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Intrahepatic cholangiocarcinoma as a rare secondary malignancy after allogeneic hematopoietic stem cell transplantation for childhood acute lymphoblastic leukemia: A case report

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Abstract

Secondary malignancies are a significant cause of non-relapse mortality in patients who undergo allogeneic HCT. However, secondary liver cancer is rare, and ICC following HCT has never been reported in the literature. Secondary solid cancers typically have a long latency period, and cholangiocarcinoma is classically a malignancy occurring in older individuals. Here, we report the first case of secondary ICC, which presented just 3 years after HCT in a young adult with a history of childhood ALL. A 26-year-old male with history of precursor B-cell ALL presented with asymptomatic elevated liver function tests 3 years after HCT. Laboratories were indicative of biliary obstruction. ERCP showed focal biliary stricturing of the common and left hepatic ducts. MRCP revealed left intrahepatic duct dilatation, suggestive of intrahepatic obstructing mass. Additional workup lead to a clinical diagnosis of ICC. The patient underwent left hepatectomy with extrahepatic bile duct resection and portal lymphadenectomy. Surgical pathology was consistent with moderately differentiated cholangiocarcinoma. Our case illustrates a rare SMN following HCT for ALL. It is the first case report of ICC occurring as a secondary

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AUTHORS' CONTRIBUTIONS

MLG: Assembled, analyzed, and interpreted the patient data. NNS: Identified, consented, and treated the patient as principal investigator. JLD, JMH, MLG, PM, and IRK: Managed the patient's surgical care. DEK and KC: Interpreted the patient's pathology specimens. MLG, PM, IRK, and NNS: Contributed to writing the manuscript. All authors: Read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's family for publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

cancer in this patient population. Although cholangiocarcinoma is characteristically diagnosed in the older population, it must remain on the differential for biliary obstruction in post-HCT patients.

Keywords

acute lymphoblastic leukemia; bone marrow transplant; case report; cholangiocarcinoma; hematopoietic stem cell transplant; Intrahepatic cholangiocarcinoma; secondary malignancy

1 | INTRODUCTION

SMNs pose a considerable health risk in childhood cancer survivors, with a 30-year cumulative incidence approaching 8% (excluding non-melanoma skin cancers).¹ ALL, the most common leukemia in children, accounts for about 25% of all childhood cancers.² Due to advances in treatment strategies, patients with childhood ALL have improved long-term survival leading to increased risk of subsequent late effects, one of the most serious of which is the development of SMN. In fact, patients with childhood ALL who survive at least 25 years from diagnosis have a five-fold increased risk of SMN compared with the general population.³ Patients who undergo allogeneic HCT, which is an important component of treatment for those with high-risk or relapsed disease, are at increased risk for SMN.^{4–6}

Secondary cancers following allogeneic HCT can occur as hematologic malignancies (ie, B- and T-cell malignancies, myelodysplastic syndrome, and acute myeloid leukemia) or, more commonly, solid tumors. Compared with the general population, HCT recipients are at increased risk of SMN of the skin, thyroid, oral cavity, esophagus, brain/nervous system, bone, and connective tissues.⁵ An increased risk of secondary hepatocellular carcinoma in long-term survivors following HCT has also been demonstrated in some studies, with reported risk factors including younger age at HCT (<34 years), TBI-based conditioning, liver cirrhosis, chronic hepatitis C viral infection, and possibly iron overload from prior transfusions.⁵ However, the incidence of secondary liver cancer is rare, and most reports categorize it into the miscellaneous group of “other solid neoplasms.” To date, there are no reports of cholangiocarcinoma occurring as a secondary malignancy following HCT.

Here, we describe a young adult male with a history of HCT for childhood ALL who developed a rare secondary solid liver cancer, ICC. Our case highlights two unusual manifestations of ICC, namely, the young age at diagnosis and the first report of ICC as a secondary cancer following HCT for ALL.

2 | CASE PRESENTATION

A 26-year-old Hispanic male presented with asymptomatic mildly elevated liver function tests suggestive of biliary obstruction (Table 1). He had a history of high-risk precursor B-cell ALL diagnosed at age 18 (Figure 1A) and received a standard therapy that incorporated 4-drug induction. Cytogenetics at diagnosis demonstrated 46XY with low-level gain of chromosomes 9, 12, 17, 21, and 22 and was molecularly negative for fusion transcripts. He achieved remission after the first cycle of induction, was considered a rapid early responder,

and completed 2 years of therapy. Shortly after the completion of therapy, he was found to have isolated CNS relapse and again received a full induction regimen and another 2 years of therapy, including CNS-directed radiation of 1800 cGy. One year later, he presented with bone marrow relapse and low-grade CNS disease. He was subsequently referred for CD19 CAR T-cell therapy, which was preceded by preparative fludarabine, cyclophosphamide, and prophylactic intrathecal methotrexate. After achieving a minimal residual disease negative complete remission (Figure 1B) following CD19 CAR, he underwent a cyclophosphamide/TBI-based (1200 cGy) myeloablative conditioning regimen with a CNS boost of 6 cGy followed by a 10/10 matched sibling donor allogeneic peripheral blood stem cell transplant with activated NK cells post-HCT at age 23. Due to a matched sibling donor and low risk of GVHD in the setting of CD34 selection and T-cell depletion, no GVHD immunosuppression was provided. His treatment was complicated by mild cutaneous GVHD, which resolved with triamcinolone. He subsequently remained in remission for 3 years.

At routine follow-up 3 years after BMT, the patient was found to have asymptomatic mildly elevated liver enzymes (Table 1). Clinical examination was unremarkable. AFP, CA 19–9, and IgG4 levels were all within normal limits, and serum CMV, ANA, AMA, and ASMA were all negative. Viral hepatitis serologies were also negative. Ultrasound showed left intrahepatic biliary ductal dilatation. Subsequent MRI with MRCP showed hilar biliary obstruction involving the confluence and extending into the left hepatic duct with no definite obstructing mass or stone identified (Figure 2). Additionally, there was near obliteration of the left portal vein with clear parenchymal flow abnormality in the left compared with right liver. He underwent ERCP with findings of focal biliary stricturing in the common and left hepatic ducts. Brushings from ERCP were negative, and there was no family history of solid malignancies. All workup to try to determine a diagnosis was unrevealing.

Due to concern for extrinsic lesion causing compression of venous and biliary structures, along with imaging and ERCP findings highly suggestive of hilar cholangiocarcinoma, he was taken to the operating room for diagnostic laparoscopy with exploration and resection. During the operation, a frozen section of the left hepatic duct was taken and was positive for carcinoma. The team proceeded with left hepatectomy with extrahepatic bile duct resection and portal lymphadenectomy. Final surgical pathology results revealed T2b, N1, Mx, and moderately differentiated cholangiocarcinoma (Figure 3) with loss of MSH1 and PMS2. Unfortunately, his post-operative course was complicated by fulminant hepatic failure, leading to mortality 3 days after the operation.

3 | DISCUSSION

Cholangiocarcinoma is the second most common primary hepatic malignancy after hepatocellular carcinoma and can be divided into intra- and extrahepatic. ICC accounts for approximately 20% of cholangiocarcinomas in the United States, with an estimated incidence of 0.5–2.0 cases per 100 000.^{7,8} ICC typically presents between the fifth and seventh decades of life with a median age at diagnosis of 65–70 years and is infrequent in patients younger than 40 years old.^{7,9} Older age at diagnosis may partly explain why ICC has not previously been reported as a secondary malignancy after HCT. In addition, the latency period for solid malignancies following HCT is typically long (> 10 years), with an

increasing incidence with longer time after transplant.^{4,5} In this exceptional case, our patient developed ICC at age 26, just 3 years following HCT.

With the increasing rate of HCTs performed annually, as well as improved survival following HCT, secondary cancers have become a significant cause of non-relapse mortality among HCT recipients.^{3–5,10} Although highly dependent on tumor histology, SMN has been demonstrated to account for up to 5%–10% of late deaths in patients who survive more than 2–5 years post-transplantation.¹⁰ Although an increased risk of secondary liver cancer in long-term survivors following HCT has been demonstrated in some studies,⁵ secondary cholangiocarcinoma has not been previously reported.

Of the reported risk factors for liver cancer among HCT recipients, our patient was young at the time of transplant and underwent TBI-based conditioning. Other than male gender and Hispanic ethnicity,¹¹ he did not have any of the well-established risk factors for ICC: diabetes, obesity, alcohol use, viral hepatitis, cirrhosis, biliary tract diseases, choledochal cysts, and parasitic infection with liver flukes. However, assessing risk factors for SMN after HCT is complicated due to the complexity of treatment exposures and changes in clinical transplantation practices. Previous investigations into the role of conditioning regimens have focused on exposure to TBI and pre-HCT chemotherapy, but with conflicting results. Other research has focused on immune drivers and reactivation of oncogenic viruses, as may be seen after solid organ transplant.⁴ Although there are no currently available data, prior CAR T-cell therapy may play an additional role in the development of secondary malignancies, which becomes an important consideration as its use as a bridging therapy to HCT increases. Further studies are needed to delineate risk factors for SMNs to allow for risk reduction as well as identification of patients who would most benefit from prevention and surveillance efforts.

With increasing rates of HCT, improved long-term survival, and significant risk of secondary cancers in HCT recipients, it is crucial that patients undergo a long-term follow-up that includes awareness of the risk of secondary malignancies with early investigation of any symptoms. Patients must be educated regarding the risk of SMNs in multiple organ systems and therefore report any changes in physical condition, including those that are seemingly insignificant. In fact, although our patient was asymptomatic at presentation, he later recalled a few self-resolving episodes of epigastric and right upper quadrant abdominal pain associated with nausea and emesis which had occurred over the previous 2 months.

4 | CONCLUSION

To our knowledge, this is the first case report of ICC occurring as a secondary cancer following HCT in a young adult with ALL. Although ICC is characteristically a malignancy of older individuals, it must remain on the differential for biliary obstruction in post-HCT patients.

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Abbreviations:

ALL	acute lymphoblastic leukemia
BMT	bone marrow transplantation
CAR	chimeric antigen receptor
CNS	central nervous system
GVHD	graft-versus-host disease
HCT	hematopoietic stem cell transplantation
ICC	intrahepatic cholangiocarcinoma
SMN	secondary malignant neoplasm
TBI	total body irradiation

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FIGURE 1.

Acute lymphoblastic leukemia diagnosis and remission. A, Paucicellular bone marrow aspirate with 24% blasts. B, Cellular aspirate with trilineage hematopoiesis and no increase in blasts. Corresponding flow cytometry showed no immunophenotypic evidence of B-lymphoblastic leukemia (not shown)

FIGURE 2.

Abnormal MRI of the liver. A, Volume loss involving the left lobe of the liver with moderate left lobe intrahepatic biliary dilatation. Right lobe of the liver demonstrates diffuse loss of signal intensity compatible with hepatic steatosis. B, Diffuse dilatation of the left hepatic lobe intrahepatic ducts without dilatation of the common bile duct or the right intrahepatic ducts

FIGURE 3.

Cholangiocarcinoma. A, Sections showed a moderately differentiated adenocarcinoma arising from the left hepatic duct and mainly infiltrating the connective tissue around the duct (H&E, 40×). B, Focally the tumor was less differentiated, with poorly formed glands infiltrating through a dense fibrotic stroma (H&E, 400×)

TABLE 1

Presenting laboratory values

Laboratory test	Value	Reference range
AST	59	0–40 (U/L)
ALT	97	0–41 (U/L)
Alk. Phos.	196	40–130 (U/L)
Total Bili.	1.7	0.0–1.2 (mg/dL)
Direct Bili.	0.3	0.0–0.3 (mg/dL)
Total Protein	7.2	6.4–8.3 (g/dL)
Albumin	4.3	3.5–5.2 (g/dL)

Abbreviations: Alk.Phos., alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; Bili., bilirubin.