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Rapidly Progressive Pulmonary Lymphangitic Carcinomatosis After Liver Transplantation Due to Diffuse Infiltrative Sarcomatoid Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a heterogeneous tumor that shows a range of clinical manifestations, from indolent growth of well-differentiated HCC to rapid growth with a significantly poorer prognosis.[1] Edmondson and Steiner[2] and World Health Organization classifications[3] are given by grade of differentiation, which is correlated with the rates of HCC recurrence after liver transplant (LT).[4] More specific subclassification has been attempted, although these subtypes are still controversial.[5] Sarcomatoid HCC, which consists of poorly differentiated components with sarcomatoid features, has been recognized as a rare subtype with a notably poor prognosis. Importantly, diffuse infiltration of sarcomatoid HCC is rarely known to cause acute decompensation and liver failure (LF).

On the other hand, an expedited LT evaluation is key to saving patients with a narrow transplant window in the context of LF. However, it is often difficult to determine the morphology of HCC before LT relying on imaging studies. Preoperative tumor biopsy may provide an accurate diagnosis before LT.

This report describes a patient with sarcomatoid HCC who underwent LT after an expedited evaluation and progressed to pulmonary lymphangitic carcinomatosis.

CASE DESCRIPTION

The patient was a 71-y-old man with a history of type 2 diabetes, psoriasis, chronic kidney disease, and biopsy-proven metabolic dysfunction-associated steatohepatitis diagnosed about 40 y ago. He presented with acute liver decompensation with hepatic encephalopathy and kidney failure, requiring hemodialysis from the day of presentation, hyperbilirubinemia with a bilirubin of 27 mg/dL, and coagulopathy with an international normalized ratio of prothrombin time of 2.7. His transaminase levels in the 200s IU/L. The etiology of his decompensation including an autoimmune, ischemic, and infectious workup, was negative. Drug-induced liver injury from his upadacitinib for psoriasis was considered. Imaging including a dynamic contrast-enhanced computed tomography (CT) and magnetic resonance imaging showed a cirrhotic liver morphology, a 3.4-cm mass with characteristics of HCC in segment 8 (organ procurement and transplantation network [OPTN]-5B) (Figure 1A and B), an indeterminate 3.8 cm mass in segment 8 (OPTN-3) (Figure 1C), and a bland appearing thrombus in the left portal vein (Figure 1D). There was mild splenomegaly but otherwise no evidence of severe chronic portal hypertension. Because the patient manifested slightly lower oxygen saturation levels (91%–95% on room air), dynamic contrast-enhanced chest CT and pulmonary ventilation/perfusion scans were performed. These studies did not show signs of pulmonary embolism, and his manifestation was considered a status of over-fluid volume because of kidney failure. In addition, this CT scan also did not reveal definitive evidence of metastases of HCC, although the presence of an indeterminant nodule (Figure 1E) and interlobular septal thickening (Figure 1F) in the right upper lobe were noted. A positron emission tomography (PET) scan was not performed since his HCC was recognized as a localized lesion with a low

Received 21 October 2023. Revision received 19 December 2023.

Accepted 4 January 2024.

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T.N. and S.K. participated in the research design. T.N., R.T., A.S., K.L., E.B., T.T., and S.K. participated in the writing of the article. T.N., R.T., T.Y., L.D., H.Y., N.E., A.B., T.K., J.M., and S.K. participated in the care of the patient. T.N., T.T., and S.K. participated in data analysis.

The authors declare no funding or conflicts of interest.

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001594

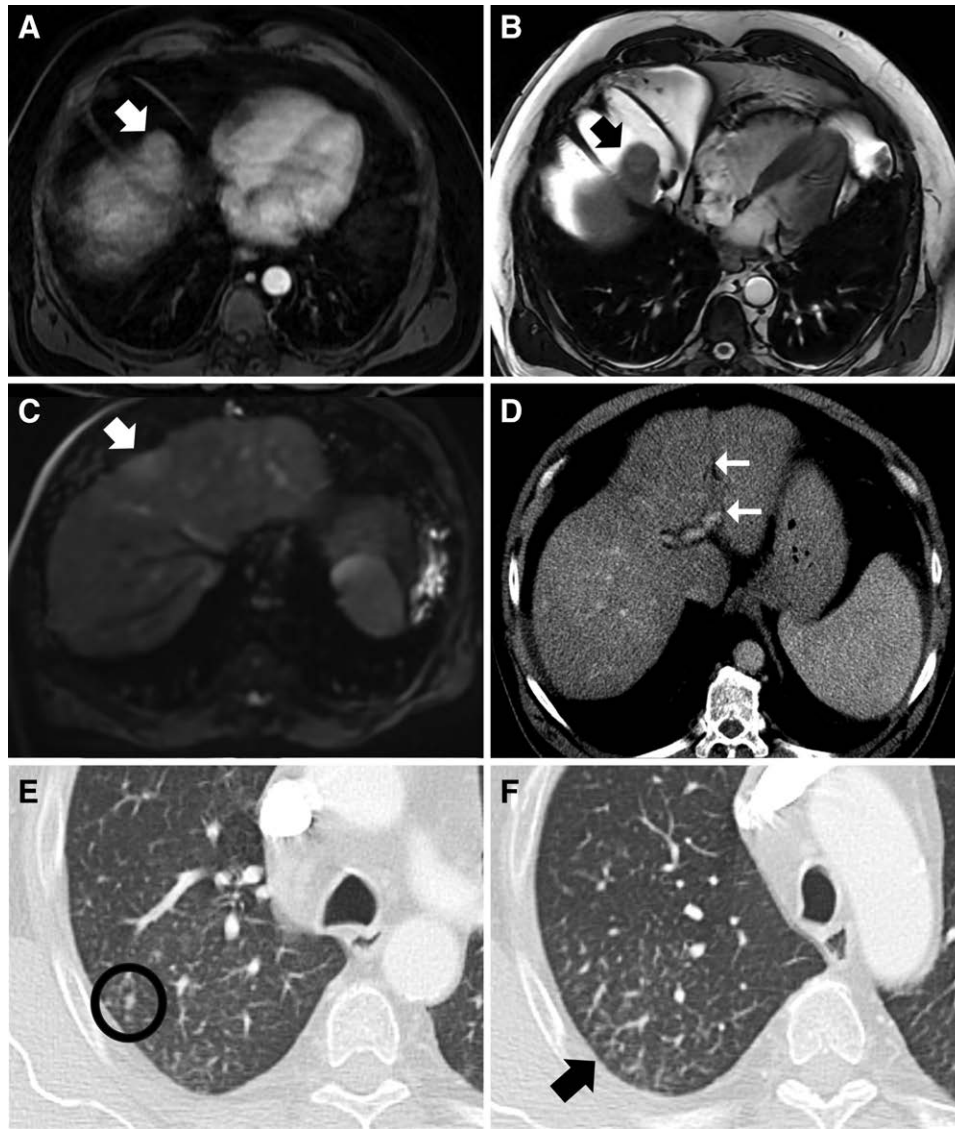

FIGURE 1. Preoperative magnetic resonance imaging and computed tomography studies. A and B, 3.4 × 3.0 cm arterially enhanced segment 8 lesion demonstrates washout and pseudocapsule. It is categorized as an liver imaging reporting and data system-5 and organ procurement and transplantation network (OPTN)-5B lesion in arterial phase and T2-weighted imaging, respectively (arrows). C, A white arrow indicates that it is adjacent to a legion of capsular retraction in segment 8, which is categorized as an LR-3 and OPTN-3 lesion (diffusion-weighted imaging). D, There is a filling defect in the distal left portal vein (between arrows). E, An indeterminant nodule (encircled). F, Interlobular septal thickening in the right upper lobe.

suspicion of metastases at this point based on imaging studies and a low alpha-fetoprotein (AFP) level of 1.8 ng/mL.

After confirming his stable heart function, he was urgently listed for a simultaneous liver-kidney transplant with a model for end-stage liver disease of 47 and HCC within the Milan criteria, 2 d after his admission. A liver from a brain-dead donor became available 4 d after listing and an LT was performed in the standard fashion without major issues, although the kidney transplant was canceled due to an inadequate organ quality.

His clinical course was not significant, with extubation on postoperative day (POD) 1, although the patient required low-level supplemental oxygen. The patient did not demonstrate apparent surgical complications such as vascular or biliary issues. However, his oxygen requirement increased on POD 10, and on POD 12 he developed acute pulmonary edema requiring intubation, as well as shock of unclear etiology requiring vasopressors. An infectious workup was negative, and his shock progressed over a week despite broad-spectrum antibiotics and vasopressor support. Ultimately, he was palliatively extubated on POD 17 and died (Figure 2).

Gross pathologic evaluation of his explanted liver revealed a 3.3-cm mass in segment 8 with a 1.1-cm satellite nodule and tumor thrombi within multiple intraparenchymal veins (Figure 3A). Microscopic examination of the segment 8 mass lesion and satellite nodule showed conventional HCC, with a predominantly well to moderately differentiated histology (Figure 3B). Adjacent to the mass lesion, however, was an abrupt transition to a high-grade malignancy with a markedly atypical spindle cell morphology, morphologically consistent with sarcomatoid carcinoma (Figure 3C). The high-grade malignant component was diffusely infiltrative into the sinusoids as well as numerous small and large caliber vessels

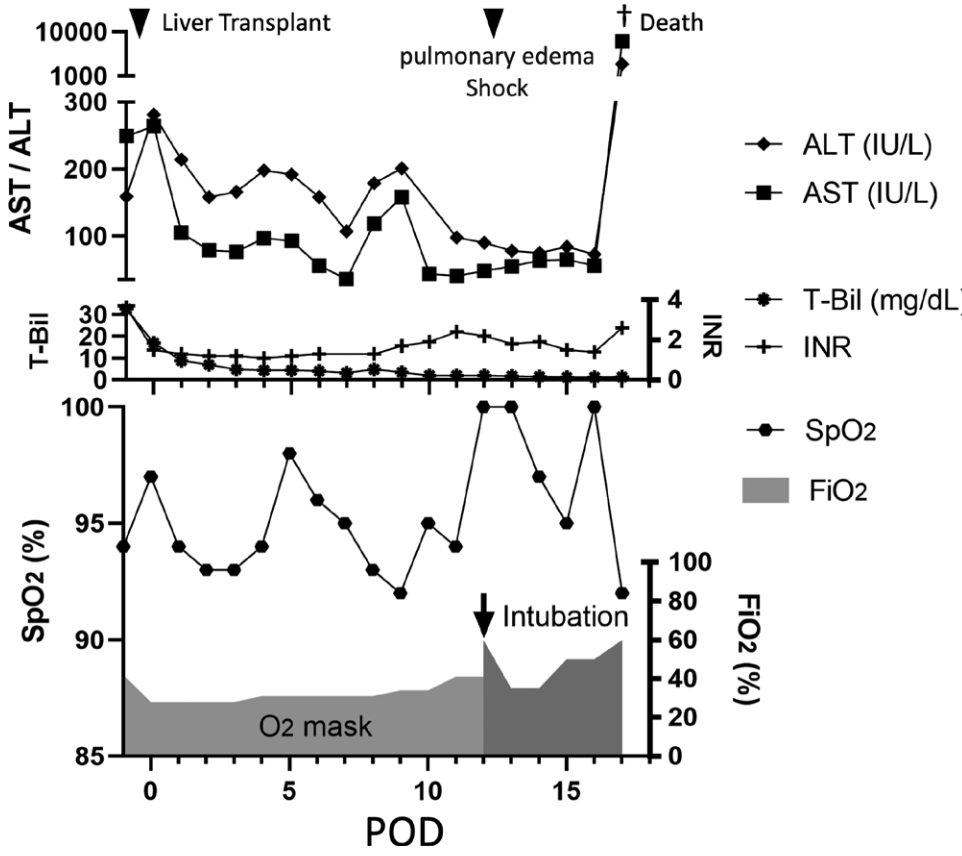

FIGURE 2. Schematic presentation of the clinical course. ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio of prothrombin time; POD, postoperative day.

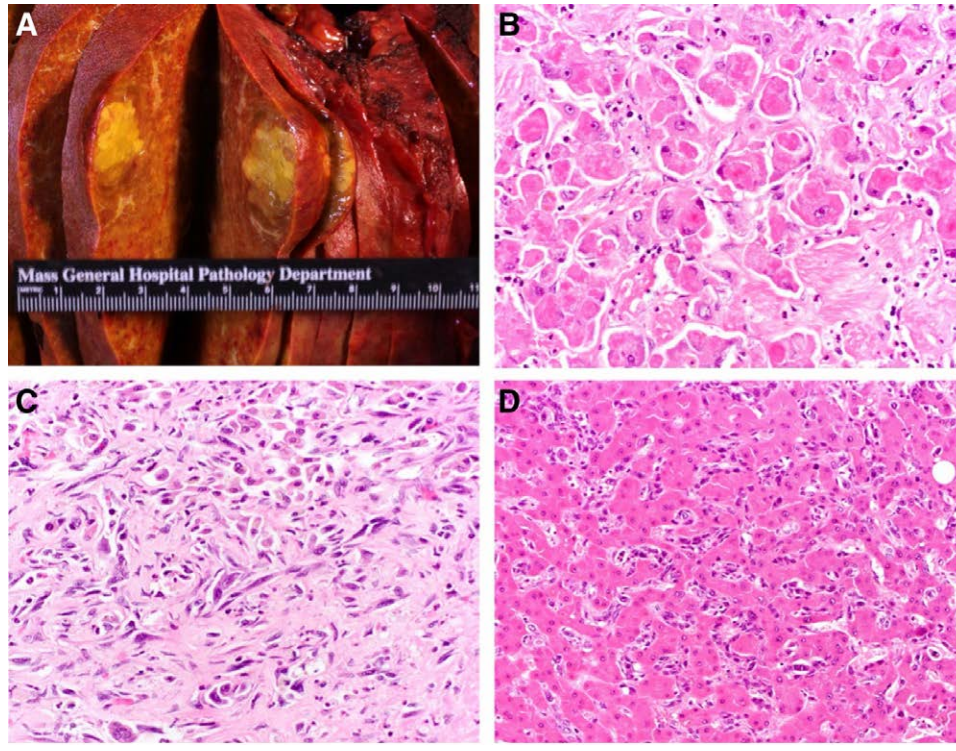

FIGURE 3. Liver explant. Gross photographs of the liver explant demonstrate a subcapsular 3.3-cm nodule, which shows a well-defined heterogeneous yellow-brown cut surface (A). The background liver showed extensive cholestasis with macroscopic nodular changes. Microscopic examination of the subcapsular nodule on routine H&E stain shows an atypical epithelioid proliferation with abundant eosinophilic cytoplasm, forming small nests in a fibrotic stroma, consistent with moderately differentiated hepatocellular carcinoma (B). Adjacent to the nodule was an area with a morphologically distinct high-grade spindle cell proliferation, comprised of elongated and spindled cells with atypical nuclei morphologically suggestive of sarcomatoid carcinoma (C). Histologic examination of the background liver away from the mass lesion demonstrated extensive sinusoidal involvement (D).

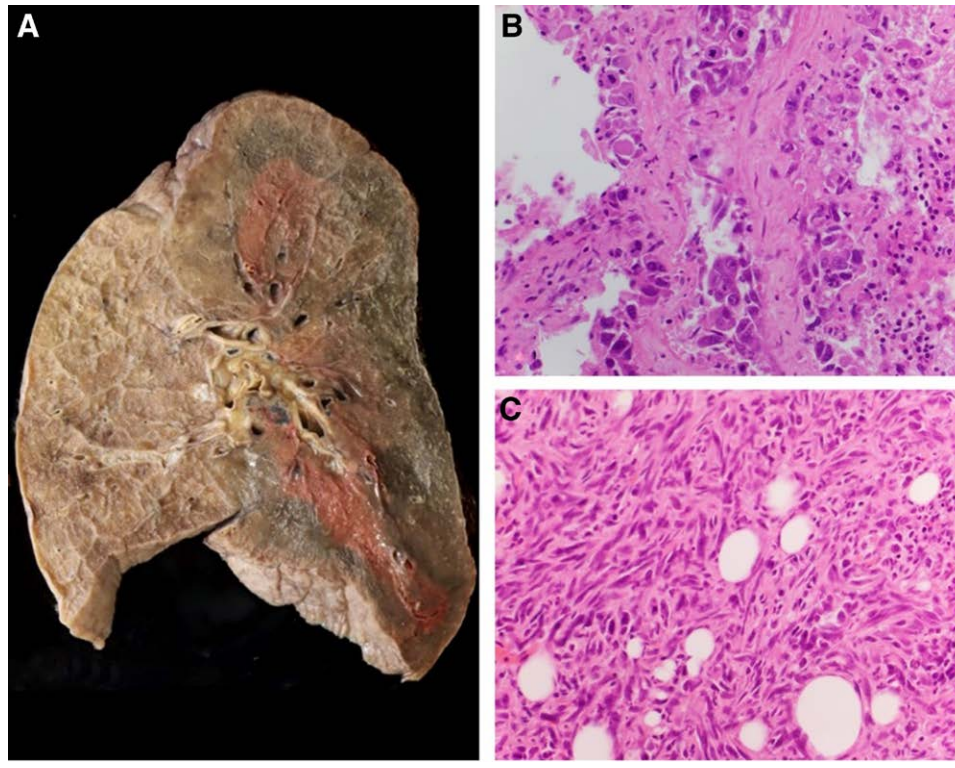

FIGURE 4. Postmortem examination. Postmortem examination showed lungs with grossly evident patchy consolidation (A). Microscopic examination of routine H&E stains showed that the lung parenchyma was extensively involved by a high-grade malignancy extensively involving lymphovascular spaces and without definitive mass formation (B). The malignant epithelioid cells have abundant eosinophilic cytoplasm and marked cytologic atypia, showing morphologic overlap with the known primary liver primary. Similarly, the bone marrow shows extensive replacement by a high-grade malignant neoplasm showing morphologic overlap with the sarcomatoid component of the known liver primary (C).

(including major branches of the hepatic vein) (Figure 3D). The majority of the background liver parenchyma was diffusely involved by the spindle cell malignancy. Overall, the explanted liver is estimated to be involved by approximately 15% conventional HCC and 85% sarcomatoid carcinoma morphologies.

Immunohistochemistry revealed that the well to moderately differentiated HCC component was positive for arginase 1 and glypican 3, and negative for CK7 and CK19; in situ hybridization confirmed that this component was also positive for albumin. The findings are diagnostic of conventional HCC. However, the high-grade and diffusely infiltrative component showed a different immune profile and was positive for CK7 and CK19, and negative for arginase 1, glypican 3, and albumin. Mucicarmine stains were negative for definitive intracytoplasmic mucin in the high-grade spindle cell component. These features support an overall diagnosis of undifferentiated sarcomatoid carcinoma; in this clinical context, the findings are likely to represent sarcomatoid HCC with extensive sinusoidal infiltration.

On postmortem examination, the lungs were heavy with a weight of 1796 g (Figure 4A). Histologic examination revealed a diffuse high-grade carcinoma throughout the lungs in lymphovascular spaces and within the bone marrow (Figure 4B–C). The malignant cells had an epithelioid morphology with abundant eosinophilic cytoplasm, marked cytologic atypia with prominent nucleoli, and numerous atypical mitotic figures. Morphologically, these malignant cells were similar to those of the carcinoma present in the explanted liver. These findings confirm the extensive lymphovascular and hematogenous spread of an undifferentiated carcinoma. In this clinical context, the findings are consistent with widespread metastatic involvement from sarcomatoid HCC.

DISCUSSION

We present a case where a radiographically occult infiltrative sarcomatoid HCC led to the abrupt LF. Infiltration of primary HCC is rarely on the differential when considering precipitating events that result in acute decompensation. An accurate preoperative diagnosis would have precluded the patient with HCC infiltration from LT.

Regardless of baseline liver conditions, acute liver failure (ALF) secondary to malignant infiltration of the liver is rare. Rich et al[6] presented 27 patients with malignant infiltration of the liver presenting as ALF, of which 1 of 3 had primary malignancies of lymphoma or leukemia. Two patients who underwent LT and one of them for B cell lymphoma achieved more than 5 y of survival after transplant with a CHOP (combination treatment of cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) chemotherapy. However, the 3-wk mortality of the series was 89%, reflecting the dismal prognosis of this presentation. The rapid deterioration to death due to malignant infiltration was also reflected in a case series of 18 patients, 2 of 3 of which were lymphoma cases, with only 1 survival.[7] Although there are few reports that hepatic angiosarcoma,[8] or cholangiocarcinoma[9] cause ALF, it is recognized that ALF, or acute initial decompensation of chronic liver disease secondary due to infiltrative HCC is extremely rare.

Imaging modalities play important roles in identifying infiltrative HCC and its differentiation. A combination of CT and magnetic resonance imaging suggests that infiltrating HCC may be identified by the presence of poorly identified margins, heterogenous washout appearance, or aberrant signal intensity.[10] Furthermore, PET scan is proposed as an imaging modality to identify an infiltrative HCC process in the liver. However, information from imaging studies, coupled with other clinical data such as AFP, still have limitations in accurately recognizing infiltrative HCC.

Therefore, the role of preoperative tumor biopsy has been discussed. Liver and tumor biopsies play key roles in assessing the background liver condition. This can help avert unnecessary LT in patients without advanced fibrosis who may tolerate alternative approaches such as surgical resection and avoid LT, particularly for unfavorable HCC subtypes. Although no prior studies have investigated LT outcomes for sarcomatoid HCC specifically, there is no doubt that LT for poorly differentiated HCC shows unfavorable outcomes.[11] Given the imperfections of imaging studies to detect HCC subtypes, tumor biopsies could be the only method to confirm histologic features of HCC. Preoperative percutaneous liver tumor biopsy is not recommended for all HCC because assessments based on the preoperative variables are typically correct[12] and to avoid needle-track HCC seeding.[13] However, regarding HCC seeding, it is true that the incidence is less than 3% overall.[14] Fuks et al[15] reported preoperative HCC biopsy did not have a negative impact on the outcomes of LT. Thus, preoperative biopsy can be justified especially for being newly diagnosed and with an unknown decompensation etiology. However, a percutaneous liver biopsy would not be preferable in the context of LF due to coagulopathy. Transjugular liver biopsies may be an alternative method, although the diagnostic value for deep lesions would be low and inaccurate. Further, understanding the implications of sarcomatoid HCC on oncological prognosis after LT would improve patient selection and more successful outcomes.

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