LETTERS TO THE EDITORS

Accidental transplantation of hepatic graft with incidental T2 gallbladder carcinoma: a report of 3 cases

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Dear Editors,

Transplantation is associated with a low but unavoidable risk of cancer transmission [1–3]. Physical examination and CT scan are routinely performed to detect unknown malignancy before donation, but some cancers, such as gallbladder cancer (GBC), can be difficult to rule out.

We report the outcomes and subsequent management after three liver transplantations (LT) of GBC-bearing grafts at Paul Brousse Hospital, Villejuif, France, over the 1993-2019 period. All patients who were given a graft with invasive GBC could be identified retrospectively because each case of invasive cancer in donors diagnosed during donation has to be declared to the *Agence of Biomédecine*, the national organization in charge of organ allocation.

In France, the vast majority of deceased donors undergo a body CT scan, and images can be read by the procurement team. During retrieval, macroscopic examination of the intra-abdominal cavity is carried out to exclude potential malignant disease. In case of suspicion of a malignant lesion, a biopsy with frozen section examination is recommended. Cholecystectomy is

Table 1. Summary of liver transplantation cases with GBC-bearing graft

Variables	Case 1	Case 2	Case 3
Donor age, yrs	77	82	75
Donor sex	Female	Male	Male
Cause of death	Stroke	Stroke	Stroke
Donor medical history	Pulmonary embolism	Diabetes, hypertension, chronic alcohol abuse	Hypertension, Previous cerebral stroke
Liver-related CT scan findings	None	None	Common bile duct dilatation but no tumour. Microlithiasis
Intraoperative findings during retrieval	None	None	Thickening of the cystic duct
Histopathological findings*	pT2b Nx adenocarcinoma – Diffuse infiltration of the gall balder wall No PNI – No VI – No LN analysed	pT2aNx adenocarcinoma– Cystic duct tumour free– Size: 5 mm – No PNI – No LN analysed	pT2aN+ – Invasion of Cystic duct and CBD – 1 metastatic LN /1 LN examined– No PNI – No VI
Recipient management	Retransplantation	No retransplantation	Retransplantation
Explant histology (liver and bile duct)	No remaining tumour	No remaining tumour	adenocarcinoma bile duct section
Recipient outcomes	GBC-free at 7 years	Lung metastases likely from colorectal origin	GBC-free at 16 months

PNI, Perineural invasion; VI, Vascular invasion; LN, Lymph node; GBC, Gallbladder cancer.
*TNM stage according to AJCC eight edition.

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routinely performed before clamping or during the 'back-table' preparation. The gallbladder is systematically analysed by pathologists, and the pathological report is available a few days after transplantation.

Of 4009 LT from 1993 to 2019, 3 (0.07%) hepatic grafts with undiagnosed invasive gallbladder adenocarcinoma were transplanted. Donor characteristics, pathological data and management are given in Table 1.

Case 1

The recipient was a 49-year-old male, suffering from end-stage cirrhosis. He received a 77-year-old hepatic graft. The histopathological analysis of the donor's gallbladder revealed a well-differentiated multifocal adenocarcinoma. One of the tumour samples showed a tumour extension to the perimuscular connective tissue (pT2Nx). The patient underwent reLT 68 days afterwards. The pathological examination of the explanted graft did not find any remaining tumour. The patient died of oropharyngeal cancer seven years after the reLT, without evidence of GBC recurrence.

Case 2

A 51-year-old male was transplanted for liver-only unresectable colorectal liver metastases. He received an 82-year-old hepatic graft. The histopathological analysis of the gallbladder revealed a moderately differentiated adenocarcinoma associated with extensive lesions of carcinoma in situ of the fundus and body of the gallbladder. The tumour infiltrated the peritoneal surface without reaching the serosa (pT2aNx). The patient was not retransplanted because of severe postoperative complications. He finally recovered but developed several lung metastases two years after LT. We concluded that these lesions were more likely related to colorectal cancer, given the high rate of lung recurrence after LT for colorectal liver metastases and the absence of abdominal recurrence. However, a biliary origin cannot be ruled out because no histology of lung lesions is available. Pulmonary disease is currently stable under systemic chemotherapy.

Case 3

The recipient was a 57-year-old male who underwent LT to treat unresectable liver-only colorectal liver metastases. He received a liver graft from a 75-year-old male. During the back-table preparation, abnormal thickening of the cystic duct was discovered. Frozen section analysis of the cystic duct showed low-grade dysplasia of the mucosa without an invasive tumour. However, definitive pathological examination after LT revealed a well-differentiated infiltrating adenocarcinoma of the cystic duct and the gallbladder's neck, developed on biliary intraepithelial neoplasia. A metastatic lymph node at the cystic duct was also observed. The resection margin of the common bile duct was compromised (carcinoma in situ with microfocus of invasive adenocarcinoma). GBC was staged as pT2aN+. The patient was retransplanted 12 days afterwards. Pathological examination reveals a moderately differentiated infiltrating cholangiocarcinoma of the cystic duct, the main hepatic duct and the right hepatic duct, without evidence of lymph node metastasis. The resection margin of the recipient's common bile duct was free of tumour. The patient is alive and recurrence-free 16 months after LT.

Brief discussion

According to European guidelines, biliary cancers in donors are classified as unacceptable risk and should contra-indicate transplantation [4]. Only one LT of a graft with GBC has been described [5]. The recipient underwent reLT for a primary nonfunction but died two days later, thus precluding the detection of a possible cancer transmission. One case of transmitted adenocarcinoma after kidney transplantation with CK7-positive staining in favour of biliary cancer origin was described [6]. Strikingly, complete remission was obtained one year after transplant nephrectomy and cessation of immunosuppressive therapy.

Early-stage GBC is difficult to detect by imaging and is often diagnosed fortuitously after cholecystectomy. No donor CT scan had suspected GBC biliary malignancies in any of our 3 cases, suggesting the need to carefully examine gallbladder during procurement, especially in old donors or in the presence of cholecystitis [7]. In case 3, the procurement team discovered an unusual thickening of the cystic duct. The frozen section showed the presence of mild dysplasia, but the definitive pathological examination revealed invasive GBC. This underlines the need for careful interpretation of the frozen section [8].

In the absence of effective systemic therapies, surgical resection is the only chance of prolonged survival or cure for T2 GBC. Cholecystectomy alone is not recommended to treat T2 GBC since several studies have shown that re-resection is associated with improved survival [9,10]. A residual disease is a strong prognostic

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factor after re-resection [10]. Two of our three patients could be retransplanted to remove potentially residual cancer cells. Such a decision proved to be meaningful in one patient (case 3) because histological examination of the explanted graft found a residual infiltration of the bile duct by adenocarcinoma and a single metastatic lymph node. Re-resection with extended lymphadenectomy could also have been discussed. However, it seems to us that oncological and safe resection of residual disease would be better achieved by reLT.

In conclusion, discovering an incidental GBC is a rare but possible complication after LT. Gallbladder should be examined both macroscopically by the procurement surgeon and microscopically by the pathologist. Re-resection or reLT to treat potentially residual disease should be discussed on a case-by-case basis.

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