Case Report
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A Case of Lymphocyte-Rich Hepatocellular Carcinoma in a Patient Who Was Treated for Colon Cancer

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Hepatocellular carcinoma (HCC) primarily originates in the liver with hepatic differentiation. However, HCCs are not homogenous, and approximately 35% of HCC cases are classified as histopathological variants that present distinct pathologic characteristics. In particular, the lymphocyte-rich variant is the rarest subtype accounting for less than 1% of HCCs, which is not well known to date about molecular features and pathophysiology. Herein, we present a case of a patient who was suspected of metastatic liver cancer and confirmed as lymphocyte-rich HCC pathologically. A 78-year-old woman who underwent a right hemicolectomy for colon cancer was referred to our hospital for a newly detected liver mass. We could not make a decision because of insufficient evidence for diagnosis from imaging studies. After resection, we found that it was a lymphocyte-rich HCC. The pathologic features and prognostic trends of this subtype are also discussed. **(J Liver Cancer 2021;21:69-75)**

Keywords: Hepatocellular carcinoma; Hepatocellular carcinoma variants; Lymphocyte-rich subtype

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INTRODUCTION

Liver cancer is the fourth leading cause of cancer-related deaths worldwide.[1] In Korea, liver cancer is ranked sixth in terms of incidence and second in terms of cancer-related mortality.[2,3] Hepatocellular carcinoma (HCC) accounts for 75-85% of primary liver cancer cases.[1]

HCC primarily originates in the liver with hepatic differentiation. However, HCCs are heterogonous in pathogenesis, and further studies have been performed to classify the subtypes of HCC, specifically based on the morphological characteristics of tumor cells.[4,5] Primary hepatic tumors that have distinct pathologic features are known as HCC variants.[6] As many as 35% of HCCs can now be classified into histopathological variants.[7-9] According to the latest World Health Organization (WHO) Classification of Digestive System Tumors, 5th Edition, variants can be classified into subgroups based on genomic and molecular analyses, including steatohepatitic, clear cell, macrotrabecular-massive, scirrhous, chromophobe, fibrolamellar HCC, neutrophil-rich, and lymphocyte-rich subtypes.[8]

In particular, lymphocyte-rich HCC is the rarest subtype. Its molecular features have not been characterized yet, and pathophysiology is not well known to date.[6-8] We present a rare case of a patient who was suspected of metastatic liver

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cancer and confirmed with lymphocyte-rich HCC pathologically. As this report is based on protected health information, the need for institutional review board approval has been waived.

CASE REPORT

1. Clinical findings

A 78-year-old woman treated for colon cancer at another hospital was referred to our hospital for further evaluation of abnormal imaging findings. She was diagnosed with colon cancer (stage II) 2 years ago. She underwent a right hemicolectomy and received adjuvant chemotherapy for 6 months. After treatment, there was no evidence of disease during regular follow-up. However, a hepatic mass was detected on computed tomography (CT) performed for surveillance of colon cancer recurrence 3 months ago. She did not have any other risk factors for HCC, such as alcoholism and metabolic disorders. We did not check the serologic test for viral hepatitis at the initial evaluation because she was referred from another medical center during the follow-up period and had no history of hepatitis. As she had been treated for colon cancer, liver metastasis of colon cancer was most suspected clinically at that time. Dynamic liver magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) was also performed. Although imaging studies were conducted fully, the differentiation between metastasis and primary liver cancer was still unclear. The patient wanted a second opinion and thus visited our hospital. At the initial inspection, she had no specific symptoms or abnormal findings on physical examination. On initial laboratory examination, her complete blood count profile revealed a WBC count of 5.33×10^3/μL, a hemoglobin level of 12.3 g/μL, and platelet count of 239×10^3/μL, which were within the normal ranges. Liver function tests also showed nearly normal results, with a serum bilirubin level of 0.4 mg/dL, albumin level of 4.8 g/dL, prothrombin time international normalized ratio of 1.01, aspartate aminotransferase level of 44 IU/L, and alanine aminotransferase level of 34 IU/L. Serum levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) were 3.0 ng/mL (reference range: 0.0-9.0 ng/mL) and 34 mAU/mL (reference range: 0-35 mAU/mL), respectively. Considering the history of colon cancer, we performed a carcinoembryonic antigen (CEA) assessment also, level 3.06 ng/mL (reference range: 0.0-5.0 ng/mL).

2. Imaging findings

An abdominal CT scan that detected a hepatic mass first revealed a 3.6-cm-sized lobulated mass in segment VII of the liver. It showed peripheral rim enhancement in contrast images (Fig. 1). The background features of the liver parenchy-

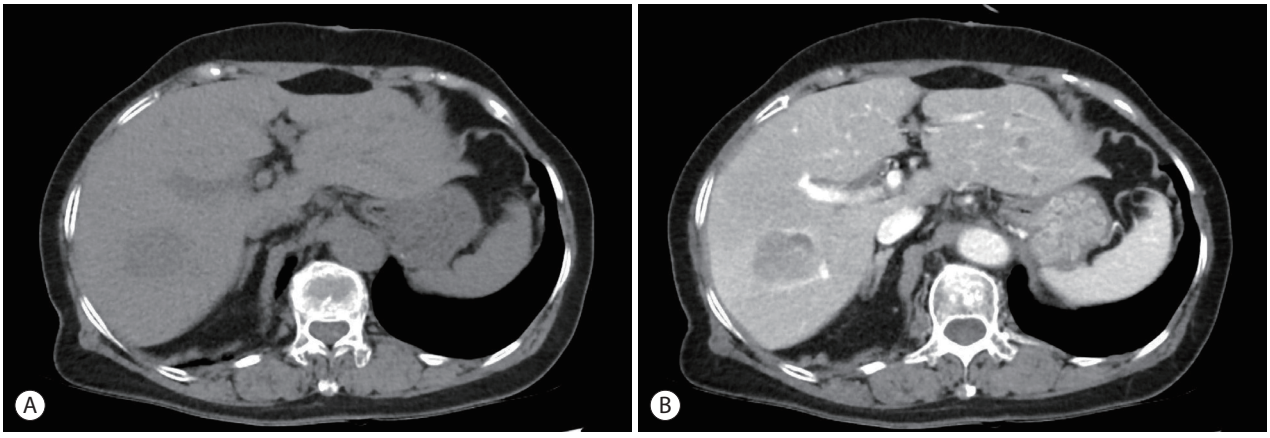

Figure 1. Initial computed tomography scan findings. A 3.6 cm sized lobulated mass is observed in segment VII, showing hypodensity compared to normal liver tissue in the pre-contrast phase (A) and peripheral rim enhancement in contrast images (B).

ma were not remarkable. As the CT scan did not involve dynamic phase images, it was limited for evaluating the lesion precisely. Dynamic liver MRI showed heterogeneous enhancement in the arterial phase and wash-out in the portal phase. Hyperintensity was observed in T2-weighted images (Fig. 2). PET-CT showed FDG uptake in the hepatic mass without evidence of any other lesions (Fig. 3).

3. Diagnosis and treatment

Although there were typical findings for HCC based on imaging studies, liver metastasis of colon cancer could not be definitively ruled out due to the clinical history. We planned surgical resection for diagnosis and treatment. The patient underwent a volume-preserving right hemihepatectomy, and the tumor was completely resected. Gross findings of the specimen exhibited a lobulated round mass (Fig. 4). Hematoxylin and eosin (H&E) staining revealed moderately differentiated hepatic tumor cells, which represented trabecular patterns of polygonal cells with distinct cell membranes, abundant granular eosinophilic cytoplasm, and a higher nuclear-cytoplasmic ratio. Moreover, there was an infiltration of a large number of lymphocytes, known as the lymphoepithelioma-like pattern (Fig. 5). The immunohistochemical staining results suggested that the tumor cells originated in the liver, as arginase-1 was positive, while cytokeratin 7 and 19 (CK7 and CK19) and epithelial membrane antigen (EMA) were negative. T-lymphocyte infiltration was demonstrated through diffuse staining of the cluster of differentiation 3 and 8 (CD3 and CD8). Programmed death-ligand 1 (PD-L1) was positive with a 90% tumor proportion score. Epstein-Barr virus-encoded RNA (EBER) in situ hybridization (ISH) was

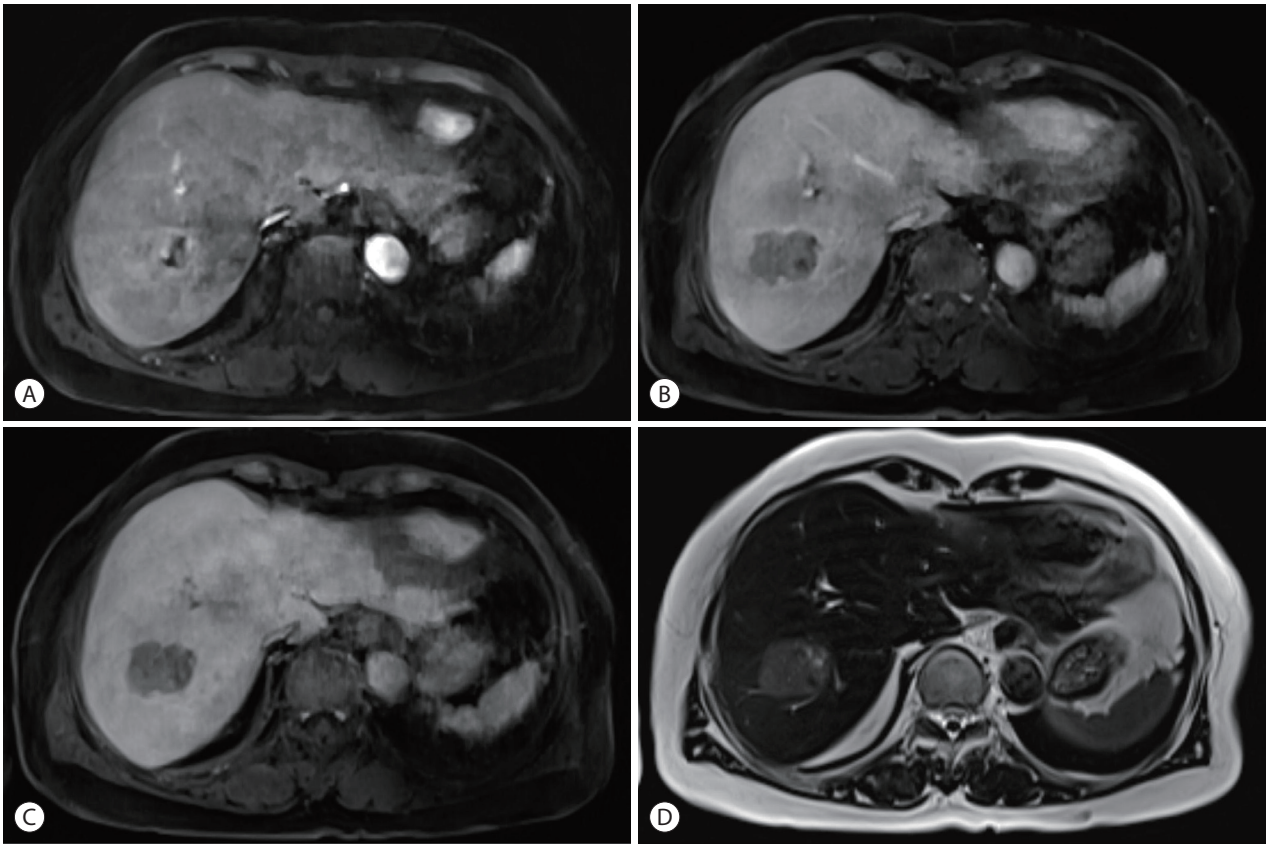

Figure 2. Dynamic liver magnetic resonance imaging findings. The mass is enhanced heterogeneously and also shows peripheral rim enhancement in the arterial phase (A). Wash-out in portal phase (B). Hypointensity in hepato-biliary phase (C). In T2-weighted images, it presents moderate hyperintensity (D).

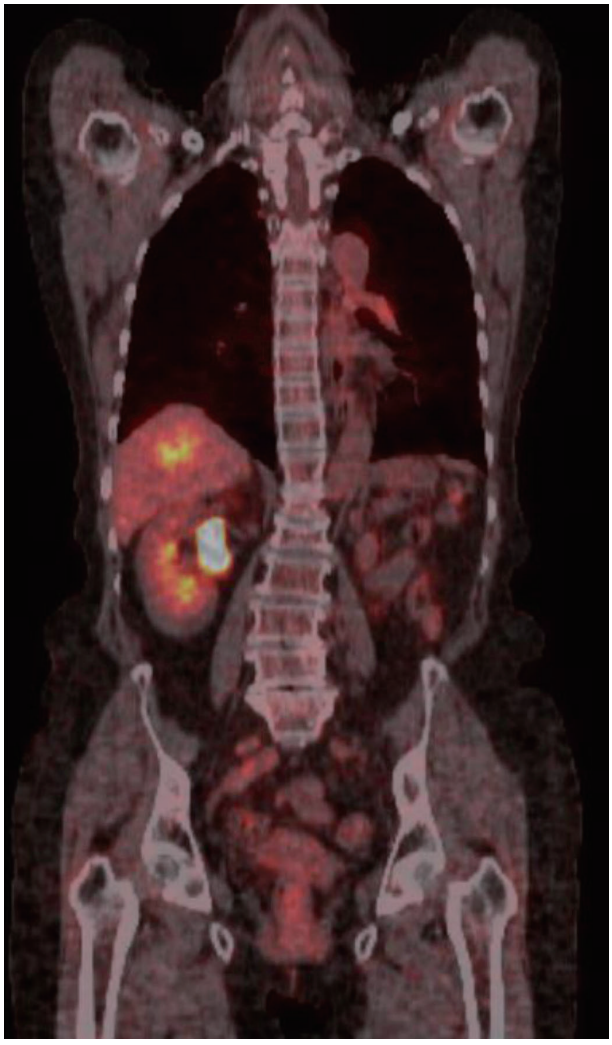

Figure 3. Positron emission tomography-computed tomography findings. Increased FDG uptake in the liver mass is observed.

negative (Fig. 6). The pathology of the liver parenchyma showed mild inflammation and periportal fibrosis. Based on the above findings, we made a diagnosis of lymphocyte-rich HCC characterized by infiltration of lymphocytes into hepatic tumor cells. As the patient did not undergo a serologic screening test for hepatitis, we checked the viral markers of hepatitis B and C virus (HBV and HCV) after surgery, and she was found positive for anti-HCV antibody and HCV-RNA. Therefore, she had this risk factor for HCC that was detected retrospectively. She recovered well without complications and was discharged 10 days after surgery.

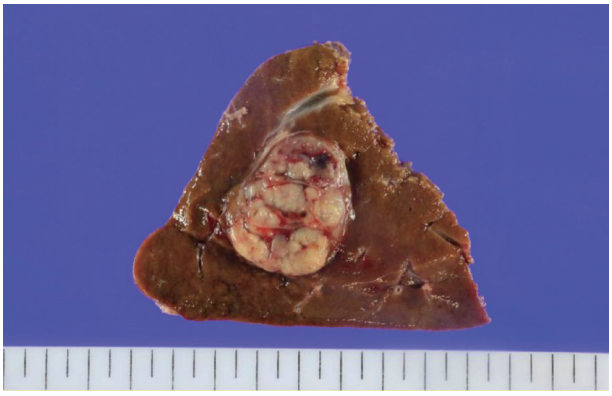

Figure 4. Macroscopic findings of the specimen from surgical resection. It exhibits a 3.5×2.5×2.5 cm sized lobulated mass with a thin capsule encapsulating the mass. It contains a small portion of peliosis and necrotic change. Portal vein and bile duct invasion are not seen.

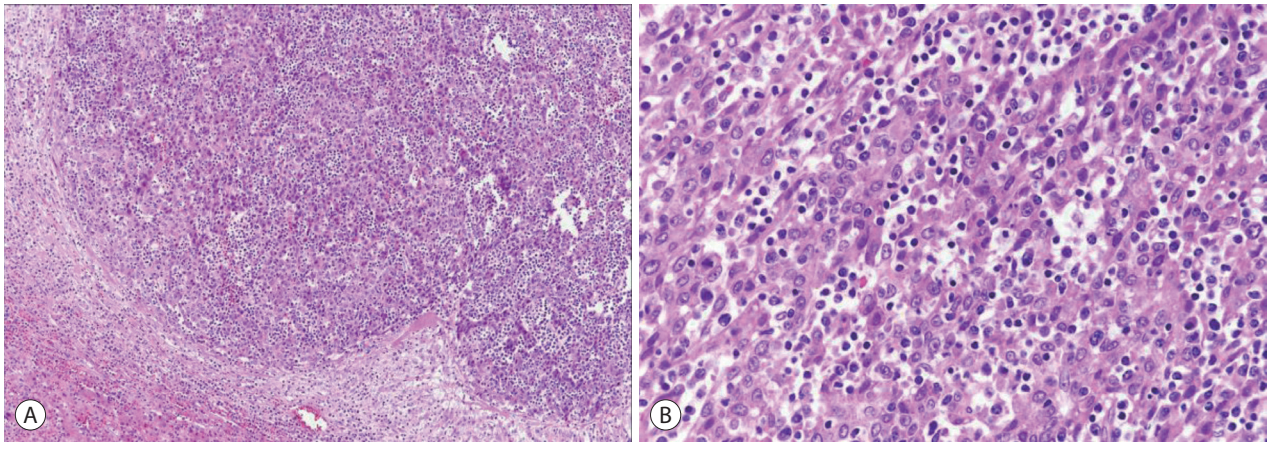

Figure 5. Findings on microscopy. Hematoxylin and eosin (H&E) staining showing moderately differentiated hepatic tumor cells and large numbers of intra-tumoral infiltration of lymphocytes, which is referred to as a lymphoepithelioma-like pattern (H&E; ×100 [A], ×400 [B]).

DISCUSSION

In this report, we present a very rare case of lymphocyte-rich HCC, one of the histopathological variants of HCC. As mentioned earlier, approximately 35% of HCC cases consist of variants. Among these, lymphocyte-rich HCC is the rarest subtype, accounting for less than 1% of histopathological variants.[7,10] To date, 67 cases of lymphocyte-rich HCC have been reported.[11] It has also been referred to as lymphoepithelioma-like HCC.[5,9,10]

Histologic findings of this subtype are characterized by massive intratumoral infiltration of lymphocytes.[4,5,9] In 1998, Wada et al.[12] reported that it was defined by the presence of more than 100 tumor-infiltrating lymphocytes in 10 high-power fields. Although lymphocyte infiltration needs to be observed for its diagnosis, a unified definition for the density of lymphocytes required for diagnosis has not been established.[11]

Immunohistochemistry generally shows positive findings with routine markers of hepatic differentiation, such as arginase and hepatocyte paraffin 1 (HepPar1).[4,13] Many studies have shown the infiltrates of inflammatory cells composed predominantly of CD4- and CD8-positive T-lymphocytes, along with scattered germinal centers that contain B cells.[4,14,15] According to several case reviews, most cases of lymphocyte-rich HCC show negativity for Epstein-Barr virus encoding region in situ hybridization (EBER-ISH), in contrast to lymphoepithelioma-like carcinoma originating in the nasopharynx.[14,16] A recent study that investigated the expression of PD-L1 in HCC demonstrated that lymphocyte-rich HCC correlated with high expression of PD-L1.[17]

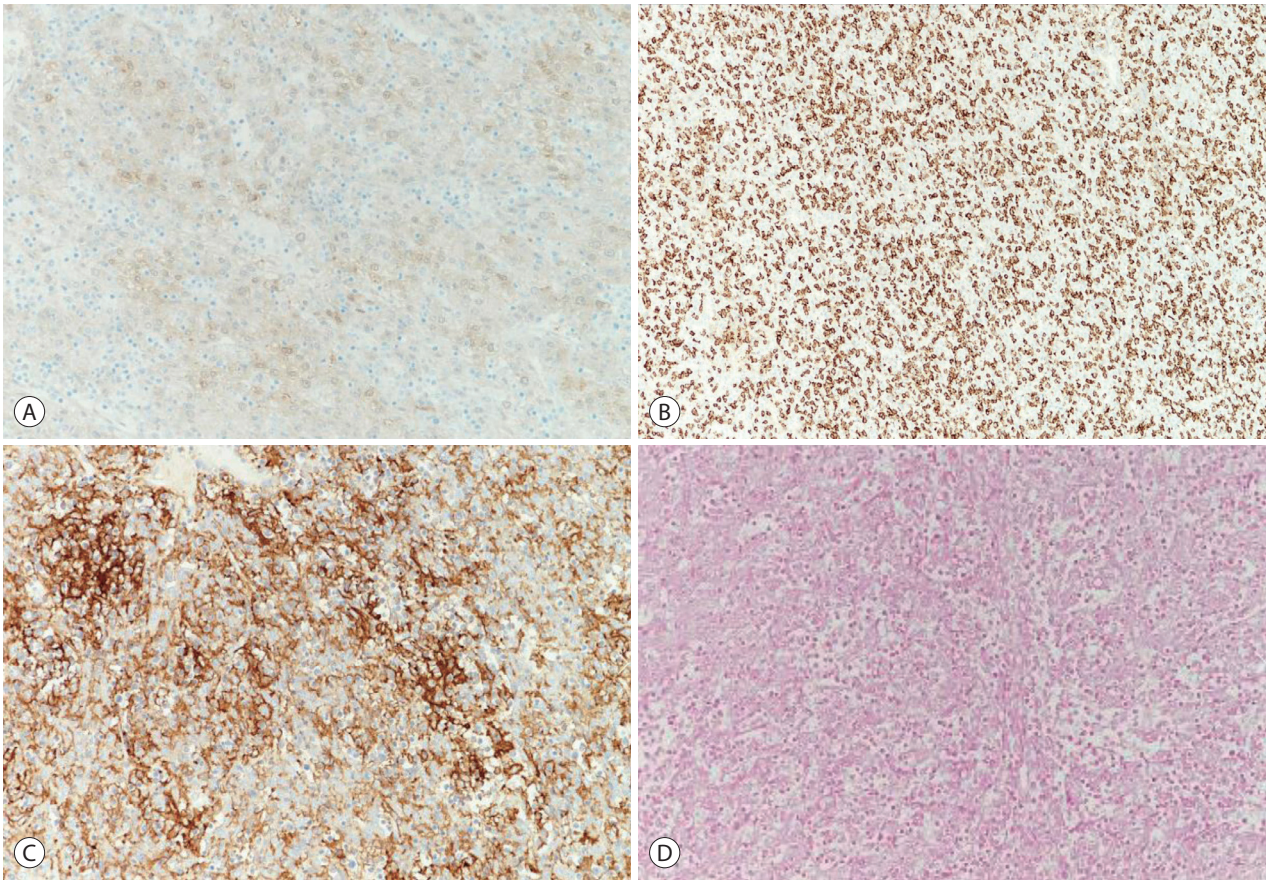

Figure 6. Findings on microscopy. Immunohistochemistry showing weakly positive arginase-1 (original magnification, ×200) (A). The cluster of differentiation 3 and 8 (CD3 and CD8) showing diffusely positive T-lymphocyte markers (original magnification, ×100) (B, showing the result of CD8). Programmed death-ligand 1 is positive with 90% of tumor proportion score (original magnification, ×200) (C). Negative findings of Epstein-Barr virus-encoded RNA in-situ hybridization (original magnification, ×200) (D).

The clinical outcomes and prognosis of lymphocyte-rich HCC are more favorable than those of conventional HCC.[12,14] Lymphocyte-rich HCC showed better overall survival (5-year survival, 94.1% vs. 63.9%; $P<0.05$) and progression-free survival (5-year survival 87.8% vs. 46.6%, $P<0.05$) compared to HCC without lymphocyte infiltration.[14] The reason is not fully understood, but it may be due to the immunosuppressive effect of inflammatory cells that control tumor progression.[18] Which contradicts the fact that PD-L1 is generally associated with poor prognosis in malignancy.[17] As there are not enough reported cases of this subtype to define the prognostic significance, further research is needed to clarify this question.

Genetic characterization of lymphocyte-rich HCC remains largely unknown. Recently, a study has defined the genomic landscape of 12 lymphocyte-rich HCCs using whole-exome sequencing.[19] According to this, mutations in *CTNNB1*, *AXIN1*, *APC*, N*OTCH1*, and *NOTCH2* were less frequently observed in lymphocyte-rich HCC than in conventional HCC. They also established that the amplification of oncogenes (*CCND1*, *FGF19*, and *FGF4*) from chromosome 11q13.3 was prevalent in lymphocyte-rich HCC, which was associated with high immune cell infiltrates and increased checkpoint gene expression. These molecular alterations suggest that lymphocyte-rich HCC is possibly more susceptible to immunotherapies.[19,20]

In the present case, it was challenging to make an accurate diagnosis using imaging studies alone because the patient had been already diagnosed and treated for colon cancer, and imaging findings could not completely differentiate between primary liver cancer and liver metastasis. Besides, we did not detect that the patient had hepatitis C infection as a risk factor for HCC before surgery. As she was followed up regularly for colon cancer, HCC was found at an early stage when it could be totally resected and did not need adjuvant treatment. This case also showed the pathologic features described above, which included massive infiltration of T-lymphocytes, high expression of PD-L1, and negative findings of EBER-ISH.

In conclusion, we encountered a case of lymphocyte-rich HCC, which is the rarest histopathological variant of HCC. We hope that this case broadens our knowledge of rare HCC variants.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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