INTRODUCTION

A 70-year-old woman was diagnosed with poorly differentiated lymphocyte-rich hepatocellular carcinoma (HCC). In this case, programmed cell death 1 expression was observed. Immune checkpoint inhibitor treatment may be effective in such cases, although there has been only one report of their use for poorly differentiated lymphocyte-rich HCC.

In the past, poorly/undifferentiated hepatocellular carcinoma (HCC) with high lymphocytic infiltration was classified as lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC). In the 2019 revision of the WHO classification, it was incorporated into the lymphocyte-rich subtype, regardless of differentiation. We present a case of poorly differentiated lymphocyte-rich HCC, which corresponds to LEL-HCC in the previous classification, and performed a pathological investigation.

Abstract

Our pathological study of a case of poorly differentiated lymphocyte-rich hepatocellular carcinoma suggested that immune checkpoint inhibitor may be an effective therapy. The histological type is an important factor in determining treatment choices.

KEYWORDS

hepatocellular carcinoma, immune checkpoint inhibitors, lymphocyte-rich, lymphoepithelial hepatocellular carcinoma, programmed cell death ligand 1
In 2019, a 70-year-old woman visited her local doctor with a complaint of 15 kg of weight loss over a month. Abdominal ultrasound revealed a liver tumor, and she was referred to our hospital. There was no history of alcohol intake. Blood examination (Table 1) showed aspartate aminotransferase elevation (AST; 66 U/L, normal <30 U/L), alanine aminotransferase elevation (ALT; 68 U/L, normal <23 U/L), positive HBs antigen, HBV-DNA elevation (5.6 LogIU/ml), and negative hepatitis C virus antibody. Alpha-fetoprotein (AFP) was markedly elevated (3946 ng/ml, normal <7.0 ng/ml). Abdominal ultrasound revealed a 22 × 20 mm mass with an internal mosaic pattern in segment five of the liver (Figure 1). Angiographic computed tomography (AGCT) scan revealed low absorption in CT during arteriopography (CTAP) and uniformly high absorption in both early and delayed CT during hepatic arteriography (CTHA; Figure 2). EOB-MRI revealed a high signal in early phase, low signal in hepatocellular phase, high signal in diffusion-weighted image, and low signal in ADC (Figure 3). The lesion was solitary and there were no findings suggestive of vascular invasion. Laparoscopic partial hepatectomy was performed subsequent to the diagnosis of classical HCC UICC (Union for International Cancer Control) Stage Ib. Microscopically, there were many infiltrating lymphocytes in the background, and tumor cells with round to oval nuclei with prominent irregularities and abundant eosinophilic cytoplasm had grown in a plump, sheet-like pattern. Some tubular structures corresponding to the moderately differentiated type
remained at the tumor margins; however, the majority of the cells were the poorly differentiated type (Figure 4). Immunostaining of the tumor cells was positive for glypican 3 and negative for EBER. Programmed cell death ligand 1 (PD-L1) was positive in about 40% of tumor cells, and inflammatory cells around the tumor were also partially positive, showing scattered positive cells in the form of small clusters. The infiltrating lymphocytes showed a mixture of CD3- and CD8- positive cytotoxic T cells and CD4- and FOXP3-positive regulatory T cells (Figures 5-7). Twenty months have passed since hepatectomy and no recurrence has been observed to date.

3 | DISCUSSION

Among undifferentiated cancers with abundant lymphocyte infiltration, those derived from the head and neck region are called lymphoepithelioma. Undifferentiated cancers with abundant lymphocyte infiltration in organs other than the head and neck region are called lymphoepithelioma-like carcinomas (LELC), and in the WHO classification 4th edition, LELC in the liver were classified as lymphoepithelioma-like hepatocellular carcinomas (LEL-HCC). However, in the 2019 revision of the WHO classification, HCC with abundant lymphocyte
infiltration was included in the classification of "hepatocellular carcinoma, lymphocyte-rich" regardless of the degree of differentiation. The frequency of lymphocyte-rich HCC among all HCC cases is less than 1%, and it is reported that its prognosis is better than that of classical HCC. Most cases of LELC in other organs are associated with Epstein-Barr virus (EBV) infection, but most cases of HCC, lymphocyte-rich are negative for EBV. We searched PubMed for articles from 1995 to 2021 using the keywords "lymphoepithelioma-like hepatocellular carcinoma" or "hepatocellular carcinoma lymphocyte-rich". As a result, there were 59 cases corresponding to poorly differentiated lymphocyte-rich HCC (Table 2). We examined a total of 60 cases including the current case. The median age was 61 years; 27 cases were hepatitis B virus (HBV) positive and 19 were hepatitis C virus (HCV) positive. EBV was negative in all but one case. Although there are few reports on the proportion of infiltrating lymphocyte types, there are many cases in which both CD4-positive cells, including regulatory T cells, and CD8-positive cells, considered to be cytotoxic T lymphocytes (CTLs), were present to the same extent. In this case as well, CD4 and CD8 were equally positive. FoxP3 was positive in some of the CD4-positive cells, indicating the presence of regulatory T cells.

In the IMbrave150 trial, the combination of the immune checkpoint inhibitor (ICI) atezolizumab and the
angiogenesis inhibitor bevacizumab for unresectable HCC significantly prolonged overall survival compared with sorafenib. As a result, this combination therapy has come to be used clinically for unresectable HCC. The response rate for this treatment in unresectable HCC is 27.3%, which is a good result, but it is still necessary to identify biomarkers for predicting the effect of ICIs in terms of pharmacoeconomics and personalized medicine. In addition, Chan et al. reported that there are many mutations in the Wnt pathway, including CTNNB1, in normal HCC, as well as many mutations in CCND1 in LEL-HCC. These findings suggest that LEL-HCC may have different tumor properties compared with normal HCC. Therefore, we decided to histopathologically assess the ICI treatment strategy for poorly differentiated lymphocyte-rich HCC. So far, there is only one report for the use of ICIs in LEL-HCC, and there have been multiple reports of cases in which ICIs were effective for LELC in other organs. In a study of 217 cases of HCC by Calderaro et al., the PD-L1 positive rate (>1% of tumor cell-positive cases were
defined as PD-L1 positive) of LEL-HCC tumor cells was three of 13 cases, which was not different from the positive rate of 17% for all HCC. However, the PD-L1 positive rate of surrounding inflammatory cells was significantly high (PD-L1 expression by inflammatory cells was classified as high if the number of PD-L1 positive clusters around the tumor was equal or superior to six [median of the full series]) in 12 of 13 cases (92%). In this case as well, multiple PD-L1-positive immune cell clumps were found around the tumor (Figure 7). It is known that ICIs induce an immune response by inhibiting PD-L1 on tumor-related macrophages, and ICIs may be effective in poorly differentiated lymphocyte-rich HCC. In the study by Calderaro et al., the analysis of the PD-L1 positive rate of LEL-HCC and tumor cells were limited to only 13 cases. In the present case, 40% of the tumor cells were also PD-L1 positive. There are other reports that have shown PD-L1 positive in tumor cells and infiltrating lymphocytes of poorly differentiated lymphocyte-rich HCC, which is consistent with our case. To better understand the tendency for PD-L1 expression in tumor cells in poorly differentiated lymphocyte-rich HCC cases, it is necessary to accumulate more cases. Considering the aforementioned details, it is likely that poorly differentiated lymphocyte-rich HCC, which was once designated as LEL-HCC, can be expected to have a good therapeutic response to ICIs, and these findings may contribute to the stratification of HCC treatment in the future.

4 | CONCLUSION

We presented a rare case of poorly differentiated lymphocyte-rich HCC, which may be present in HCCs showing typical imaging findings. For treatment of advanced cases, ICIs may be effective, and it was considered necessary to confirm pathological findings when selecting treatment.

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CONFLICT OF INTEREST

The authors have no conflict of interests.

AUTHOR CONTRIBUTIONS

GO, TO, and KM collected and analyzed data and wrote and edited the manuscript. KH, ST, HO, KT, KM, and JK involved in the patient’s care. MN, YK, and IT were abdominal surgeons providing hepatectomy. YK and TT were pathologists providing diagnosis.

ETHICAL APPROVAL

This study complied with the standards of the Declaration of Helsinki and the current ethical guidelines.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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