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CASE REPORT | LIVER

A Cholangioblastic Variant of Cholangiocarcinoma

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ABSTRACT

Cholangioblastic variant of cholangiocarcinoma is rare and may be encountered in young adults with a liver mass. On biopsy, the pathologic features may mimic neuroendocrine or other tumors. Increased awareness of this unusual variant and the typical strong expression of the immunohistochemical marker inhibin may help prevent diagnostic errors. Because only a few cases have been reported, we also discuss treatment options in a 26-year-old man.

INTRODUCTION

Incidence of primary hepatic and bile duct malignancy has tripled since 1980, and mortality has doubled.[1] Cholangiocarcinoma (CC) is the second most common primary liver malignancy, accounting for approximately 15% of cases.[2,3] Although magnetic resonance imaging may be suggestive of CC, the gold standard for definitive diagnosis remains pathologic characterization.[4,5] In some cases, the diagnosis may be challenging because of tumor mimickers, metastasis, and less well-recognized morphologic CC variants. In 2017, a novel histological variant of CC, now classified as the cholangioblastic variant of intrahepatic CC, was described after being initially diagnosed as neuroendocrine tumors in 3 young female patients preoperatively.[6] We report a case of primary CC with a morphological and immunohistochemical pattern in keeping with this rare variant. To date, only 5 cases have been reported.[6–8] This represents the second case of cholangioblastic variant of CC in a man who was diagnosed preoperatively and treated with systemic therapy. Diagnostic considerations and the patient's treatment course are discussed to improve understanding of this CC variant.

CASE REPORT

A 26-year-old man presented with insidious right upper quadrant abdominal pain, back pain, and weight loss. He was a nonsmoker and nonalcohol drinker, without relevant medical or family history. Initial workup included thoracic and abdominal X-rays, which appeared normal for 3 months. As his symptoms progressed, he developed shortness of breath, and an electrocardiogram was performed, which demonstrated Q-waves. This led to echocardiography, which identified a compressive mass. Subsequent abdominal ultrasound showed a large heterogeneous vascular mass in the right hepatic lobe. Magnetic resonance imaging with contrast showed a 21 × 19 × 17-cm intrahepatic mass compressing the intrahepatic inferior vena cava (Figure 1). An ultrasound-guided core liver biopsy was performed.

Morphologically, tumor cells were organized in a cribriform pattern (Figure 2). Nuclei were uniform and had inconspicuous nucleoli, and the cytoplasm was eosinophilic; some nuclei showed pseudoinclusions (Figure 2). Immunohistochemistry demonstrated strongly positive CK7 and patchy positivity for synaptophysin, CD56, and CK19, with CD34 highlighting a vascular-rich delicate stroma (Figure 2). The tumor stained strongly positive for inhibin (Figure 2). Staining for hepatocellular carcinoma, germ cell tumors, melanoma, metastasis, and other diagnostic considerations showed negative results. A review of the literature recognized a rare potential diagnosis of cholangioblastic variant of CC, which is typically inhibin positive, often expresses neuroendocrine markers, and has similar morphology to low-grade neuroendocrine tumors.

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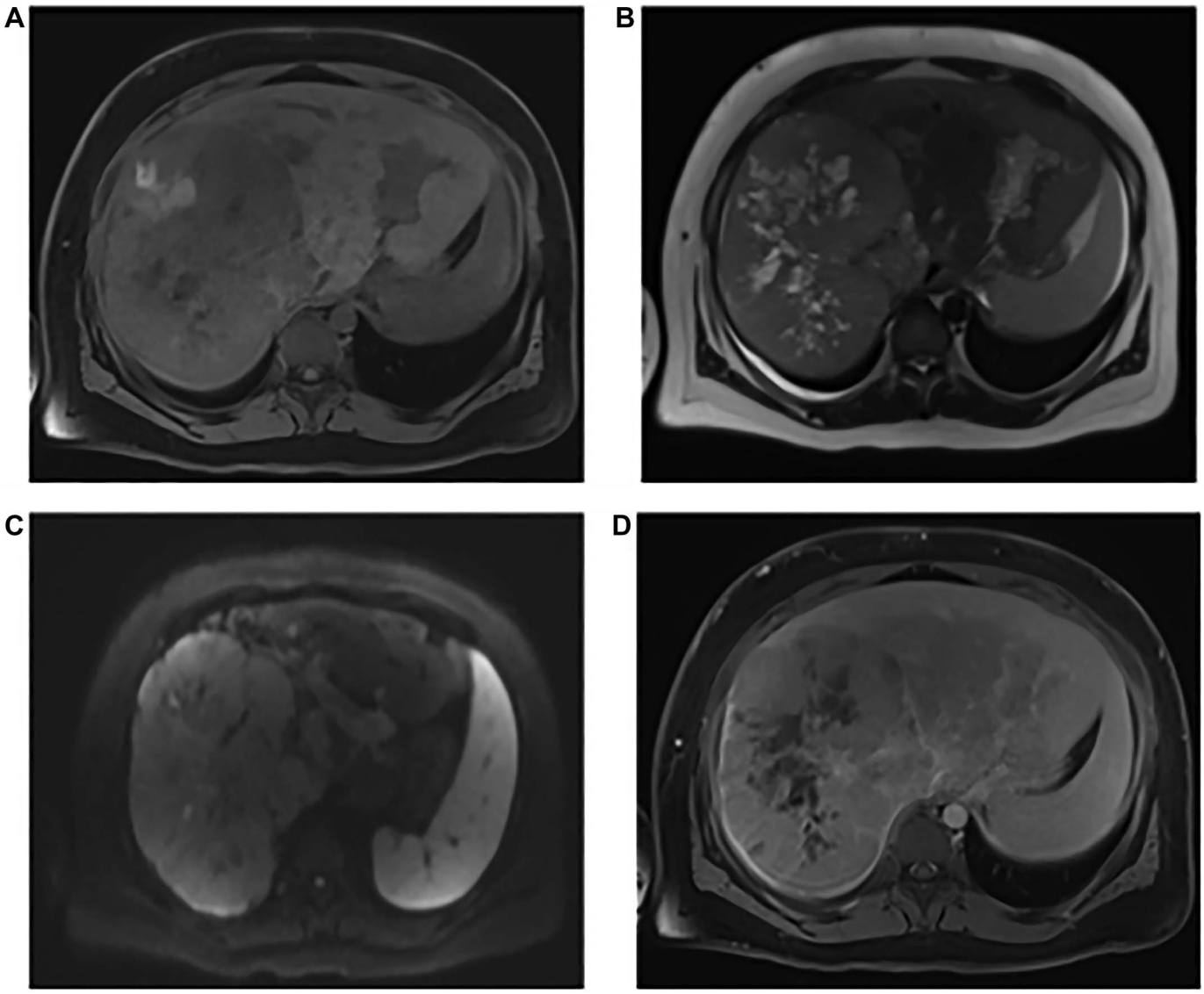

Figure 1. Magnetic resonance imaging of cholangioblastic variant of cholangiocarcinoma. (A) Axial T1 view showing a 21 × 16.7 × 19-cm mass compressing the intrahepatic vena cava. Hypointense cystic lacunae centrally with focal hyperintensity along the anterior and superior aspects of the mass potentially representing hemorrhage. (B) Axial T1 postcontrast (Gadovist) series demonstrating nonenhancing central cystic appearing lacunae. (C) Coronal T2 imaging shows high T2 signal throughout the mass with internal cystic lacunae. (D) Axial T2 imaging shows high T2 signal throughout the mass with internal cystic lacunae.

The patient underwent staging of thorax, abdomen, and pelvis, but because of the CC size and suspicious lymphadenopathy, the tumor was deemed nonresectable. He was subsequently treated medically with cisplatin and gemcitabine, in keeping with treatment for nonresectable CC. Currently, the patient has had 6 months of radiologic stability from diagnosis and 1-year of clinical stability since initial medical presentation and remains highly functional, with an Eastern Cooperative Oncology Group 1 status.

DISCUSSION

We present the second reported case of cholangioblastic variant of CC in a man and summarize diagnostic and therapeutic considerations in cases without operative intervention. To date, only 5 cases with similar diagnoses have been documented, often with difficult diagnostic and therapeutic outcomes.[6–8]

Recognizing the clinical presentation, typically in a young adult with imaging of a large solitary liver mass, the diagnostic consideration of cholangioblastic CC is of utmost importance. The first 4 reported cases of cholangioblastic CC were diagnosed postoperatively, after preliminary diagnoses of neuroendocrine tumors, which shared similar morphology and were typically positive with at least 1 neuroendocrine marker but negative for inhibin. However, inhibin may not be commonly included in a routine pathologic immunohistochemical panel because this variant is relatively newly described. Increasing awareness for

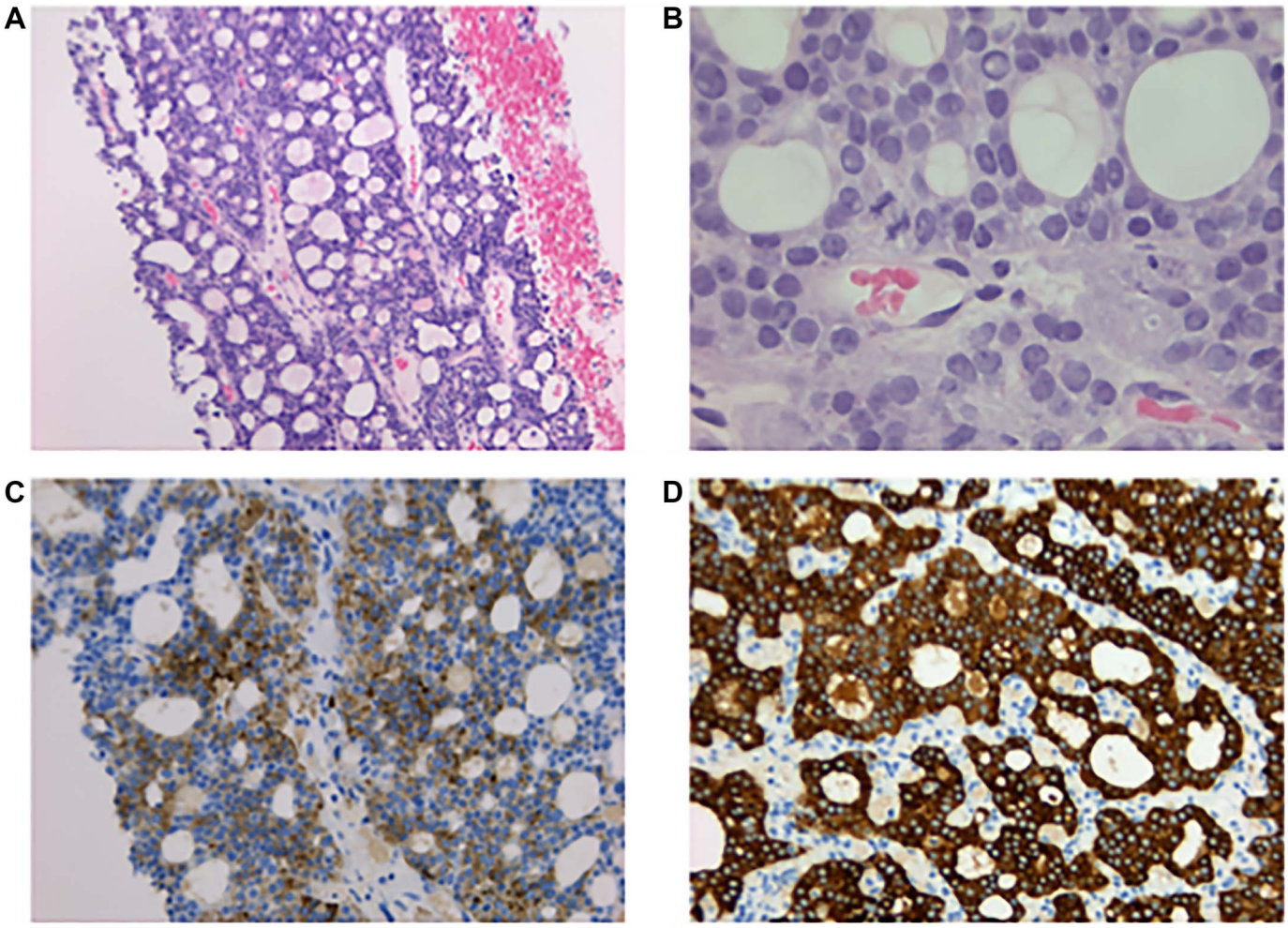

Figure 2. Pathologic characteristics of cholangioblastic variant of cholangiocarcinoma. (A) Tumor cells organized into glands with a cribriform pattern and eosinophilic material within them, without normal appearing hepatic tissue (hematoxylin and eosin stain, 100× magnification). (B) Relatively uniform nuclei with intranuclear pseudoinclusions and occasional mitoses (hematoxylin and eosin stain, 630× magnification). (C) Immunohistochemistry stain for synaptophysin at 200× showing patchy positivity; CD56, another neuroendocrine marker, also showed patchy positive staining (not shown); (D) inhibin immunohistochemistry with strong positivity at 200×; other areas showed weakly positive staining (not shown).

pathologists to include inhibin in the context of a bland cribriform tumor in the liver of a young adult may prevent future misdiagnosis.

At the time of the first reported case, only female patients had been documented, leading to consideration that this CC variant may be related to oral contraceptive use or that perhaps these tumors arose in female patients only. However, it seems both female and male patients are at risk. Thus far, all 6 reported cases were aged 20–30 years. A hepatic biopsy can assist in diagnosis and may help guide treatment, as seen in our case. Once CC is recognized, further differentiation into subtypes is suggested.[9] Esposito and Schirmacher provide a comprehensive review of demographics, pathology, and important diagnostic differences for each CC variant.[9] Prognostic differences have been demonstrated, and as we move toward personalized medicine, therapeutic options may become variant specific.[9]

Once the diagnosis is confirmed, treatment options remain unclear. Previously reported cholangioblastic variants of CC have received various neoadjuvant, adjuvant, and palliative intent chemotherapies with variable success. After multidisciplinary discussion at several tumor boards, the decision was to treat this CC variant as a locally advanced biliary tract malignancy with cisplatin and gemcitabine as per the phase 2 study by Valle et al.[10] Of the 5 previously reported patients, 1 was treated similarly with adjuvant gemcitabine and cisplatin but, because of disease progression after 1 cycle, was changed to folinic acid, fluorouracil, and irinotecan treatment; this patient was also enrolled in clinical trials evaluating guadecitabine with durvalumab and then nivolumab and ipilimumab but developed progressive disease in both trials.

Radiation therapy was not considered unless symptomatic mass-effect complications occurred; no previous similar cases have reported utility of radiation in this CC variant. However, 2

patients have received neoadjuvant therapy: 1 with preoperative transarterial chemoembolization and postoperative doxorubicin, cisplatin, zinecard, and sorafenib, followed by oxaliplatin, gemcitabine, and sorafenib, and had 41-month survival. The other patient received preoperative etoposide with ifosfamide, sorafenib, and doxorubicin with cisplatin, and postoperative folinic acid, fluorouracil, and oxaliplatin and survived 30 months. Personalized medicine continues to advance in CC, and novel treatments may become available in the future. Phase 1/2 clinical trials have demonstrated in some selected CC patients modest benefit of pembrolizumab or infigratinib.[11] Several other molecular and genetic targets continue to be investigated and may improve clinical outcomes in CC patients.[12,13]

DISCLOSURES

Author contributions: KV performed literature review, initial text draft, and edits; JB performed expert review of pathologic specimens, text review, and edits; CF performed expert review of radiologic findings, text review, and edits; LAC performed text review and project guidance. KV wrote and edited the manuscript, and reviewed the literature. JB, CF, LAC edited the manuscript and revised the manuscript for intellectual content.

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