Complete Response to Erlotinib and Bevacizumab in a Patient With Biphenotypic (Hepatobiliary) Primary Liver Carcinoma

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Abstract

Biphenotypic (hepatobiliary) primary liver carcinomas [B(H-B)PLCs] are rare tumors with features of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). These tumors are associated with a poor overall prognosis and treatment is not well defined. Research over the past 20 years has identified aberrations in several molecular pathways, including epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) in hepatocellular and biliary tract cancers. These discoveries led to the evaluation of targeted therapies, such as tyrosine kinase inhibitors, for the treatment of HCC and ICC. We report a case of a patient with metastatic B(H-B)PLC found to have a single nucleotide variant in the *EGFR* gene locus R521K who achieved a complete response on imaging after treatment with the combination of an EGFR inhibitor and a VEGF inhibitor. This case prompts consideration of further genomic analysis of these rare tumors and the potential use of targeted therapies in the treatment of patients with B(H-B)PLCs. (J Natl Compr Canc Netw 2015;13:1468–1473)

Biphenotypic (hepatobiliary) primary liver carcinomas [B(H-B)PLCs] are rare tumors representing a heterogenous group of primary liver malignancies with evidence of both biliary and hepatocellular differentiation. These tumors have been referred to by several other names, including *hepatocholangiocellular carcinoma*, *mixed hepatocellular cholangiocarcinoma*, and *combined hepatocellular cholangiocarcinoma*. These tumors account for approximately 1% to 14% of all primary liver cancers.[1] B(H-B)PLCs have been increasingly recognized as distinct from hepatocellular carcinomas (HCCs) and intrahepatic cholangiocarcinomas (ICCs) since the first report in 1903 by Wells[2] and further characterization by Allen and Lisa[3] in 1949. In general, patients with B(H-B)PLCs tend to have a worse prognosis than those with HCCs,[4,5] with overall survival (OS) outcomes similar to those of ICCs; however, this is controversial, because studies have shown variability in outcomes, likely due to small sample sizes.[6,7] No clear guidelines exist regarding the management of B(H-B)PLCs. Hepatic resection remains the preferred treatment; however, for patients with unresectable lesions, locoregional or systemic therapy is considered. HCCs and ICCs respond poorly to chemotherapy, and novel targeted agents are currently being explored in the treatment of these tumors.

This article reports a case of a patient with metastatic B(H-B)PLC who experienced a complete response on imaging after treatment with the combination of an epidermal growth factor receptor (EGFR) inhibitor and a vascular endothelial growth factor (VEGF) inhibitor.

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Case Presentation

During a workup for chest pain in a 77-year-old Caucasian woman, a 3-cm liver lesion was found incidentally. CA19-9, carcinoembryonic antigen (CEA), and α-fetoprotein (AFP) were all within normal limits and hepatitis serologies were negative. She subsequently underwent a biopsy, which showed large cells with abundant eosinophilic cytoplasm and nuclear hyperchromasia forming glands and trabecular structures in an extensively hyalinized stroma. Immunohistochemical (IHC) studies showed strong immunoreactivity to

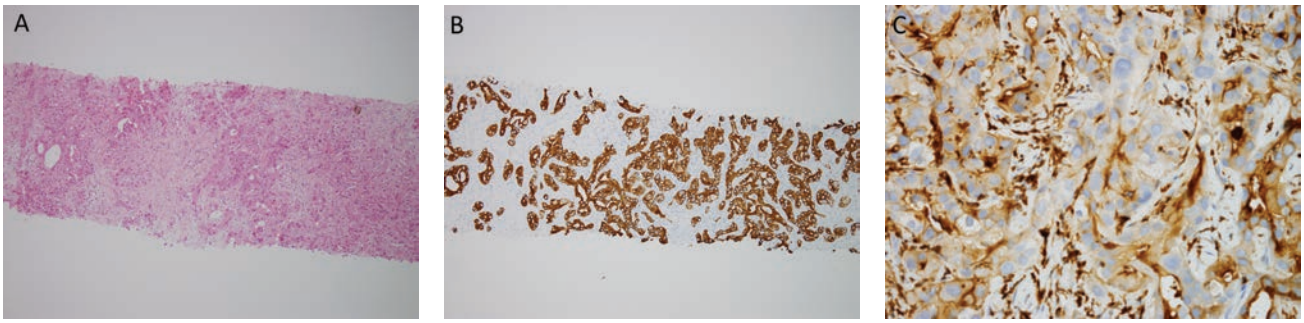

Figure 1 Histopathologic examination of biopsy specimen. (A) Hematoxylin and eosin staining shows poorly formed glands (original magnification x20). (B) Kinase 19 immunostaining shows diffuse reactivity (original magnification x20). (C) Polyclonal carcinoembryonic antigen staining shows canalicular reactivity (original magnification x40).

keratin 7 (K7) and keratin 19 (K19), and polyclonal CEA showed variable reactivity, including abundant tumor cells with canalicular formation consistent with a diagnosis of biphenotypic hepatocellular carcinoma/cholangiocarcinoma (Figure 1). She underwent a segment 4 and 5 hepatic resection with negative surgical margins; however, there was evidence of tumor extension through the liver capsule and a pericystic duct lymph node was positive for tumor involvement, consistent with stage IV disease.

She was seen by Medical Oncology and underwent 8 cycles of adjuvant chemotherapy with single-agent gemcitabine. Six months after completion of adjuvant therapy, she was found to have peritoneal lesions concerning for recurrent metastatic disease on abdominal MRI (Figure 2A). Next-generation sequencing of her tumor from the initial biopsy demonstrated a single nucleotide variant in the *EGFR* gene locus R521K. This polymorphism is of unclear clinical significance in hepatobiliary tract malignancies, but prompted consideration for treatment with an EGFR inhibitor. She was subsequently started on erlotinib, an anti-EGFR small tyrosine kinase inhibitor, at 150 mg orally daily and bevacizumab at 15 mg/kg intravenously every 3 weeks. She tolerated treatment well, with minimal toxicity, and a repeat MRI after 7 cycles of therapy showed complete resolution of the previously seen peritoneal lesions (Figure 2B). She continued on therapy for an additional 2 months and a repeat MRI again showed no radiologic evidence of disease.

She was subsequently given a treatment break, with no evidence of disease recurrence on repeat MRI following 6 months off-therapy. A month after that scan, however, she developed increasing ascites and abdominal pain. Workup revealed recurrent diffuse omental metastases. She was then restarted on erlotinib and bevacizumab, with prompt resolution of her ascites and abdominal discomfort. Bevacizumab was subsequently held a month after retreatment because of hypertension and chest pain, but she was continued on erlotinib at 150 mg daily alone. A repeat MRI after 3 months of therapy showed stable omental disease. She has continued on single-agent erlotinib for almost a year, with imaging continuing to show stable disease and no evidence of new me-

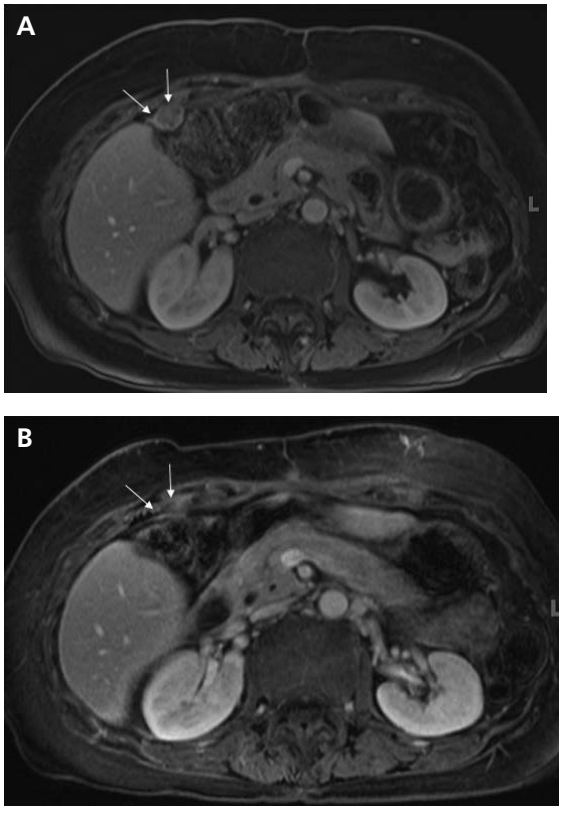

Figure 2 MRI imaging pretreatment and posttreatment. (A) Initial postoperative MRI images show an enhancing soft tissue peritoneal nodule (arrows) compatible with metastases. (B) Follow-up imaging after 3 months of treatment shows complete resolution of the nodule.

tastases. At the time of this report, 42 months have elapsed from the time of initial diagnosis and 27 months since the time of metastatic disease.

Discussion

The WHO defines B(H-B)PLCs as tumors containing unequivocal elements of both HCC and ICC, which are intimately admixed,[8] with further subtypes, including those with stem cell features. These tumors should be distinguished from cases of separate HCC and ICC that arise in the same liver or collision-type tumors in which HCC and ICC are present at adjacent sites. For a diagnosis of B(H-B)PLC to be made, the tumor must have IHC features of biliary (K7, K19) and hepatocellular (eg, polyclonal CEA [pCEA] and CD10 with canalicular staining, cytoplasmic hepatocyte paraffin 1 [HepPar1], thyroid transcription factor-1 [TTF-1]) differentiation, although it is important to note that not all of the IHC markers are consistently positive.[9–12]

The cell or cells of origin in B(H-B)PLC tumors are unknown. It is postulated that the biphenotypic features may be derived from liver progenitor cells or dedifferentiation of mature hepatocytes or HCC. Several studies have shown that HCC and ICC may originate from stem cells[13,14] and that B(H-B)PLC tumor cells display staining for liver progenitor (K19, epithelial call adhesion molecule [epCAM]) and/or stem cell (CD133, CD44) markers,[15,16] supporting the former theory. Comparison of gene expression profiling in HCC, ICC, and B(H-B)PLC tumors found that HCC and ICC groups could be clearly distinguished from one another.[17] Interestingly, more than 70% of B(H-B)PLC tumors clustered with the ICC group, suggesting a closer association of B(H-B)PLC to ICC at the gene expression level.

The clinical presentation of B(H-B)PLCs may be similar to HCCs and ICCs, with incidental finding of a liver mass on imaging or symptoms of abdominal pain, jaundice, ascites, fatigue, weight loss, cholangitis, or pruritus with more advanced disease. Serum tumor markers, such as CA 19-9 or AFP, are not specific for B(H-B)PLCs and would not differentiate them from HCCs or ICCs; however, B(H-B)PLCs may be suspected if both are simultaneously elevated or there is discordance between tumor marker elevation and imaging findings. The etiologic, epidemiologic, and clinical features of B(H-B)PLCs that have been described are variable and may differ by geographic region. The association with chronic liver disease and cirrhosis, for example, may differ between Eastern and Western populations. Case reports from Asia demonstrate that B(H-B)PLCs are more frequently observed in older male patients with chronic hepatitis (more frequently hepatitis B) or cirrhosis,[7,18,19] whereas in contrast, the few US case reports demonstrated no significant difference in gender distribution, and patients were frequently without chronic liver disease, including in our own institutional experience.[1,20]

A recent review of the world's literature summarizes clinical, histologic, and molecular findings up to the current time.[21] One important concept is that, although B(H-B)PLCs may be classified under a single rubric, this is not a single entity and these tumors have several different phenotypes. Thus, identification of histopathologic features often requires application of various IHC stains on otherwise "typical" HCCs or ICCs. This feature may be one of the reasons for differing outcomes among series.

Dynamic contrast-enhanced MRI and CT are the preferred imaging modalities in the evaluation of B(H-B)PLCs. MRI may have greater sensitivity than CT and be more preferable given the absence of ionizing radiation and superior contrast resolution.[22,23] The imaging appearances of B(H-B)PLCs may display overlap between HCC and ICC. Characteristic findings of HCC on CT or MRI include arterial enhancement with washout on portal venous or equilibrium phase imaging, and an enhancing pseudocapsule on delayed images, whereas characteristic findings of ICC include peripheral arterial rim enhancement with progressive centripetal enhancement of fibrous stroma, capsular retraction, and associated biliary ductal dilatation.[22] A case series report from our institution demonstrated that many of the B(H-B)PLC tumors more closely resembled ICC on imaging,[20] and similar findings were observed in a recently published retrospective case series from the Mayo Clinic.[24]

Treatment of B(H-B)PLCs is not well defined given the rarity of these tumors, and current treatment modalities have been extrapolated from the treatment of HCCs or ICCs, which may include hepatic resection, liver transplantation, transarterial chemoembolization, local radiofrequency ablation, or chemotherapy, depending on the stage of the

disease. The prognosis for B(H-B)PLCs is generally worse compared with that of HCCs and ICCs, with most studies demonstrating decreased OS.[1,5,7,25] Our own institutional experience has found that patients with B(H-B)PLC have an OS of 39.2% at 1 year, with the presence of tumor thrombus and satellite lesions being the strongest predictors of poor survival.[26] A case series on liver transplantation for these rare tumors demonstrated a high 5-year recurrence rate of 78% compared with only 17% in patients with HCC.[27] Hepatic resection may offer patients the longest OS; however, the risk of recurrence is high even after resection, with a median time to recurrence of 6 to 9 months.[7] Our institutional study of 65 patients with B(H-B)PLC found that male sex and the presence of satellite lesions were strongly predictive of disease recurrence after resection.[26] HCC generally does not respond to chemotherapy, and although gemcitabine-based regimens have demonstrated improved survival in patients with advanced ICC, the median OS is still less than 1 year.[28] Data for the use of chemotherapy in patients with advanced B(H-B)PLC are limited to a few case reports, with a recent case demonstrating disease control for approximately 12 months with gemcitabine and cisplatin.[29]

Over the past 20 years, research has identified aberrations in several molecular pathways in hepatocellular and biliary tract cancers, which has led to the evaluation of targeted therapies such as tyrosine kinase inhibitors for the treatment of HCC and cholangiocarcinoma. Sorafenib, an oral multikinase inhibitor of VEGF receptor, platelet-derived growth factor receptor, and Raf, has demonstrated improvement in median OS (10.7 months) compared with placebo (7.9 months) in patients with advanced HCC, leading to its subsequent FDA approval.[30] EGFR is expressed in most biliary tract cancers,[31] and overexpression, sustained activation, and mutation have been described in human cholangiocarcinoma cells.[32] This led to the evaluation of EGFR inhibitors in the treatment of patients with advanced biliary cancers. In a phase II study of 42 patients with advanced biliary tract cancers, erlotinib at 150 mg daily demonstrated a median OS of 7.5 months and median time to disease progression of 2.6 months, although no conclusions could be made regarding the correlation of EGFR expression to disease response given the small sample size.[33] Subsequently, a phase III randomized controlled trial with gemcitabine and oxaliplatin with or without erlotinib was conducted, which demonstrated no difference in median progression-free survival (PFS) or OS between the cohorts.[34] A similar study was conducted using another EGFR inhibitor, cetuximab, which also failed to demonstrate an improvement in PFS or OS.[35] The significance of the EGFR R521K polymorphism in B(H-B)PLCs or any other cancer is still unclear. This particular EGFR polymorphism, located in the CT2 domain of the *EGFR* gene, has been associated with improved outcomes with anti-EGFR therapy use in colorectal and head and neck cancers.[36–38] The EGFR R521K polymorphism seen in our patient was thought to be most consistent with a constitutional variant.

VEGF is a key factor of angiogenesis that facilitates tumor growth and metastasis. It is expressed in approximately 30% to 50% of biliary tract cancers and may correlate with a worse prognosis.[39] Bevacizumab, a VEGF inhibitor, has been evaluated in advanced biliary tract cancers in combination with erlotinib and chemotherapy. In a small phase II study of 53 patients with unresectable biliary tract cancers, the combination of erlotinib at 150 mg daily with bevacizumab at 5 mg/kg every 2 weeks was well tolerated with 12% of patients demonstrating a partial response at a median duration of 8.4 months and 51% of patients demonstrated stable disease.[40] The combination of bevacizumab with gemcitabine and oxaliplatin demonstrated an overall response rate of 41% with a median PFS of 7.6 months and median OS of 14.2 months for patients with ICC.[41]

The use of next-generation sequencing has helped to identify additional targetable pathways in patients with biliary tract tumors. A recent abstract presented by Ross et al[42] at the Gastrointestinal Cancers Symposium reported the results of next-generation sequencing on 554 biliary tract cancer specimens, including patients with ICC, extrahepatic cholangiocarcinoma (ECC), and gallbladder cancer. Interestingly, two-thirds of patients were found to harbor a clinically relevant genomic alteration. ICCs demonstrated increased FGFR1–3 fusions and amplifications and IDH1/2 substitutions compared with ECC and gallbladder cancers, whereas all 3 malignancies shared genomic alterations in cell cycle (CDKN2A/B loss) and chromatin remodeling (ARID1A alterations). The abstract described 4 patients who were found individually to have al-

terations in *ERBB2*, *FGFR3*, *BRAF*, and *EGFR* and who achieved partial clinical response to treatment with their respective inhibitors, but none showed a complete remission on imaging. Genomic analysis via targeted next-generation sequencing of 18 B(H-B)PLC patient samples from our institutional biliary registry revealed high rates of mutations in *p53*, *FGFR4*, *FLT3*, and *EGFR*, and a statistically significant increase in *p53* mutations was observed in B(H-B)PLC tumors compared with HCC and CC.[43] The incidence of *p53* mutations in B(H-B)PLC tumors has previously been reported at 10% to 29%.[44] Additionally, loss of heterozygosity in 4q, 8p, 13q, 16q, and 17p are frequently seen in B(H-B)PLCs, along with 3p and 14q, and mutations in *KRAS* have also been rarely described.[44]

To our knowledge, this case represents the only report of a patient with B(H-B)PLC who experienced a complete response to targeted therapy with EGFR and VEGF inhibitors. Whether the presence of the EGFR R521K polymorphism contributed to the patient's dramatic response to targeted therapy is unclear, because it is likely to represent a germline single nucleotide polymorphism rather than a driver mutation. Therefore, the reason for the patient's dramatic response to targeted therapy and prolonged survival has yet to be elucidated.

Conclusions

B(H-B)PLCs are heterogenous, rare tumors that are distinct from HCCs and ICCs and are associated with a poor overall prognosis. Treatment of B(H-B)PLC is not well defined, but the use of targeted therapies may prove to be effective, as illustrated in this case. Further research and improved understanding of the disease pathogenesis may ultimately improve the treatment and prognosis of these cancers.

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