ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Acute-on-Chronic Liver Failure Incited by Cyclin-Dependent Kinase Inhibitor Therapy for Breast Cancer Effectively Treated With Liver Transplantation

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ABSTRACT

Cyclin-dependent kinase 4/6 inhibitors are targeted therapies demonstrated to significantly improve overall survival as adjuvant treatment of estrogen receptor-positive breast cancers. Although intended to preferentially arrest cell cycle transitions in tumor cells, these agents can have undesirable systemic side effects, including hepatotoxicity. We report the first case of cyclin-dependent kinase 4/6 inhibitor therapy leading to acute-on-chronic liver failure requiring liver transplantation. Our case highlights the multidisciplinary approach required to manage acute-on-chronic liver failure induced by cancer-directed therapies in those with extrahepatic malignancies.

KEYWORDS: acute on chronic liver failure (ACLF); breast cancer; cyclin-dependent kinase (CDK) inhibitor; drug-induced liver injury (DILI); liver transplantation

CASE REPORT

A 52-year-old woman presented to the emergency department for a 4-week history of progressively worsening jaundice, fatigue, altered sleep cycle, abdominal distention, and lower extremity edema. Medical history was notable for obesity, obstructive sleep apnea, and nonalcoholic fatty liver disease (NAFLD). She also had stage IIa estrogen receptor-positive right-sided breast cancer diagnosed 2 years prior to admission (PTA) status post lumpectomy, chemotherapy, and radiation. Surgical history was notable for cholecystectomy. Medications included duloxetine and breast cancer adjuvant therapy, which comprised abemaciclib and letrozole for the past 11 months. She last worked as a substitute teacher 8 weeks PTA. She traveled to Lake of the Ozarks 3 weeks PTA, approximately 1 week after the onset of jaundice; no travel companions had similar symptoms. She denied significant alcohol use, smoking, recreational drug use, herbal or over-the-counter supplement use, recent infections, or recent vaccinations. Review of systems was negative for fever, weight loss, shortness of breath, vomiting, diarrhea, melena, or rashes.

On presentation, the patient was afebrile, with blood pressure 132/67 mm Hg, heart rate 115 beats per minute, respiratory rate 18 breaths per minute, oxygen saturation 95% on room air, and body mass index 36. Physical examination revealed a fatigued-appearing woman with jaundice, right upper quadrant tenderness, abdominal distention with fluid wave, bilateral lower extremity edema, and inability to perform Serial Seven Test. Asterixis was absent on the day of presentation but developed within 24 hours. Laboratory studies showed a cholestatic liver injury pattern with synthetic dysfunction, thrombocytopenia, and acute kidney injury (Table 1). Phosphatidylethanol level was undetectable. A rising bilirubin and declining platelet count were evident 2–3 months PTA, but these rapidly worsened 2 weeks PTA (Table 1) prompting abemaciclib and letrozole discontinuation. The presence of hepatic encephalopathy with coagulopathy prompted admission for expedited liver transplantation (LT) evaluation for suspected liver failure.

Magnetic resonance cholangiopancreatography showed diffuse hepatic steatosis without biliary ductal dilatation, patent hepatic and portal vasculature, and moderate ascites. Paracentesis revealed a high-serum-ascites albumin gradient with low total protein. Liver

ACG Case Rep J 2024;11:e01253. doi:10.14309/crj.0000000000001253. Published online: January 25, 2024

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Table 1. Evolving biochemical profile of patient including during the abemaciclib treatment course (initiation 11 months PTA) until the day of admission

	Day of admit	3 d PTA	1 wk PTA	2 wk PTA	1 mo PTA	2 mo PTA	3 mo PTA	11 mo PTA
Na	138	135	132	139	138	140	137	139
Cr	2.13	1.69	1.25	0.8	1.1	0.7	0.8	1.0
Albumin	4.0	2.7	2.7	1.8	2.1	2.9	3.6	4.2
ALT	35	38	47	40	54	64	66	42
AST	70	85	84	74	92	129	96	34
T bili	39.8	29.8	29.9	13.4	14.5	6.7	1.3	0.4
D bili	23.6	17.4		9.1	11.0			
ALP	253	254	275	234	277	317	337	122
Platelet	99	110	133	123	117	170	196	261
INR	1.6	1.7	1.3	1.3				
MELD	33	31	27	20				

AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PTA, prior to admission.

biopsy was notable for cirrhosis and steatohepatitis with mild macrovesicular steatosis (~5%), lobular inflammation, occasional ballooning degeneration, rare Mallory bodies, cholestasis with bile ductular reaction, and no evidence of malignancy (Figure 1). A comprehensive serologic workup was only notable for patatin-like phospholipase domain-containing protein 3 (PNPLA3) I148M heterozygosity. Upper endoscopy demonstrated the presence of portal hypertensive gastropathy without esophageal or gastric varices. A breast MRI was normal (Breast Imaging-Reporting and Data System-1), as was positron emission tomography. Circulating tumor DNA was undetectable, consistent with low risk (<10%) of invasive disease occurrence within 5 years.

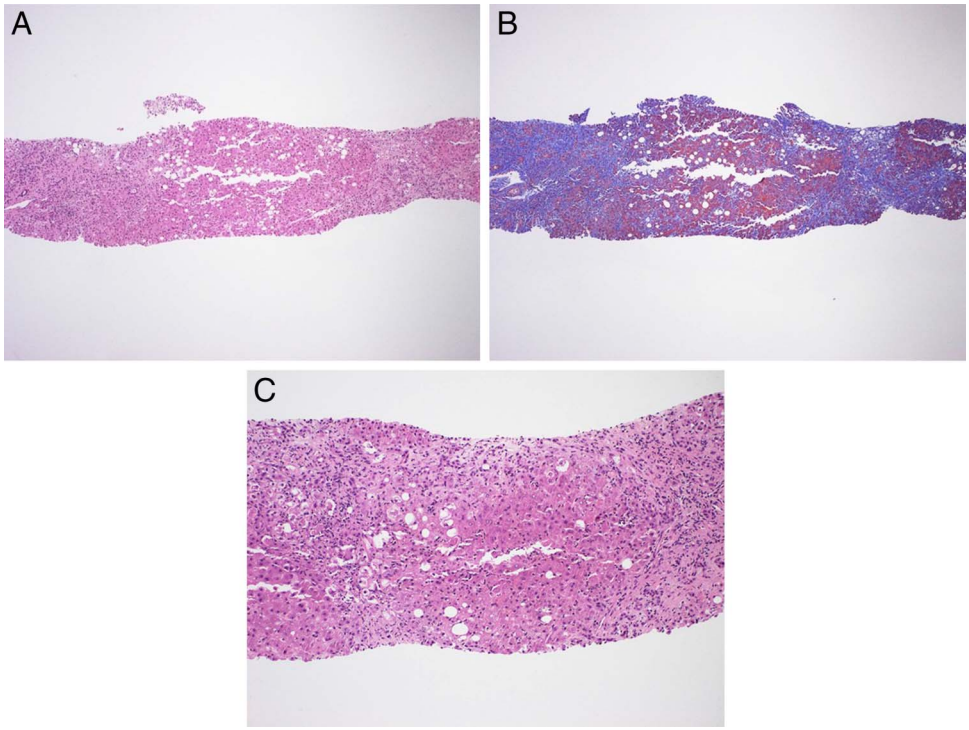

Figure 1. Liver biopsy. (A) Histologic sections show mild macrovesicular steatosis (~5%) with bridging fibrosis with nodule formation consistent with cirrhosis. H&E. 40× magnification. (B) Masson trichrome special stain shows bridging fibrosis with nodule formation confirming cirrhosis. 40× magnification. (C) Higher magnification shows there is lobular inflammation composed predominantly of neutrophils with occasional ballooning degeneration and rare Mallory-Denk bodies. There is also mild hepatocellular cholestasis, focal feathery degeneration, and extensive bile ductular proliferation. No definitive evidence of malignancy is identified. H&E. 100× magnification. H&E, hematoxylin and eosin.

The patient was deemed an appropriate LT candidate by the multidisciplinary selection committee and listed for LT with a calculated Model for End-Stage Liver Disease-Sodium of 35. She underwent deceased donor LT within 7 days of admission. The explanted liver weighed 1,520.6 g with pathology redemonstrating cirrhosis, extensive bile duct proliferation, marked ballooning degeneration, hepatocellular and canalicular cholestasis, ~10%–15% macrovesicular steatosis, and no evidence of malignancy. Thus, after exclusion of other etiologies, the final diagnosis was determined to be acute-on-chronic liver failure due to abemaciclib-induced liver injury in the setting of nonalcoholic steatohepatitis. The patient remains off adjuvant therapy. She fully recovered postoperatively with good graft function at 90 days post-LT and continues to undergo active surveillance for breast cancer recurrence.

DISCUSSION

Cyclin-dependent kinase (CDK) 4/6 inhibitors represent an emerging class of medications implicated in drug-induced liver injury (DILI). CDK4/6 inhibitors are targeted adjuvant therapies for breast cancer designed to preferentially induce apoptosis by blocking the G1-S phase transition in hyperproliferating cells. Review of adverse events from clinical trials and postmarketing reports suggests that mild transaminase elevation less than 5 times the upper limit of normal occurs in 5%–20% of CDK4/6 inhibitor recipients and transaminase elevations greater than 5 times the upper limit of normal is seen in up to 10% of CDK4/6 inhibitor recipients.[1] Several of these recipients also experienced jaundice. Reports of liver failure secondary to CDK4/6 inhibitors are rare. One case report described an individual who died of acute liver failure secondary to thrombotic portal venopathy induced by abemaciclib and fulvestrant.[2] In fact, concomitant use of an aromatase inhibitor with abemaciclib has been identified as a significant risk factor of abemaciclib-induced liver injury.[3] The mechanism by which CDK4/6 inhibitors induce liver injury is not fully elucidated but may involve an idiosyncratic reaction from toxic or immunogenic intermediates or direct toxicity to hepatocytes by CDK inhibition.[1] Review of CDK4/6 inhibitor toxicity in a recent retrospective study suggests the possibility of safely rechallenging with an alternative CDK4/6 inhibitor, which may support the hypothesis that CDK4/6 inhibitors mediate idiosyncratic liver injuries.[4]

To our knowledge, this is the first reported case of CDK4/6 inhibitor-induced hepatotoxicity leading to liver failure and successfully treated with LT. Hepatotoxicity from CDK4/6 inhibitors may truncate the recommended duration of breast cancer treatment. Our patient developed a severe cholestatic liver injury pattern after approximately 11 months of exposure to abemaciclib in the setting of hepatic steatosis. Just as 2 hits can increase the severity of liver dysfunction, the patient's history of NAFLD and metabolic comorbidities may have put her at elevated risk of DILI by CDK4/6 inhibitors. Furthermore, she was found to be heterozygous for PNPLA3 I148M, a mutant triacylglycerol lipase implicated in increased risk of NAFLD/nonalcoholic steatohepatitis, cirrhosis, and even susceptibility to hepatotoxins.[5] Therefore, recognition of underlying liver disease or genetic risk factors such as PNPLA3 mutations can serve to predict those that may develop DILI. In addition, attention to liver injury risk factors can enhance the pharmacovigilance around CDK4/6 inhibitors and prompt early referral to a hepatologist for assistance with drug monitoring if hepatotoxicity results from such critical cancer treatments. Initially, the mild elevations in bilirubin, aspartate aminotransferase, and alanine aminotransferase noted approximately 2–3 months PTA were not immediately linked to CDK4/6 inhibitor therapy and did not meet the recommended aminotransferase-based thresholds for dose interruption.[6] Thus, this case highlights the importance of maintaining a low index of suspicion for DILI as an etiology for any liver test abnormality (including bilirubin elevations) during CDK4/6 inhibitor use.

Consideration of LT in individuals with a history of breast cancer or other extrahepatic malignancies poses unique challenges, especially given the increased risk of malignancy conferred by chronic immunosuppression in the post-transplant setting.[7] Thus, we leveraged advances in next-generation sequencing by measuring circulating tumor DNA as a sensitive, noninvasive way of prognosticating risk of recurrent disease, which aided in the assessment of LT eligibility and post-transplant management. For the first 90 days post-transplant, the patient remains off adjuvant therapy and has been maintained on our transplant center's standard immunosuppression protocol. She will undergo close clinical follow-up and oncologic surveillance with potential to resume aromatase inhibitor adjunct therapy pending clinical course. Altogether, this case features an emerging source of DILI with implementation of a multidisciplinary approach spanning oncology, transplant hepatology, and transplant surgery to successfully care for a patient with acute-on-chronic liver failure secondary to CDK4/6 inhibitor-induced hepatotoxicity.

DISCLOSURES

Author contributions: V. Kalas: conception and design of work, data acquisition, data interpretation, manuscript preparation. J. Nguyen: data acquisition, data interpretation, manuscript revision. AW Wan: data interpretation, manuscript revision. ZC Dietch: data acquisition, data interpretation, manuscript revision. L. Kulik: conception and design of work, data interpretation, manuscript revision. DL Hughes: conception and design of work, data interpretation, manuscript preparation. DL Hughes is the article guarantor.

Financial disclosure: None to report.

Informed consent could not be obtained for this case report.

Received April 18, 2023; Accepted December 7, 2023

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