aortic areas. The largest one reached 70 mm × 41 mm (Figure 3A,B). An ^{18}F-FDG PET/CT was performed to screen the tumor origin, but no other abnormal radiation uptake outside the above parts was found (Figure 2A). Meanwhile, the ^{18}F-FDG PET/CT conferred the enlargement of lymph nodes in the abdomen (Figure 2B,C), with maximal standardized uptake value (SUV_{max}) = 6.53. No elevation of tumor markers was noted in blood analysis. Thus, based on his past medical history and above results, a diagnosis of advanced hepatic LELC was made.

Then, we did multiple immunofluorescences (IF) to assess the TME of this LELC patient in both neoplastic hepatic LELC cells and tumor stromal cells (Figure 4). Tumor proportion score (TPS) and combined positive score (CPS) were used to evaluate the expression of PD-L1. Immunofluorescence results showed that both the TPS and CPS were 24%, indicating a high level of PD-L1 expression in tumor cells. Moreover, CD8+, CD4+, and CD3+ T cells were infiltrated in both tumor cells and stromal cells (0.94% vs 4.21%, 1.29% vs 8.96%, 6.88% vs 32.85%, respectively). PD-L1–positive tumor combined with TILs indicated this patient should be categorized as type II "adaptive immune resistance" in microenvironment classification. Furthermore, tumor-associated macrophage (TAM) type M1 (CD68+CD163-), which mainly acted as an antitumor cell, was more predominant than M2 (CD68+CD163+) in tumor cells (7.11% vs 2.23%) (Figure 4A). CD56 staining also showed a high proportion of CD56+ (both CD56bright and CD56dim) NK cells (7.78%) (Figure 4B), suggesting the possibly favorable antitumor immune response. In addition, low levels of PD-1+CD8+ (0.14%) and CD4+FoxP3+ (0.48%) expressions may limit the inhibition of Treg (Figure 4B). All of the above information indicated this patient belonged to "overregulation of activated TILs" and was more likely to benefit from immune therapy, particularly anti-PD-1/PD-L1 therapy.[6] Findings from next-generation sequencing (NGS) were positive for mutations in TP53, RB1, and ROBO2, along with low tumor mutation burden (TMB-L) and microsatellite stability (MSS).

Due to the existence of cirrhosis and thrombocytopenia, and the potential toxicities of chemotherapy, the patient was initially administrated a combination regimen of lenvatinib (8 mg po, qd) and toripalimab (240 mg ivgtt, q3w) on June 1, 2021. After three cycles, we assessed the curative effect according to an enhanced CT scan,

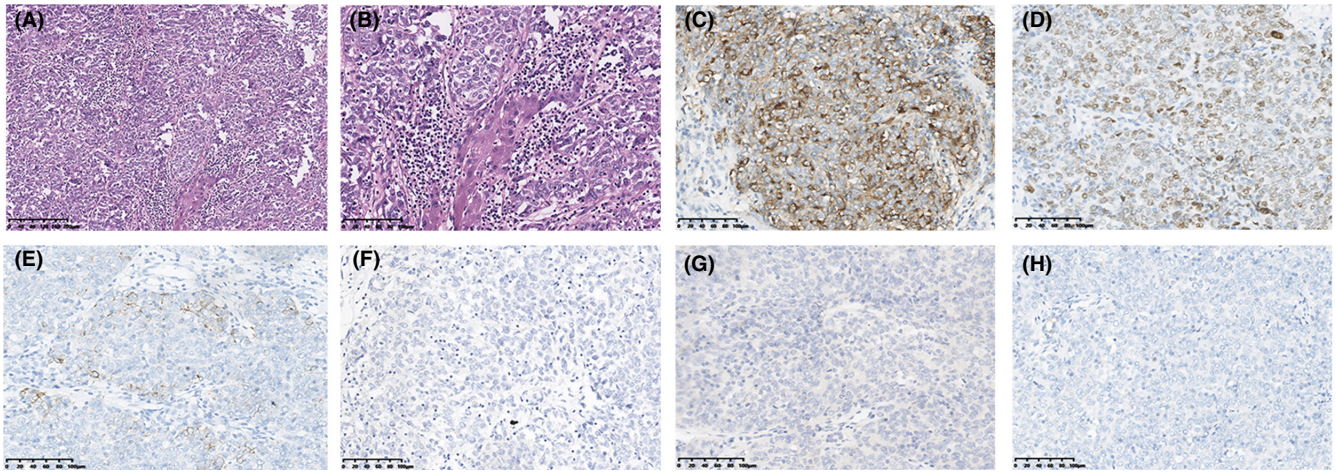

FIGURE 1 Immunohistochemical staining of hepatic lymphoepithelioma-like carcinoma (LELC). Hematoxylin and eosin staining 10X (A), 20X (B) depicted infiltrated lymphocytes in tumor cells. Tumor cells were positive for EMA (C), P63 (D), and CK8/18 (partial) (E) and negative for hepatocyte (F), GPC-3 (G), and CK7 (H)

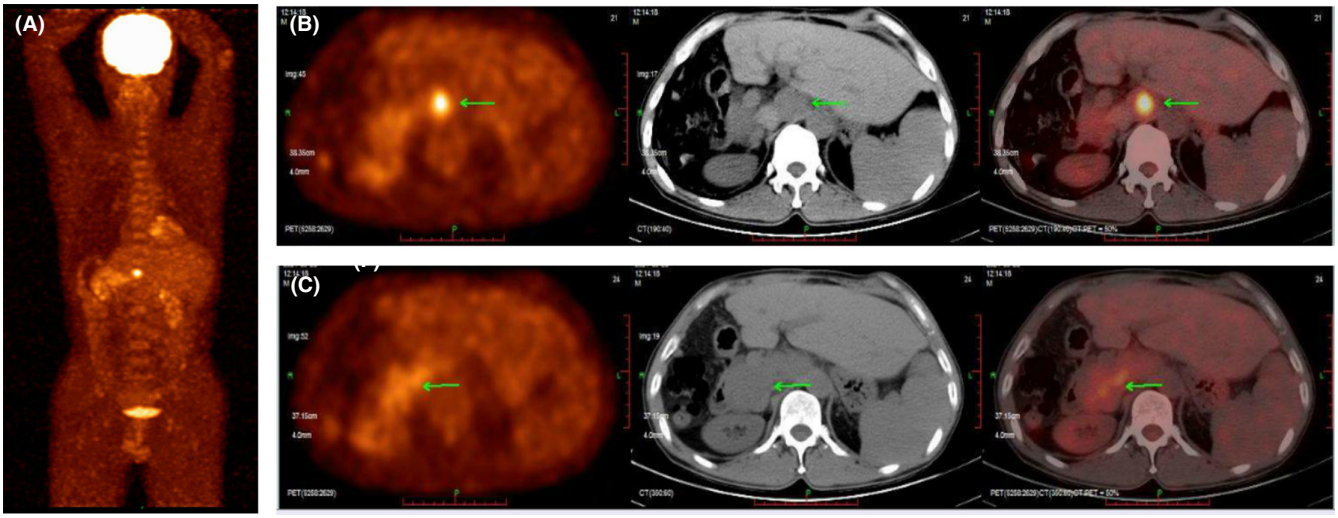

FIGURE 2 Positron emission tomography/computed tomography scan before chemotherapy. A, Positron emission tomography/computed tomography scan revealed abdominal multiple lymph node enlargements with increased glucose metabolism, with maximal standardized uptake value (SUVmax) as 6.53. B, C, Green arrows show two primary enlarged irregular nodes

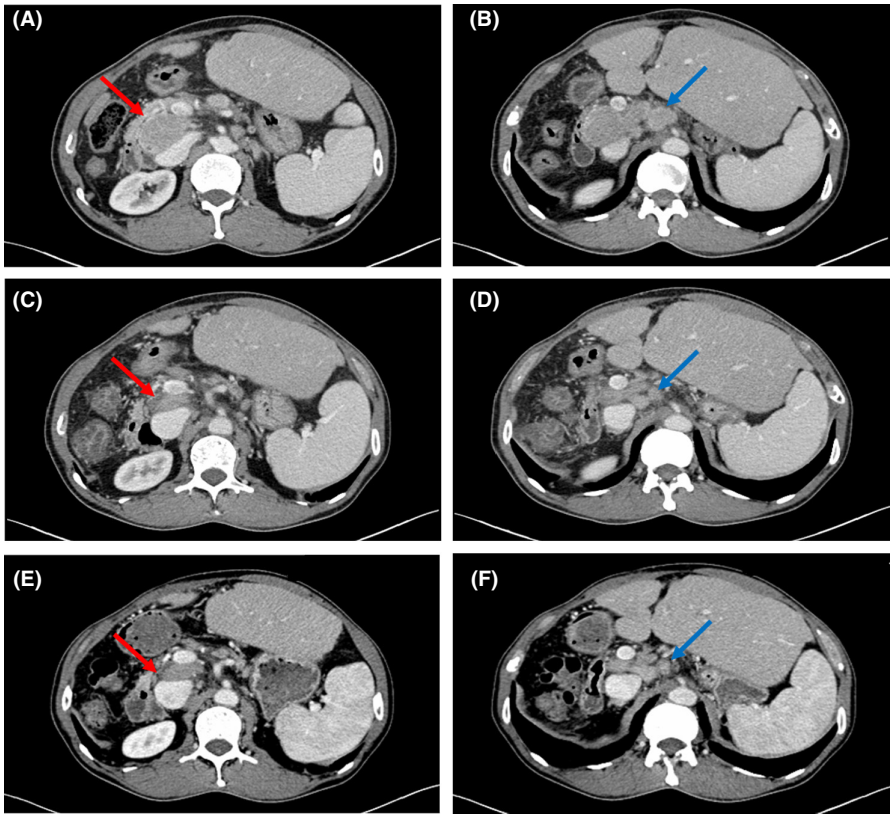

FIGURE 3 Computed tomography scan before and after treatment. A, B, Computed tomography scan demonstrated multiple enlarged lymph nodes in the hepatic hilar, hepatogastric ligament, and para-aortic areas. C, D Computed tomography scan after three cycles. E, F Computed tomography scan after six cycles. Red and blue arrows indicate two typical enlarged nodes

and we noticed the enlarged lymph nodes had reduced remarkably (Figure 3C,D). Subsequently, the patient received another three cycles of combination therapy, and the CT scan indicated the lesions decreased further (Figure 3E,F). According to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), the evaluation result reached partial response (PR). The progression-free survival (PFS) has been more than 7 months. No treatment-related adverse events (AEs) have been observed so far.

3 | DISCUSSION

Hepatic LELC is a relatively rare subtype of liver cancer, with retrospective analysis showing its incidence varies from 4.9% to 6.7%.[7,8] To date, only 110 cases of LELC have been reported, including 71 cases of LEL-HCC, 38 cases of LEL-CC, and 1 case of mixed LEL-HCC and LEL-CC. In most cases, positive hepatocyte and GPC3 indicated a hepatocellular origin, while CK19 and CK7 are specific

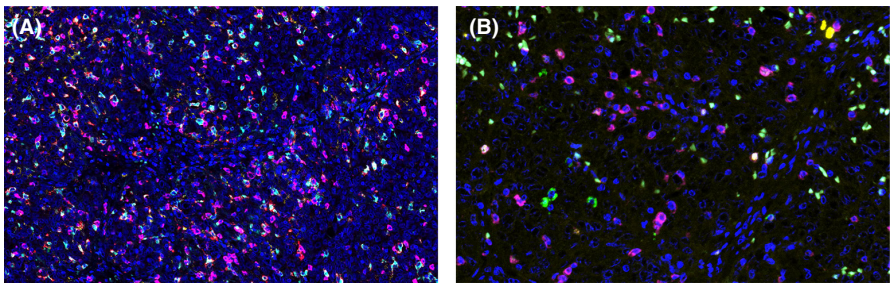

FIGURE 4 Multiple immunofluorescences of hepatic lymphoepithelioma-like carcinoma (LELC). PD-L1 was evaluated by tumor proportion score (TPS), defined as the proportion of viable tumor cells showing partial or complete membrane PD-L1 staining at any intensity, and combined positive score (CPS) by dividing the number of PD-L1–stained cells (tumor cells, lymphocytes, macrophages) with the total number of viable tumor cells and multiplying by 100. Tumor microenvironment analysis, including PD-1, tumor-associated macrophage, natural killer cells, and Treg cells, was also performed. The merge of fluorescence signals is shown. A, Representative immunofluorescence staining for PD-L1 (yellow), PD-1 (green), CD8 (magenta), CD68 (cyan), and CD163 (red). B, Representative immunofluorescence staining for CD3 (magenta), CD4 (red), CD20 (green), CD56 (cyan), and FoxP3 (yellow)

characteristics of cholangiocellular carcinoma.[9] None of the pathological stainings mentioned above was positive in the present patient. However, considering that there were a large number of lymphocyte infiltration in the tumor tissue, and no extrahepatic tumor origins were revealed, we diagnosed the case as hepatic LELC. Zhang et al. also diagnosed a case of LELC with CK7(-), CK19(-), hepatocyte(-), and CK18(2+).[9] Epstein-Barr virus (EBV) infection is associated with LELC arising in stomach, salivary gland, lung, and thymus.[10] Most cases of LEL-HCC are EBV negative,[11] while only one case with EBV positivity has been reported.[12] According to the negative pathological ERBR1/2-ISH result, no link between EBV and hepatic LELC was found in the present patient.

Treatments for localized hepatic LELC disease mainly focus on surgical resection, but no consistent opinion for adjuvant therapies has been reached. Several cases of patients with hepatic LELC who experienced local recurrence or metastasis after liver resection have been reported. As for the first-line treatment strategy, cisplatin-based chemotherapy was the primary choice,[9,13,14] but it only yielded moderate benefits. Subsequently, more optimal regimens have been brought forward. One patient with LEL-HCC received oral sorafenib,[15] and another case with advanced LEL-HCC was treated with nivolumab.[16] Despite a relatively low level of tumor PD-L1 expression, the latter patient still had evidence of disease stability for 2 years.[16] However, no advanced hepatic LELC cases receiving rTKI combined with immune checkpoint inhibition (ICI) have been reported.

Previous studies have indicated favorable responses to ICI in primary pulmonary LELC, especially those with high PD-L1 expression.[17-21] In our present case, high expression of PD-L1 and dense TIL infiltration in LELC tumor cells were noted. In addition, TME analysis also showed a high proportion of TAM type M1, NK cells, and weakened Treg action, suggesting this patient might derive a benefit from immunotherapies. Meanwhile, rTKI plus ICI showed significant improvement in overall survival in hepatocellular carcinoma patients with manageable safety profiles.[22] Hence, we combined multikinase and ICI to treat this case. Although no specific mechanism for how the combination of ICI and rTKI lead to enhanced antitumor activity has been fully explained, evidence implies that lenvatinib can exert immunomodulatory activities in the TME.[23] When combined with PD-1/PD-L1 blockade, lenvatinib can improve antitumor activity by reducing tumor PD-L1 expression and Treg infiltration, decreasing TAMs, and increasing the percentage of activated $CD8^+$ T cells, thus affecting antitumor immune responses.[23-25]

In conclusion, this work is a first report of a patient who had advanced hepatic LELC with increased PD-L1 expression, categorized as "overregulation of activated TILs". This patient responded well to lenvatinib plus toripalimab combination therapy, which indicates that advanced hepatic LELC with a high level of PD-L1 expression and immune activation status may benefit from rTKI plus PD-1/PD-L1 blockade. Further prospective studies are warranted for patients with rare LELC in the liver to investigate the effectiveness of potential treatments.

ACKNOWLEDGMENTS

TME analysis was performed in 3DMed Clinical Laboratory certificated by the College of American Pathologists.

DISCLOSURE

The authors declare no conflict of interest.

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How to cite this article: Zhu Y, Dang Z, Xu H, Yuan Y, Chen Y, Li Z. High PD-L1 level of advanced hepatic lymphoepithelioma-like carcinoma response favorably to lenvatinib plus toripalimab. *Cancer Sci*. 2022;113:1880–1884. doi:10.1111/cas.15339