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CASE REPORT

Donor-transmitted metastasis of colorectal carcinoma in a transplanted liver

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[Correction added after online publication December 13, 2011: Hans Dubbink was changed to Hendrikus Jan Dubbink]

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Summary

A 62-year-old man with alcoholic liver cirrhosis underwent liver transplantation. The transplantation went uneventful and the ultrasound imaging of the liver performed after transplantation did not show any abnormalities. Eighteen months later, an intra-hepatic focal lesion was found on ultrasound. A contrast-enhanced ultrasound revealed a lesion with a malignant pattern of contrast uptake. The histo-pathological and subsequent molecular-pathological analysis concluded a colorectal metastasis of donor origin. The donor had no history of malignancy but no complete autopsy had been performed which illustrates the importance of the meticulous donors' screening. Transplanted patients carry a high risk of developing malignancy in general but donor related-tumors are very rare. The therapeutic considerations differ substantially between recipient- and donor-related malignancies. Therefore, considering the possibility of donor-related tumor by raising suspicion of malignant lesion with appropriate imaging and distinction from recipient-related malignancy by molecular analysis are crucial for proper therapeutic decision.

Introduction

Transmission of cancer from donor to recipient is a rare complication of solid organ transplantation. These donor-related tumors have been divided into two distinct entities, donor transmitted and donor derived tumors [1]. Donor transmitted tumors are defined as tumors present in the donor at the time of transplantation, in contrast to donor derived tumors that develop *de novo* in transplanted donor cells. To state the diagnosis of donor-related tumor, a good quality imaging and a molecular-pathological analysis are required. Here, we report a case of a donor transmitted metastasis of colorectal carcinoma in a liver transplant recipient in which the contrast-enhanced ultrasound (CEUS) directed further evaluation of a focal lesion detected in the transplanted liver.

Clinical history and imaging – part I

A 62-years-old man with alcoholic liver cirrhosis was placed on the waiting list for liver transplantation. During the period on the waiting list, he developed two intra-hepatic localizations of hepatocellular carcinoma (HCC) that were treated with radio-frequency ablation. Three years later, he underwent a liver transplantation with a deceased donor liver from a 69-years old female patient who died of cerebral vascular event and without a history of malignancy. The explanted liver of the patient showed three localizations of hepatocellular carcinoma. There were no macroscopic abnormalities noticed of the donor liver and the ultrasound performed after transplantation showed no lesions. The post-transplantation period went uneventful with a good graft function and the only long-term complication was the development of *de novo* diabetes mellitus.

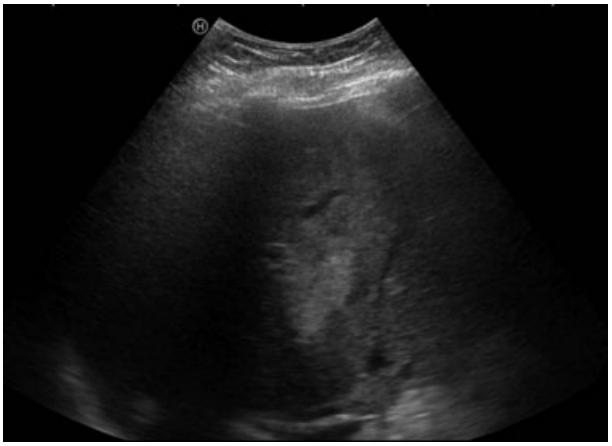

Figure 1 Ultrasound performed 18 months after liver transplantation showing an irregularly shaped hyperechogenic lesion of 5 cm in segment 8 in the transplanted liver.

Ultrasound at 18 months after transplantation showed lesion in the liver (Fig. 1) of irregular shape, diameter of 5 cm and a homogenous hyperechogenic character. The overall aspect of the liver parenchyma and vasculature was normal. The differential diagnosis of this lesion was focal steatosis or recurrence of HCC. As a result of the patient's claustrophobia, a computed tomography (CT) scan instead of MRI was performed and showed the lesion with no characteristic features of malignancy. CEUS using 2.5 ml Sonovue® revealed an enhancement pattern suspicious of malignancy with a rapid arterial enhancement and a wash-out in the late venous phase within 2–3 min after administration of contrast (Fig. 2). Therefore, an ultrasound-guided biopsy of the lesion was performed, showing a small fragment of tissue possibly of colonic origin. Therefore, a colonoscopy was performed, but no abnormalities were revealed. A CT scan repeated 2 months later showed a growth of the focal lesion from 5 to 7 cm and a new adjacent lesion of 2.7 cm. The histological evaluation of the repeated biopsy showed an adenocarcinoma compatible with a metastasis of colorectal carcinoma. The colonic origin was confirmed by additional immunohistochemical staining, cytokeratin 20 and caudal related homeobox-2 (CDX-2) were both positive in the tumor cells, and cytokeratin 7 was negative (Fig. 3). The repeated colonoscopy being negative, the suspicion of donor-transmitted tumor was raised and molecular analysis was performed.

Molecular analysis

First, tumor and normal tissues were genotyped. DNA was extracted from formalin-fixed paraffin-embedded (FFPE) tissues. A tissue area enriched for a high percentage of tumor cells and normal transplanted liver tissue were collected from sections by manual microdissection (Fig. 4). Reference DNA was obtained from explanted FFPE liver tissue.

Genotyping was performed by short tandem repeat (STR) profiling using the Powerplex 16 system® (Promega). This system analyzes 15 STR loci and one sex chromosome marker. For each STR locus the number of repeats present was calculated using GeneMarker software (SoftGenetics). Results obtained with the green fluorescent labelled markers are shown in Fig. 5. In Table 1, the repeat numbers are given for all samples examined.

Comparison of the genotypes of tumor and explanted liver tissue showed that 13 markers display different number of repeats (Table 1). The major peaks of the transplanted liver tissue corresponded to the genotype of the tumor tissue and the minor peaks matched the genotype of the explanted tissue. These results strongly indicate that the tumor cells are of donor origin.

To further establish the female origin of the tumor cells, fluorescent in situ hybridization (FISH) of the X and Y chromosomes was carried out using Satellite Enumeration probes (DXZ1 and DYZ3, Poseidon), following standard protocols.

All tumor cells as well as the transplanted liver cells showed either one or two X chromosomes, but no Y chromosome (Fig. 6). The only cells harbouring both an X and Y chromosome were infiltrating lymphocytes.

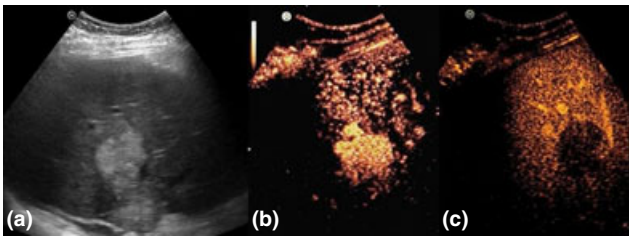

Figure 2 Contrast-enhanced ultrasound of the focal lesion in transplanted liver [B-mode, (a)] with a rapid arterial enhancement within few seconds after injection of 2.5 ml Sonovue® contrast (b) and wash-out in the late venous phase at 2 min after contrast injection (c).

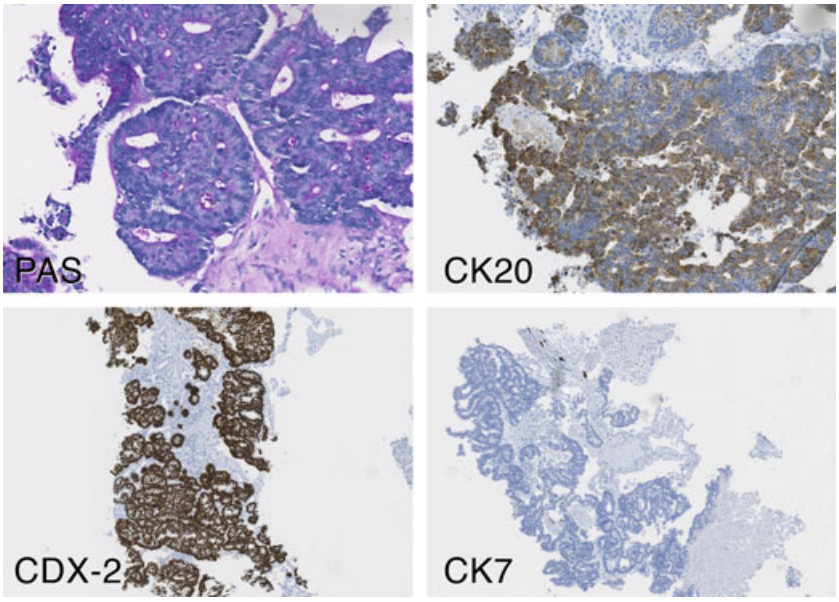

Figure 3 Biopsy of the focal liver lesion showing a mucus-producing adenocarcinoma (PAS staining), with positive staining for cytokeratin 20 and CDX-2 and no staining for cytokeratin 7, compatible with metastasis of a primary colon tumor.

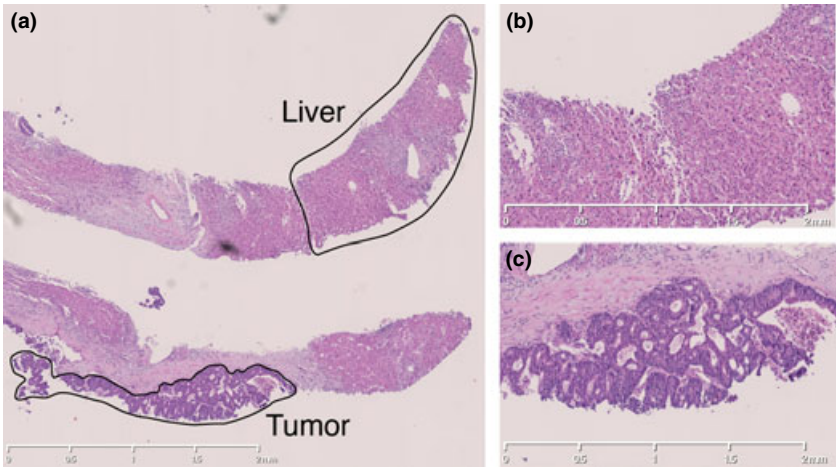

Figure 4 Tissue from the index patient (a), from which liver cells [transplanted liver, (b)] and tumor cells (c) were isolated.

These results underscore that the tumor cells are derived from female donor tissue.

Clinical history and imaging – part II

Thus, 18 months after the transplantation, the patient was diagnosed with a donor-related metastasis of colorectal carcinoma in the transplanted liver. At further evaluation, no other localizations of this tumor were found. As a result of a recent myocardial infarction, cerebral stroke, and the development of psychiatric disorder with paranoid features, neither re-transplantation nor the local or systemic therapy could be offered. Patient died several months later, less than 3 years after the liver transplantation.

Discussion

We report a case of a donor-transmitted metastasis of colorectal carcinoma, identified 18 months after liver transplantation. This condition is very rare, the evaluation of the deceased donor-related tumor rate based on United Network for Organ Sharing (UNOS) registry (1994–2001) in almost 35 000 deceased donors being 0.04% [1]. Additional two cases of donor-transmitted tumors (glioblastoma and melanoma) were reported in the UNOS registry of the period between 2000 and 2005 [2]. In the UNOS registry between 2005 and 2007, 15 tumors were confirmed in the solid organ transplantation and six recipients died as the result of a donor-transmitted disease [3].

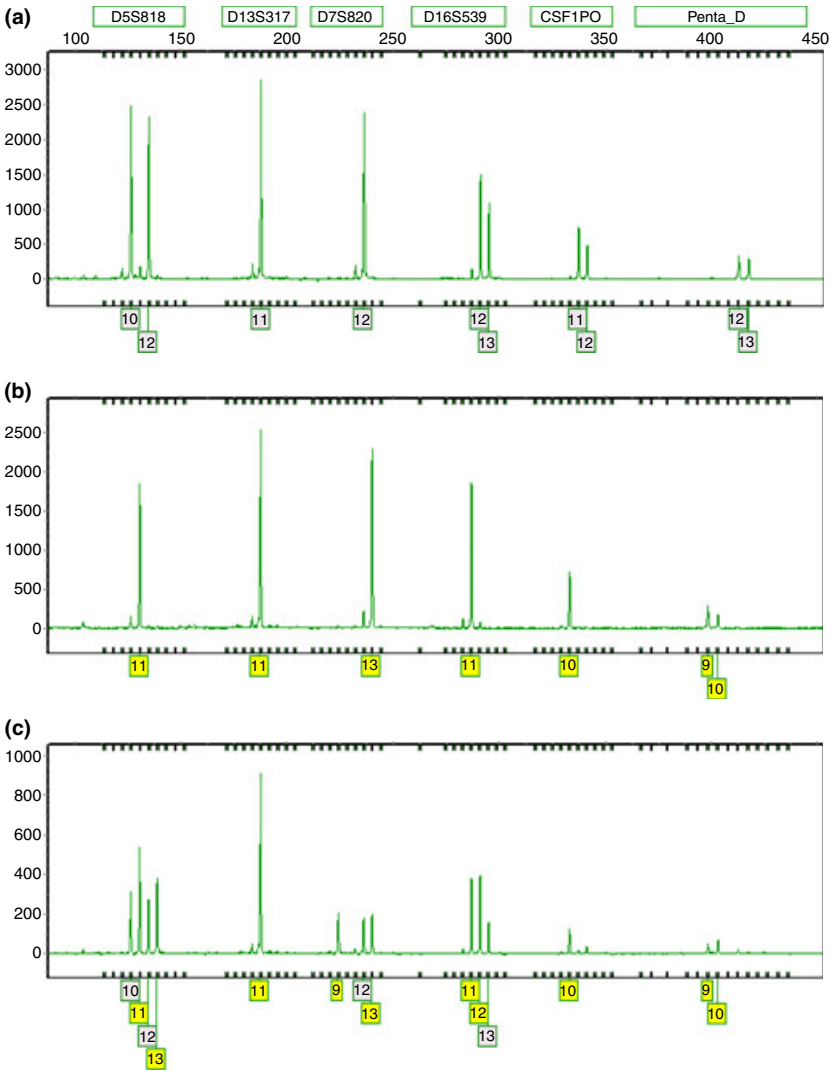

Figure 5 STR profiles of six markers (D5S818, D13S317, D7S820, D16S539, CSF1PO, Penta_D) for explanted liver tissue (a), tumor tissue (b) and transplanted liver tissue (c). The transplanted liver sample (c) shows a combined donor (yellow boxes) and acceptor (grey boxes) STR pattern. All alleles of the tumor sample (b) are present in the transplanted liver sample and (except the alleles from marker D13S317) not in the explanted liver (a), indicating that the tumor cells are of donor origin. Several donor derived alleles in the transplanted liver are not present in the tumor tissue demonstrating DNA loss in the neoplastic cells (with markers D5S818, D7S820, and D16S539).

Table 1. Repeat numbers at short tandem repeat loci for explanted liver tissue, tumor tissue and transplanted liver tissue. The alleles of the tumor tissue are similar to the major peaks of the transplanted liver tissue, and different from the explanted liver tissue. This indicates that the tumor cells were derived from donor tissue.

Short tandem repeat locus	Amelogenin	D3S1358	TH01	D21S11	D18S51	Penta_E	D5S818	D13S317
Explanted liver	X, Y	15, 16	6,10	29, 30.2	12, 15	12, 17	10, 12	11
Tumor tissue	X	16, 18	6, 9.3	28, 30	15*	NA	11*	11
Transplanted liver								
Major peaks	X	16, 18	6, 9.3	28, 30	15, 16	12, 19	11, 13	11
Minor peaks	Y	15	–	9, 30.2	–	17	10, 12	–
Short tandem repeat locus	D7S820	D16S539	CSF1PO	Penta_D	vWA	D8S1179	TPOX	FGA
Explanted liver	12	12, 13	11, 12	12, 13	16, 17	8, 10	11	20, 21
Tumor tissue	13*	11*	10	9, 10	17, 18	12, 15	8	21, 23
Transplanted liver								
Major peaks	9, 13	11, 12	10	9, 10	16, 18	12, 15	8	21, 23
Minor peaks	12	13	–	–	17	8, 10	11	20, 21

*Loss of one allele in the tumor tissue

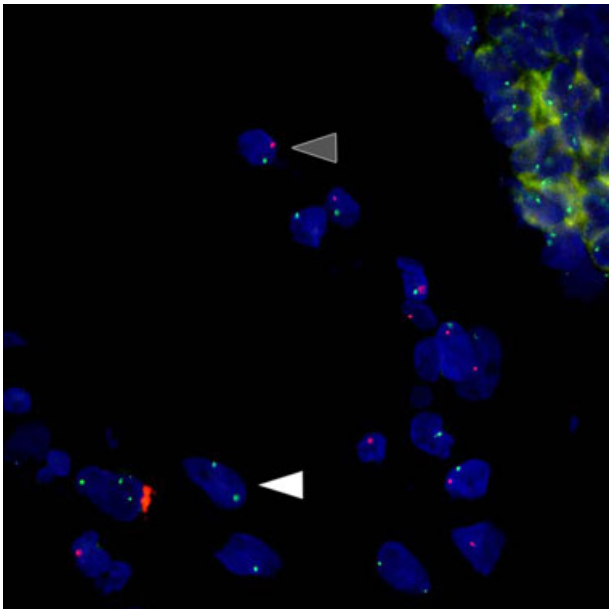

Figure 6 Fluorescent *in situ* hybridization was performed for the X and Y chromosomes, which are labeled green en red, respectively. A group of tumor cells is shown, together with some detached tumor cells (white arrowhead) and lymphocytes (grey arrowhead). The tumor cells have two X chromosomes, which confirms their female origin.

The Israel Penn International Transplant Tumor Registry covering a period between 1965 and 2003 reports only two cases of donor-transmitted colon cancer [4].

Interestingly, not every diagnosed malignant tumor in the donor is necessarily transmitted to the recipient; the UNOS registry (2005–2007) [3] reporting one donor with proven colon cancer without transmission to the recipient.

This case raises the question of the criteria for the donors‘ screening. The records of the donor showed no health problems but neither complete autopsy nor a CT scan have been performed as this is not part of the protocol. Two kidney recipients from the same donor have no signs of malignancy, which is not surprising given the specific metastatic pattern of colorectal carcinoma. Considering the still increasing age of donors and the high prevalence of colorectal carcinoma, the extent of the screening of the donors might need to be reconsidered with inclusion of a complete autopsy.

Other aspect of this report is the value of a new imaging modality, contrast-enhanced ultrasound. At CEUS, the liver metastases are characterized by a predominant arterial blood supply but hypovascular metastases can also be seen, especially in metastases of adenocarcinomas [5]. In this case, CEUS showed neoplastic features with rapid arterial enhancement and wash-out. However, the question in this case was the distinction of a secondary lesion from the recurrence of HCC, the latter being clinically the most likely diagnosis. This distinction was not possible with the CEUS image which is also the generally observed limitation of this technique [6]; however, a rapid wash-out of the contrast agent in a non-cirrhotic patient should raise the suspicion of a metastasis.

Finally, the diagnosis was revealed by histo-pathological examination. The morphology of the tumor corresponded to an adenocarcinoma, intestinal type which was confirmed by the additional staining. The clinical setting of negative colonoscopy prompted further molecular analysis. The techniques used were the STR profiling and chromosome FISH. The STR profiling has high sensitivity and is generally accepted for genotyping in forensic medicine [7].

Concerning the treatment and the prognosis of donor-derived tumors, the experience is limited. From the five donor-derived (four proven, one possible) cases reported in UNOS registry in 2007, three patients were re-transplanted with favorable clinical outcomes. Provided that the extra-hepatic localization of the tumor has been excluded, re-transplantation would be a curative treatment. As recipient-related metastatic malignancies or recurrence of HCC are much more common after liver transplantation and necessitate a different therapeutic approach, it is crucial to raise the suspicion of the donor-related malignancy and use molecular techniques to characterize the origin of the tumor.

Authorship

ZZ: analyzed data, wrote the paper. WRRG-G: performed research, wrote the paper. JV: performed research, wrote the paper. HJM: designed research, analyzed data. WNMD: designed research, contributed important reagents. HJD: designed research. PT: designed research, performed research, analyzed data, wrote the paper.

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