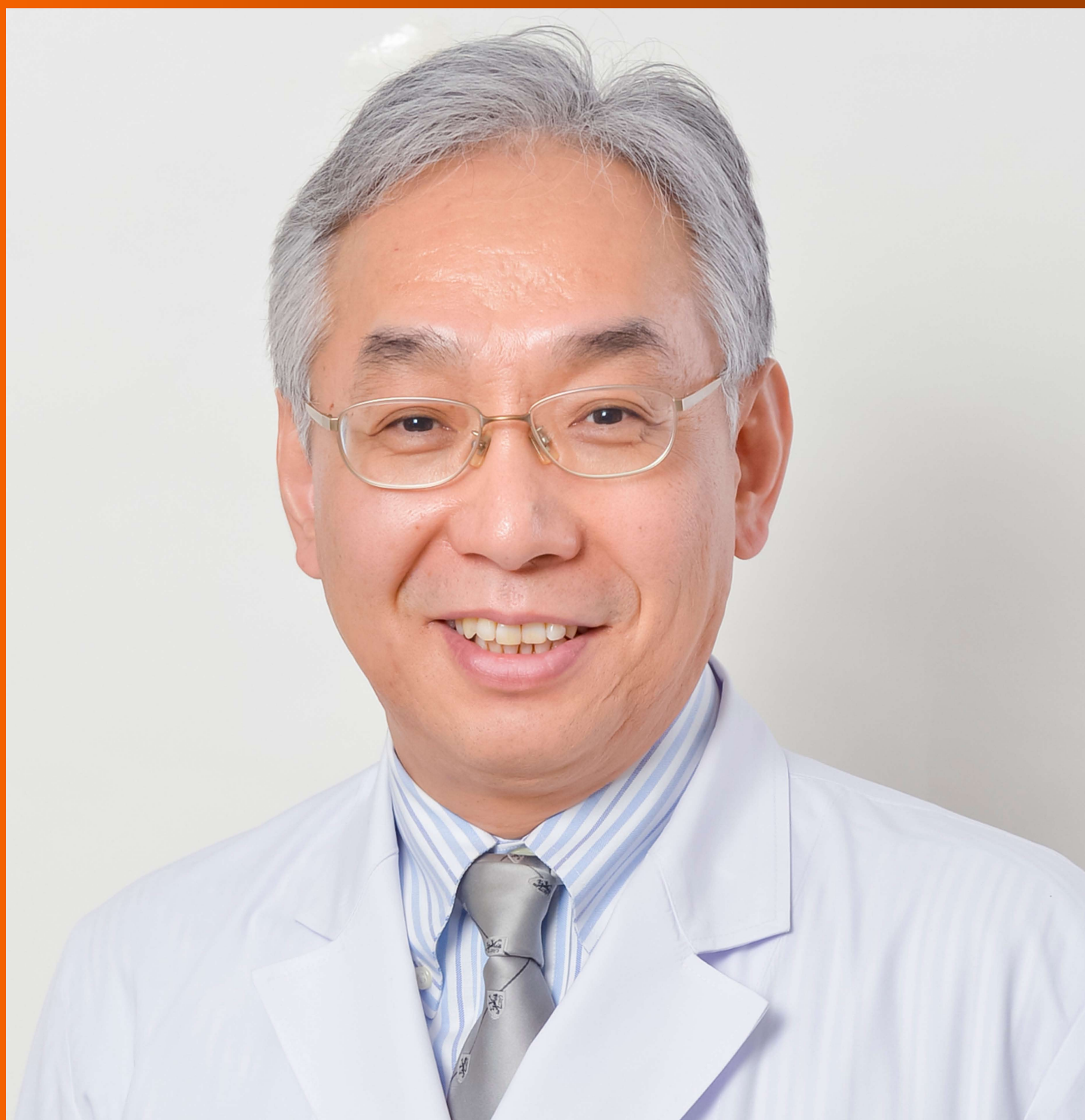


# World Journal of *Hepatology*

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*WJH* covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## De-novo hepatocellular carcinoma after pediatric living donor liver transplantation

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### Abstract

*De-novo* malignancies carry an incidence ranging between 3%-26% after transplant and account for the second highest cause of post-transplant mortality behind cardiovascular disease. While the majority of *de-novo* malignancies after transplant usually consist



of skin cancers, there has been an increasing rate of solid tumor cancers over the last 15 years. Although, recurrence of hepatocellular carcinoma (HCC) is well understood among patients transplanted for HCC, there are increasing reports of *de-novo* HCC in those transplanted for a non-HCC indication. The proposed pathophysiology for these cases has been mainly connected to the presence of advanced graft fibrosis or cirrhosis and always associated with the presence of hepatitis B or C virus. We report the first known case of *de-novo* HCC in a recipient, 14 years after a pediatric living related donor liver transplantation for end-stage liver disease due to biliary atresia without the presence of hepatitis B or C virus before and after transplant. We present this case report to increase the awareness of this phenomenon and address on the utility for screening and surveillance of hepatocellular carcinoma among these individuals. One recommendation is to use similar guidelines for screening, diagnosis, and treatment for HCC as those used for primary HCC in the pre-transplant patient, focusing on those recipients who have advanced fibrosis in the allograft, regardless of etiology.

**Key words:** Liver transplantation; *De-novo* hepatocellular carcinoma; Living donor liver transplantation; Biliary atresia

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**Core tip:** *De-novo* hepatocellular carcinoma (HCC) is a rare event compared to other *de-novo* malignancies, although the number of reported cases are increasing. The pathophysiology has been related with advanced graft fibrosis, cirrhosis and hepatitis viral serology. We report the first case of *De-novo* HCC 14 years after living related donor liver transplantation for end-stage liver disease due to biliary atresia without positive hepatitis B or C viral serology. Current screening and treatment guidelines have not been well established. This increasing phenomenon challenges us to define the utility of screening and surveillance for hepatocellular carcinoma in these individuals.

Torres-Landa S, Munoz-Abraham AS, Fortune BE, Gurung A, Pollak J, Emre SH, Rodriguez-Davalos MI, Schilsky ML. *De-novo* hepatocellular carcinoma after pediatric living donor liver transplantation. *World J Hepatol* 2017; 9(36): 1361-1366 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v9/i36/1361.htm> DOI: <http://dx.doi.org/10.4254/wjh.v9.i36.1361>

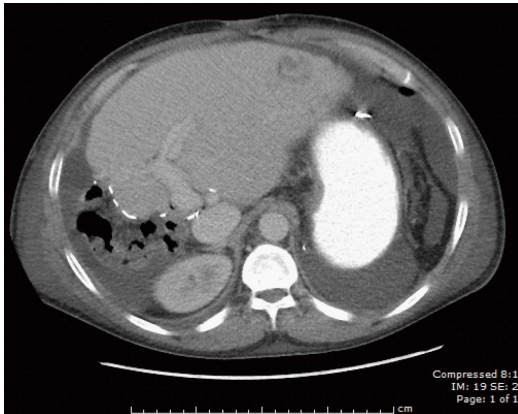
## INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary malignancy of the liver, is one of the most lethal and prevalent cancers worldwide. However, the use of liver transplantation (LT) is a well proven

treatment approach for patients with low stage tumor. The pathogenesis of HCC typically involves chronic liver injury with regeneration, fibrosis and cirrhosis leading to dysplasia within regenerating nodules with an end result of malignancy<sup>[1]</sup>. HCC development in a liver allograft occurs most often in the setting of prior HCC where it is defined as recurrence<sup>[2]</sup>. *De-novo* tumor formation that arises in the transplanted graft without evidence of tumor in the previously explanted liver is uncommon and is mainly seen in patients with advanced graft fibrosis or cirrhosis and associated with the presence of hepatitis B or C viral infection<sup>[3]</sup>. The literature reveals only 15 documented cases of *de-novo* HCC after LT<sup>[4-15]</sup>. We report the first case of *de-novo* HCC occurring 14 years after a pediatric patient received a living related donor LT for end stage liver disease secondary to biliary atresia.

## CASE REPORT

A 29-year-old male with a history of biliary atresia with failed Kasai procedure complicated with progressive cirrhosis and portal hypertension that received a left lateral segment living donor liver transplant (LDLT) from his biological father at 15 years of age. His immunosuppressive regimen included tacrolimus, and sirolimus. Eleven years after his LDLT, he developed advanced liver fibrosis and portal hypertension that manifested as refractory ascites. He received a splenectomy and a central spleno-renal shunt that eventually failed. He then underwent a side-to-side porto-caval shunt (PCS) at age 27 years. After 2 years with controlled disease, he presented with recurrent ascites and overt hepatic encephalopathy (HE) related to his progressive graft failure. His clinical course was also complicated by severe protein losing enteropathy due to his worsening portal hypertension (sprue was excluded by small bowel biopsy). Other causes of hypoalbuminemia were ruled out (*e.g.*, kidney injury secondary sirolimus, as evidenced by 24-h urine collection with minimal protein and normal creatinine). Liver biopsy at this time showed stage 3-4 fibrosis. In addition, there was a paucity of interlobular bile ducts with degenerative changes in the remaining ducts, features compatible with chronic allograft rejection. A few months after, an abdominal ultrasound of the graft revealed a hepatic mass measuring 2.9 cm × 2.2 cm located in segment 2/3 and no evidence of intrahepatic duct dilation. Dynamic CT imaging showed a 3 cm lesion in the left lateral segment that was slightly hypodense and indeterminate in nature (Figure 1). A dynamic magnetic resonance imaging (MRI) using liver mass protocol was performed due to the indeterminate nature of the lesion on CT and demonstrated increased vascularity of the lesion, raising suspicion for HCC. An ultrasound-guided percutaneous biopsy of the mass revealed a well-differentiated HCC (Figure 2). Chest CT scan and bone scan demonstrated no evidence of extra hepatic disease. Alpha-fetoprotein (AFP) level was slightly elevated at 17 ng/mL (normal < 6 ng/mL).



**Figure 1** Dynamic computerized tomography scan imaging showing indeterminate 3 cm lesion in the left lateral segment.

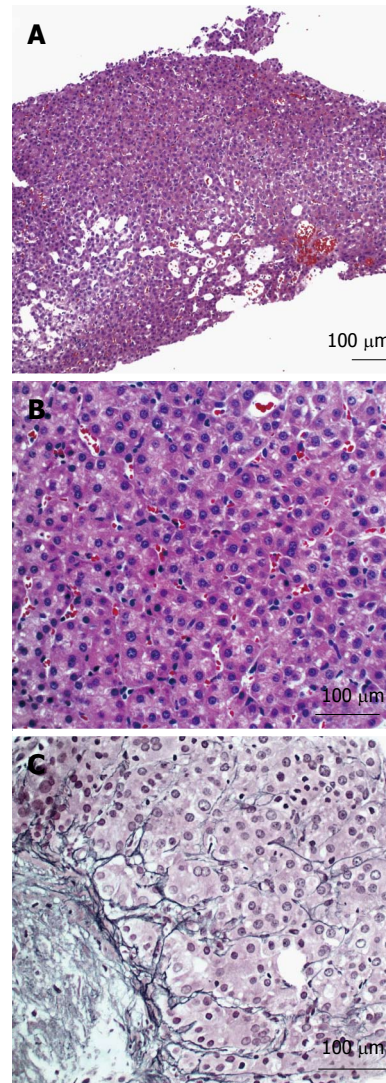
Anti-HBcAb (anti-hepatitis B core total antibodies) at this time and a year before showed negative results. The lesion was subsequently treated by percutaneous microwave ablation (PMWA).

Follow up MRI was performed 1.5 mo after the ablation and showed no residual tumor (Figure 3). The patient was subsequently listed for repeat liver transplantation. However, while on the wait-list he developed a second post-transplant malignancy, an EBV negative Burkitt's type lymphoma. He received chemotherapy for the lymphoma but succumbed to complications due to the treatment that was in part limited by his advanced liver disease.

## DISCUSSION

Liver transplantation provides the highest survival rates among patients with decompensated cirrhosis and complications of portal hypertension but recipients have a 2-4 fold increased risk of developing *de-novo* malignancies when compared to matched healthy controls<sup>[16]</sup>. *De-novo* malignancies represent 30% of post-transplant deaths and one of the most common causes of death in patients that survive beyond a year after transplantation<sup>[3,17]</sup>. Although there is an increased risk of developing malignancies, *De-novo* HCC is uncommon<sup>[3,17]</sup>.

When HCC after transplantation is identified, it is crucial to know if it is a recurrent malignancy as this carries a poor prognosis. Travesani *et al.*<sup>[17]</sup> have proposed an algorithm where they suggest suspicion primary features of a recurrent case including lymph node invasion, macro and microvascular invasion, tumor size > 5 cm, high grade tumor, bi-lobe involvement and high alpha fetoprotein levels. Secondary features include early occurrence, < 2 years, and extra hepatic localization. Without the presence of these characteristics, the suspicion turns towards a *de-novo* HCC. Other common clinical factors that suggest a *de-novo* case, even in patients transplanted for or with a previous HCC, are older donor age, alcoholic liver disease, viral hepatitis,



**Figure 2** Ultrasound-guided liver biopsy. A: Biopsy of the mass shows a solid growth pattern of hepatocytes (H+E, 100 ×); B: Neoplastic hepatocytes contain hyperchromatic, pleomorphic and enlarged nuclei (H+E, 200 ×); C: Reticulin stain demonstrates thickened trabeculae and decreased staining in the lesion (200 ×).

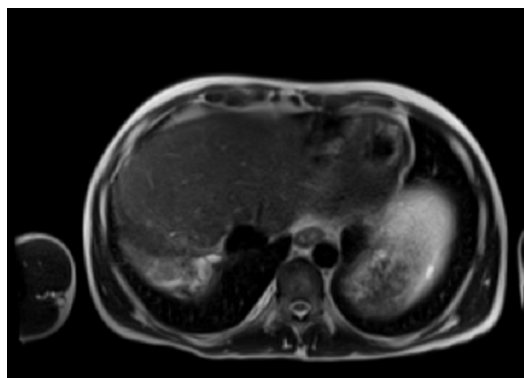
recurrent liver disease and exposure to environmental carcinogens. Although the clinical features cannot guarantee the distinction with certainty, molecular techniques may permit differentiation of donor from recipient origin<sup>[17]</sup>. In addition, allografts have a certain degree of hepatocyte chimerism (graft and recipient cells) that also correlates with the degree of hepatic injury and is strongly associated with hepatitis<sup>[18]</sup>.

The pathogenesis of HCC appears to be related to chronic hepatic inflammation that eventually leads to fibrosis and cirrhosis. The inflammatory microenvironment in the liver leads to a proliferative state that can promote dysplasia and eventually malignancy regardless of the underlying liver disease<sup>[1]</sup>. Graft rejection, which is an immunological surge against detected antigens found within the graft, can generate a chronic inflammatory state<sup>[19]</sup> and create an environment that promotes oncogenesis and dysplasia. Other well-established risk

Table 1 Modified from Saab *et al*<sup>[14]</sup>

Patient	Ref.	OLT indication	Age	Gender	Immunosuppression	Interval (yr)	Type of donor	PVS	Approach after de-novo HCC
1	Saxena <i>et al</i> <sup>[4]</sup>	HCV and ALD	63	M	CYA, AZA and Pred	7	DD	Yes	Retransplant
2	Levitsky <i>et al</i> <sup>[5]</sup>	HCV and ALD	48	M	CYA, AZA and Pred	5	N/A	Yes	NR
3	Croitoru <i>et al</i> <sup>[6]</sup>	HCV and NAFLD	61	M	CYA and Pred	6	DD	Yes	Retransplant
4	Flemming <i>et al</i> <sup>[7]</sup>	HBV	NR	M	NR	9	DD	Yes	Hepatic Resection
5	Flemming <i>et al</i> <sup>[7]</sup>	HBV	NR	M	NR	8	DD	Yes	Retransplant and Hepatic Resection
6	Torbenson <i>et al</i> <sup>[8]</sup>	HBV	51	M	NR	8.5	DD	Yes	Retransplant
7	Kita <i>et al</i> <sup>[9]</sup>	HBV	43	M	NR	14	NA	Yes	Retransplant
8	Yu <i>et al</i> <sup>[10]</sup>	HBV	36	M	TAC, MMF and Pred	2	LD	Yes	RFA
9	Sotiropoulos <i>et al</i> <sup>[11]</sup>	Budd-Chiari Syndrome	61	F	NR	22	NA	Yes	TACE
10	Sotiropoulos <i>et al</i> <sup>[11]</sup>	ALD	65	M	NR	5	NA	NR	RFA
11	Vernadakis <i>et al</i> <sup>[12]</sup>	ALD	59	M	CYA, MMF and Pred	3	DD	No	Hepatic Resection
12	Tamè <i>et al</i> <sup>[13]</sup>	HCV	54	M	TAC and Pred	6	DD	Yes	TACE
13	Saab <i>et al</i> <sup>[14]</sup>	HCV	47	F	TAC and MMF	19	-	Yes	TACE, RFA, Sorafenib, Retransplant
14	Tamè <i>et al</i> <sup>[13]</sup>	SSC	44	M	TAC and Pred	6	DD	Yes	Sorafenib
15	Navarro Burgos <i>et al</i> <sup>[15]</sup>	HCV and HBV	45	M	NR	0.75	DD	Yes	TACE
16	The present case	Biliary atresia	29	M	TAC and Sirolimus	14	LD	No	PMWA

OLT: Orthotopic liver transplantation; DD: Deceased donor; LD: Living donor; PVS: Positive viral serology; HCV: Hepatitis C virus; SSC: Secondary sclerosing cholangitis; ALD: Alcoholic liver disease; NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; NR: Not reported; CYA: Cyclophosphamide; AZA: Azathioprine; Pred: Prednisone; TAC: Tacrolimus; MMF: Mycophenolate mofetil; RFA: Radiofrequency ablation; TACE: Transarterial chemoembolization; PMWA: Percutaneous microwave ablation; M: Male; F: Female; NA: Not available.



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Figure 3 Follow-up magnetic resonance imaging showing the ablation cavity in segment III measuring 2.8 cm × 2.5 cm without evidence of residual tumor.

factors for promoting carcinogenesis include the use of immunosuppressive therapy as it reduces immune surveillance, increased age and gender specific cancer risks, development of insulin resistance and exposure to viral infections (HBV and HCV)<sup>[3,16,17]</sup>.

From the 16 cases of *de-novo* HCC occurrence reported so far in the literature, 14 had positive viral serology (HBV or HCV) (Table 1). In these cases the viral infection likely drove tumorigenesis. However, this is a novel case describing a *de-novo* HCC after a LDLT in a

pediatric patient. Our case represents the development of a hepatic tumor in the setting of advanced hepatic fibrosis, likely from chronic allograft rejection, without any underlying viral disease or other chronic infection. Interestingly both biliary atresia itself and Kasai procedure have been associated with the development of HCC<sup>[20-22]</sup>. However, given the 14 year gap from transplant to development of HCC, this probably did not contribute to the development of HCC in this particular patient.

Although current treatment guidelines for *De-novo* HCC after LT have not been well established, it was suggested that these cases be approached according to the current guidelines for primary and recurrent HCC<sup>[17]</sup>. The strategies that have been used in the reported cases to date are: re-transplantation ( $n = 6$ )<sup>[4,6-9,14]</sup>, trans-arterial chemoembolization (TACE) ( $n = 4$ )<sup>[11,13-15]</sup>, hepatic resection ( $n = 3$ )<sup>[7,12]</sup>, radiofrequency ablation (RFA) ( $n = 3$ )<sup>[10,11,14]</sup>, medical therapy with Sorafenib ( $n = 2$ )<sup>[13,14]</sup> and PMWA in our case. Two of the reported cases used more than one procedure<sup>[7,14]</sup>.

Proper age and gender appropriate cancer screening and surveillance is universally practiced among transplant recipients to diagnosis early stage malignancy. Since approximately one-fifth of all post-transplant deaths are related to *de-novo* neoplasms (including *de-novo* HCC)<sup>[3]</sup> and the incidence of HCC recurrence can be as high as 18.3% after transplant<sup>[2]</sup>, many transplant programs have in place post-LT screening and surveillance for HCC in patients transplanted for HCC along with other



appropriate cancer screening and surveillance<sup>[3]</sup>. However, these protocols for post-LT screening and surveillance are not uniform amongst centers as there is a general lack of evidence base for deciding on a specific protocol. This remains to be established.

In summary, we describe the first case of *de-novo* HCC after living donor liver transplantation in a patient with a prior history of biliary atresia who developed graft dysfunction and complications of portal hypertension. This case and the increase in reports of *de-novo* development of HCC in liver grafts of patients without HCC prior to LT challenges us to define the incidence of development of HCC in post-LT patients with chronic injury and graft fibrosis to determine when there is utility in recommending screening and surveillance of these individuals for HCC, and design appropriate protocols to carry this out.

## ARTICLE HIGHLIGHTS

### Case characteristics

A 29-year-old male with a history of biliary atresia with failed Kasai procedure complicated with progressive cirrhosis and portal hypertension that received a left lateral segment living donor liver transplant (LDLT) from his biological father at 15 years of age.

### Clinical diagnosis

Biliary atresia, complicated with progressive cirrhosis and portal hypertension that received a left lateral segment living donor liver transplant LDLT.

### Differential diagnosis

A case of *de-novo* hepatocellular carcinoma (HCC) (confirmed by ultrasound-guided percutaneous biopsy of the mass) 14 years after a pediatric living related donor liver transplantation for end-stage liver disease without positive hepatitis B or C viral serology.

### Imaging diagnosis

Follow up magnetic resonance imaging was performed 1.5 mo after the ablation and showed no residual tumor.

### Treatment

The lesion was subsequently treated by percutaneous microwave ablation. The patient was subsequently listed for repeat liver transplantation. Current screening and treatment guidelines have not been well established.

### Experiences and lessons

This increasing phenomenon challenges us to define the utility of screening and surveillance for HCC in these individuals.

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