

Living-Donor Liver Transplantation for a Large Hepatocellular Carcinoma in a Genetically Identical Twin Sister

Leber-Lebendspende bei genetisch identischen Zwillingsschwestern bei großem Hepatozellulärem Karzinom



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Key words

hepatocellular carcinoma, liver transplantation, twins, monozygotic, living donor

Schlüsselwörter

Hepatozelluläres Karzinom, Lebertransplantation, Zwillinge, eineiig, Lebertransplantation eines Lebendspenders

received 31.8.2023

Bibliography

Z Gastroenterol 2024; 62: 56–61

DOI 10.1055/a-2214-1712

ISSN 0044-2771

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ABSTRACT

Hepatocellular carcinoma (HCC) is, to date, the most common malignant tumor of the liver and is commonly staged with the Milan criteria. While deceased-donor liver transplantations (DDLT) are reserved for patients within the Milan criteria, living-donor liver transplantation (LDLT) might be a curative option for patients outside the Milan criteria. We here report a case of a 32-year-old woman who developed a giant, unresectable HCC out of a hepatocellular adenoma (HCA) after a pregnancy. The genetically identical twin sister donated her left hemi-liver after ethical approval and preoperative screening. No long-term immunosuppressive therapy was necessary, and after more than eight years, both are in perfect health and the recipient gave birth to a second child. This case shows that in certain situations large HCCs outside the standard criteria can be cured by LT. Careful evaluation of both donor and recipient should be performed for indications like this to assure optimal clinical outcome.

ZUSAMMENFASSUNG

Das Hepatozelluläre Karzinom (HCC) ist der häufigste bösartige Tumor der Leber und wird häufig anhand der Mailänder Kriterien klassifiziert. Lebertransplantationen verstorbener Spender (DDLT) sind Patienten vorbehalten, die sich innerhalb der Mailänder Kriterien befinden. Für Patienten außerhalb der Mailänder Kriterien können Lebertransplantation durch einen Lebendspender (LDLT) eine therapeutische Option sein. Diese Studie berichtet über den Fall einer 32-jährigen Frau, die nach

einer Schwangerschaft ein riesiges, inoperables HCC aus einem hepatozellulären Adenom (HCA) entwickelte. Die genetisch identische Zwillingsschwester spendete nach ethischer Genehmigung und präoperativem Screening ihre linke Leberhälfte. Eine langfristige immunsuppressive Therapie war nicht erforderlich. Mehr als acht Jahre nach der Transplantation sind beide Schwestern gesundheitlich in exzellentem Zustand und

die Empfängerin brachte kürzlich ein zweites Kind zur Welt. Dieser Fall zeigt, dass in bestimmten Situationen große HCCs außerhalb der Mailänder Kriterien durch Leber-Lebendspenden geheilt werden können. Bei solchen Indikationen muss eine sorgfältige Beurteilung sowohl des Spenders als auch des Empfängers durchgeführt werden, um ein optimales klinisches Ergebnis sicherzustellen.

Introduction

Hepatocellular carcinomas (HCCs) most commonly appear in cirrhotic liver disease. However, hepatocellular adenoma (HCA) in otherwise healthy livers might also transform into HCCs. HCAs are often diagnosed accidentally with sonography in patients who are investigated because of atypical abdominal complaints or abnormal liver biochemistry. HCAs are found mainly in young women. Risk factors for the development and growth of an HCA include usage of oral contraception (OAC), anabolic steroids, and hormonal changes, as are common in pregnancies [1, 2, 3, 4].

Risk factors for malignant transformation are rapid growth, tumor size (≥ 5 cm), male sex, OAC, and β -catenin activation [4, 5, 6]. In these settings, surgical resection should be encouraged. Staining for β -catenin should be undertaken on the resected tumor [7]. The malign transformation rate of HCAs has been reported to be as high as 5 % [4].

As these tumors generally develop in a healthy liver, no specific complaints are clinically manifest in the majority, while in cases of bleeding, pain can be the presenting symptom. In the case of a large HCA transforming into HCC, the patient might not be eligible for liver transplantation any longer due to the tumor size. Other curative options are not yet available as there are no specific drugs to treat HCC.

We present a case of a young woman with diagnosis of a large HCC, which most likely developed from an HCA shortly after child delivery, who was treated with a living-donor transplantation (LDLT) from her genetically identical twin sister.

Case report

A 32-year-old woman presented with abdominal pain in the right upper abdomen six months after childbirth to her primary care provider. The first time she noticed a painful swelling in her right upper abdomen was two months after giving birth. During pregnancy, she noticed no medical complaints, and her male child was born under normal conditions. She developed no complications during her *post partum* period. The general practitioner diagnosed a hepatomegaly and a right hepatic lobe mass at physical examination. Ultrasound confirmed the diagnosis and revealed a tumor of > 15 cm diameter in the right liver lobe and a smaller tumor in the left lobe.

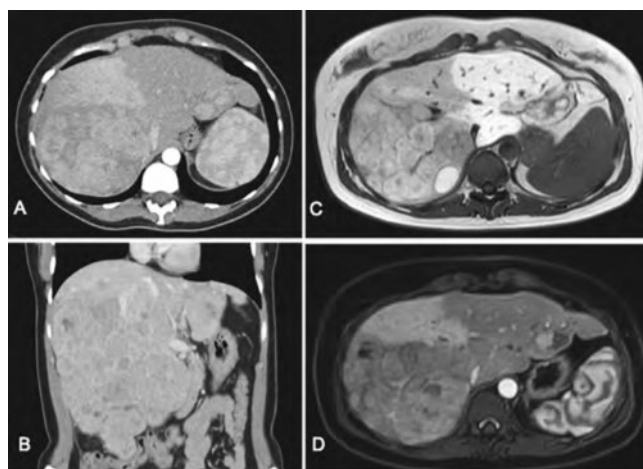
These findings were confirmed by magnetic resonance imaging that was conducted after the referral to the outpatient hepatology clinic of the secondary healthcare provider. The lesions were hypo-intense compared to the liver parenchyma on a T1 se-

quence and a mixture of hypodense and hyperdense intensity on a T2 sequence (► Fig. 1A–B). Computer tomography of chest and abdomen demonstrated the extent of the malignancy in the liver, showing no evidence of cirrhosis or extrahepatic manifestations or metastases.

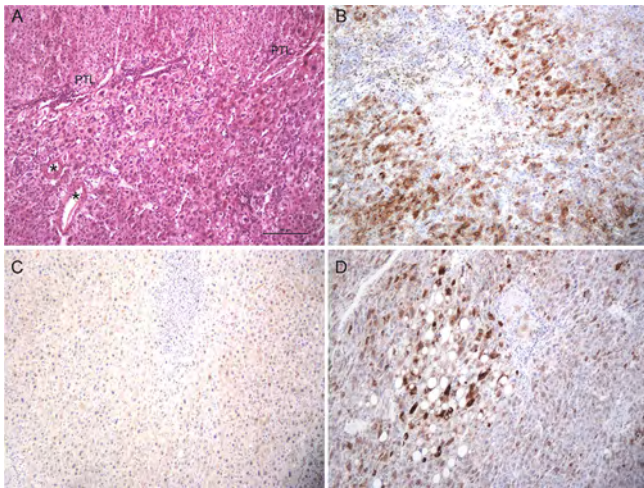
A biopsy from the liver lesion was performed showing a moderately differentiated HCC and the coexistence of a highly differentiated hepatocellular lesion. The latter revealed overexpression of serum amyloid A (SAA) and an abnormal β -catenin staining pattern (► Fig. 2A–D, ► Fig. 3A–D). The tumor tissue tested positive for *ctnnb1* mutation in exon 8 (p.N387K). Overall, the pathological features are consistent with a β -catenin-activated inflammatory HCA (b-IHCA) with progression into HCC [8]. The AFP level was 221.4 ng/ml.

According to the Milan criteria for HCC, the tumor was ineligible to be treated curatively with a deceased-donor liver transplantation (DDLT). Therefore, resection of the tumor was scheduled. During the operation, the multifocal tumor was not resectable due to infiltration of the left liver vein of the left-sided, smaller tumor, and the operation could not be carried out as planned. The opportunity of an LDLT was suggested due to the lack of other treatment options and because the patient had an identical twin sister willing to donate her left hemi-liver.

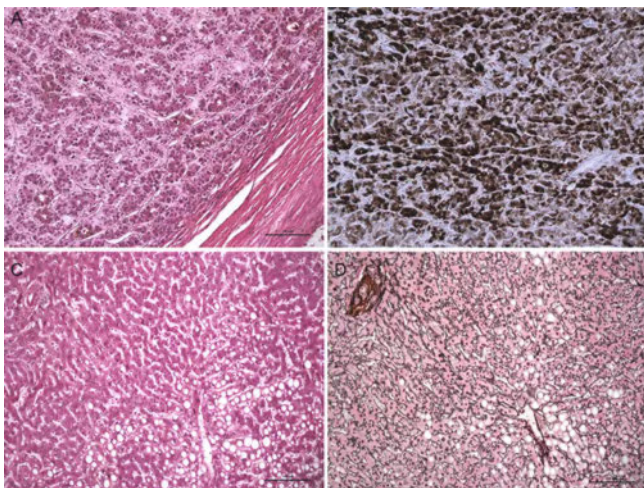
After the agreement of the twin sister, subsequent donor evaluation, and exclusion of contraindications, the shared decision-making with the two sisters, parents, and husbands was ethically



► Fig. 1 Transverse and sagittal CT images of the liver tumor (A and B). Transverse MR image of the liver (C, late T1 images post primovist and D, arterial phase post primovist).



► **Fig. 2** A) Highly differentiated liver tumor with features of hepatocellular adenoma. Note the presence of portal-tract-like structures (PTL) and isolated arteries (asterisk). B) The tumor cells reveal overexpression of SAA. C) Expression of FABP1 is reduced but maintained. D) Only individual tumor cells show GS overexpression. Overall, the histological picture is compatible with a β -activated inflammatory hepatocellular adenoma (b-IHCA).



► **Fig. 3** A) Pseudoglandular type of HCC with formation of pseudocapsule indicating a progressed HCC. B) The tumor cells show diffuse GS upregulation indicating β -catenin activation. C) Mild perivenular fatty change in the surrounding normal liver with D) mild portal fibrosis.

approved by the ethics committee of the Ärztekammer Düsseldorf. The patient and her sister had more than a week's time to think it over after they were informed about the operation and side effects. In that time, all preoperative investigations for both were performed.

An LDLT of the left lobe with biliodigestive anastomosis of her sister was carried out. The procedure and postoperative period passed without major complications.

Pathological evaluation revealed a multifocal HCC of up to an 18 cm diameter with microscopic vascular invasion (G2, pT3a, pN0 (0/6), L0, V1, R0).

Immunosuppressive treatment for one month was administered with prednisone and tacrolimus in reduction dose because of an initial elevation of the liver enzymes. Because of the genetic identity, immunosuppressive medication could be discontinued thereafter.

At present, eight years after the transplantation, the patient and her sister are in excellent physical and psychological condition without any signs of HCC recurrence or metastases. The donor twin sister has never developed any liver anomalies including HCA. Liver biochemistry and functions are normal. The recently performed MRI scan and Rx thorax, eight years after transplantation, showed postoperative sequels without any signs of recurrence or metastasis.

Discussion

This is the clinically impressive case of a successful LDLT for a large multifocal HCC in a young woman from her genetically identical twin sister. Eight years after transplantation, no recurrence or metastasis of the HCC have been found, and both sisters are in perfect health with a normal liver function and biochemistry. The graft recipient recently gave birth to her second child.

LDLT presented the only treatment option in this patient and resulted in a very favorable clinical outcome. However, due to possible recurrence of the malignancy and possible donor harm, critical evaluation of both donor and recipient must be performed prior to LDLTs in cases like this.

Selection for LT

The majority of malignant liver tumors develop due to chronic liver diseases like viral hepatitis and alcoholic and non-alcoholic liver diseases. For cirrhotic patients, tumor size can predict long-term survival and, therefore, influences the chosen therapy. The optimal curative treatment for malignant liver tumors in cirrhosis is liver transplantation (LT), which cures both cancer and the underlying disease. Selection for LT in patients with HCC is based on the Milan criteria that allow for one tumor of up to 5 cm in diameter or up to three nodules, each 3 cm or less in diameter, and exclude extrahepatic spread or macrovascular invasion [9, 10]. Our patient presented with a large multifocal HCC and was therefore excluded from DDLT according to the Milan criteria.

The critical issue is the risk of relapse or metastasis after LT in HCCs that are exceeding the Milan criteria [11]. HCCs within the Milan criteria have an 83 % recurrence-free survival after 4 years and, therefore, a comparable survival rate to patients with non-malignant liver diseases when treated with LT [9, 12]. Tumor recurrence appears to be related to tumor biology, vascular invasion, tumor size, and the degree of differentiation [12, 13, 14, 15].

There have been efforts to extend the Milan criteria as other treatment options are lacking and the survival rates of patients transplanted outside the Milan criteria are considerable [15, 16, 17, 18].

The University of California, San Francisco (UCLF)'s classification can be considered a wider classification. It allows for a single tumor <6.5 cm, no more than 3 tumors with each <4.5 cm in diameter, and a cumulative tumor size <8 cm. Applying these criteria, 5-year survival has been reported to be 75.2% [17, 19].

Another expansion of the criteria is represented by the so-called up-to-seven criteria, where the sum of the size of the largest tumor in cm and the number of tumors does not exceed seven. These criteria proved to show acceptable survival rates (5-year survival 65.3%) compared to patients within the Milan criteria or transplanted for other reasons [20, 21].

Tumor biology as a marker for risk of recurrence has recently shifted into the focus of attention. Sapisochin et al. presented the extended Toronto criteria for selection of patients for LT based on tumor differentiation and cancer-related symptoms. This makes most patients with a disease limited to the liver eligible for transplantations. Applying these criteria, they found no significant survival differences between HCCs inside and outside of Milan. Five-year survival inside and outside Milan was 76% and 68%, respectively, and 50% and 60% at 10 years after LT [22]. These data underline the importance of individual patient selection for LT beyond simple tumor size measurements.

However, due to organ shortages, DDLT is still reserved for patients with the most favorable postoperative outcome, which is widely accepted to be HCCs inside the Milan criteria [18]. In our patient, the impressive size of the HCC (18 cm diameter) has excluded her from any established transplantation criteria for DDLT.

LDLT for HCC

LDLT has been introduced as an option to reduce organ shortage and expand the selection criteria for transplantation [23, 24, 25]. Recently, data of a large multicenter cohort study revealed a comparable survival rate for patients undergoing LDLT for HCC inside and outside the Milan criteria in North America: 1- and 5-year survival rates were 90.1% and 78.5% for patients inside the Milan criteria and 90.4% and 68.6% for patients with tumors outside the Milan criteria [23]. Bhangui et al. reported favorable outcomes for LDLT for HCC, basing selection on the absence of an extrahepatic tumor burden, irrespective of tumor size and number. The 5-year survival rate for all patients was 64%. Tumors outside the UCSF criteria and biological criteria (high AFP and [¹⁸F]FDG-PET avidity) proved to be predictors for overall survival and tumor recurrence [24].

All decisions for LDLT need to balance the benefit for the recipient, who often has no other therapeutic options, with the harm for the donor. Both donor and recipient need to be involved in the process of shared decision-making. In the case presented, neither suffered from any major complication and both are in excellent condition eight years after the transplantation.

Risk factors for recurrence and role of immunosuppression

After transplantation, low-dose immunomodulation with steroids and tacrolimus was given for four weeks to facilitate a rapid adaptation of the transplanted liver segments. As the sisters were genet-

cally identical, fully matched, immunosuppressive drugs were not needed for graft survival in the long term. Immunosuppressive drugs can facilitate recurrence of disease, and higher tacrolimus levels increase the risk of tumor recurrence of HCC within 3 years after transplantation [11, 26].

There have been reports on LDLT from identical twins for hepatitis C and B cirrhosis and metastases of a neuroendocrine tumor. Given perfect HLA matching, transplantations in these cases can be performed without the need of immunosuppressive medication [27, 28].

Most likely, this also lowered the risk of HCC recurrence or metastasis development in our patient who until now, eight years later, is still recurrence- and metastasis-free and in good health. This shows that in all cases of LDLT for HCC outside the Milan criteria, careful evaluation and monitoring of immunosuppressive medication are essential.

HCA as underlying disease

In our case, HCC formation occurred in an otherwise healthy young female patient and could not be attributed to an underlying chronic liver disease. Thus, it is likely that another preexisting condition resulted in tumor development. HCA is the most prevalent benign hepatocellular tumor in young females and can be subtyped according to clinical and immunohistochemical parameters [5, 6, 29]. HCA subtypes with β -catenin activation are prone to malignant transformation into HCC.

In our case, the tumor cells showed upregulation of inflammatory markers and an abnormal β -catenin expression pattern, which could be attributed to an activating *ctnnb1* mutation, leading to the diagnosis of b-IHCA as the underlying lesion. HCA growth is promoted by steroid hormones, and complications like bleeding or malignant transformation have been reported during pregnancy and OAC therapy [3, 30]. Thus, malignant transformation of b-IHCA seems likely, and the multifocal tumor growth detected in the explant liver is suggestive of intrahepatic dissemination. While there is little evidence on therapeutic management of HCA during pregnancy, close monitoring is mandatory [29]. In the case of large tumors or complications during a previous pregnancy, surgical resection should be considered prior to pregnancy [29, 31]. Interestingly, in our case, the genetically identical twin sister, who also had given birth at a young age, has not developed HCA. Both twin sisters had a history of usage of OAC, and both had no history of alcohol or drug abuse or any other anomalies.

Ethical considerations

LDLT is only acceptable when a good prognosis can be calculated before LT. In the case of a Samaritan donorship like those more often performed in a kidney transplantation setting, it is essential to inform about the risks for the donor but also about the predicted long-term survival for the recipient to make an informed decision. Also, the post-LT immunosuppressive therapy will be an important issue in deciding which patient with an extended HCC is eligible for LT. In this context, LDLT from a genetically identical twin is to be considered of special importance because, even though rarely possible, outcomes might be excellent due to a lack of the need for immunosuppressive therapy.

Conclusion

In certain situations, large HCCs outside the standard criteria can be cured by LDLT. This requires optimal preoperative care and evaluation of both recipient and donor to avoid risks for the donor and minimize risks of recurrence for the recipient. As HCC is a growing problem with rising rates of steatotic liver diseases like metabolic-dysfunction-associated steatotic liver disease (MASLD), future research should focus on optimizing the selection criteria for recipients and minimizing morbidity for donors. In times of organ shortages, the expansion of LDLT programs is a valuable option with a high benefit for otherwise untreatable patients.

Disclosures

The manuscript has not been published previously and is not under consideration (in whole or in part) for publication elsewhere. All authors have contributed to and agreed on the content of the manuscript. The study was performed according to the Declaration of Helsinki and its later amendments. All participants provided written informed consent prior to participation.

Funding

TKI-LSH (40-41200-98-9306) | This work was supported by TKI-LSH (grant no. 40-41200-98-9306 to G. H. Koek). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgement

We thank Univ.-Prof. Dr. Dr. Nadine Gaisa, Institut für Pathologie RWTH Aachen, Universitätsklinikum Aachen, Anstalt öffentlichen Rechts (AöR), Olaf Neumann, and Albrecht Stenzinger for the molecular analysis.

Conflict of Interest

The authors declare that they have no conflict of interest.

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