

# Kidney Cancer Following Heart Transplantation is a Common Presentation of an Uncommon Malignancy: A Unique Case Series

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**ABSTRACT** **Background:** Heart transplantation (HT) success rate is limited by a high incidence of cancer post-HT. Data on kidney cancer following solid organ transplantation, especially HT, are limited, and only a few cases have been reported. **Objectives:** To report a unique case series of detected kidney cancer following HT. **Methods:** Between 1997 and 2018, 265 patients who underwent HT were enrolled and prospectively followed in the HT registry of the Sheba Medical Center. **Results:** The series included 5 patients: 4 men and a woman (age range 35–50 years at HT). The patients were diagnosed with kidney tumors 6–11 years after HT (age range at diagnosis 40–72 years). Two of the men were identical twin brothers. At HT four patients received induction therapy with anti-thymocyte globulin and all received an initial immunosuppressive regimen based on cyclosporine. All male HT recipients had a history of heavy smoking. Two male patients developed allograft vasculopathy, but all had preserved heart function. The 72-year-old woman developed a kidney tumor of the native kidney 5 years after re-HT and kidney transplantation. Two patients had features of multifocal papillary renal cell carcinoma and eventually underwent bilateral nephrectomy, while another patient underwent left partial nephrectomy with preserved renal function. **Conclusions:** To the best of our knowledge, this is the first case series study describing kidney tumors following HT. With the improving outcomes and life expectancy of HT patients, a better understanding of the factors that determine cancer risk is of the utmost importance and may have a major impact on the non-cardiac surveillance.

*IMAJ* 2020; 22: 285–288

**KEY WORDS:** heart transplantation, immunosuppression, kidney cancer, renal cell carcinoma (RCC), solid organ

Among the factors limiting the success of heart transplantation (HT) is a high incidence of cancer occurrence and recurrence, with a rate as high as 5.1% for 1-year survivors of HT and 27.4% for 10-year survivors [1]. Cancer is a global burden and a leading cause of death worldwide, especially among HT patients, and the rate is expected to increase in the future due to the prolonged HT follow-up [2].

Previous epidemiological studies have reported an overall threefold to fivefold increased risk of neoplasia in organ-transplant recipients compared to the general population, with a broad spectrum of cancers that include both infection related and unrelated malignancies [3]. Statistically, HT recipients are particularly at risk for developing de novo malignancies, with a fourfold higher rate than that of renal transplant recipients [4–9].

Among the general population, kidney cancer is estimated to comprise 3% of all cancers. The highest incidence of kidney cancer has been reported in North America and Europe, and the lowest in Africa and Asia [10]. Data on kidney cancer following solid organ transplantation, and especially HT, are limited and only a few cases have been reported [1,8]. Furthermore, immunosuppressive regimens have been developed and some, such as mammalian target of rapamycin (mTOR) inhibitors, are linked to a better malignancy profile. Here we report a unique case series of renal cell carcinoma (RCC) detected following HT.

## PATIENTS AND METHODS

Between 1997 and 2018, 265 patients who underwent HT were prospectively followed via the HT registry of the Sheba Medical Center. Data on demographics, clinical status, co-morbidities, echocardiographic measures, kidney imaging, operative and pathology reports, and follow-up were collected for each patient. Of the total cohort, five patients were diagnosed with RCC or a small renal mass post-HT.

## RESULTS

Table 1 summarizes the clinical, demographic, and pathologic characteristics of the patients diagnosed with kidney cancer.

### CASES 1 AND 2: RENAL CELL CARCINOMA IN IDENTICAL TWIN BROTHERS FOLLOWING HEART TRANSPLANTATION

Familial dilated cardiomyopathy was diagnosed in identical twin brothers. One twin underwent HT in 1999 at the age of 35 years. Immunosuppressive protocol included cyclosporine and azathioprine, which was later changed to tacrolimus and myco-

**Table 1.** Case series characteristics of heart transplant patients diagnosed with renal cell carcinoma

	Case 1 twin brother #1	Case 2 twin brother #2	Case 3	Case 4	Case 5
<b>Etiology for HT</b>	Non-ischemic cardiomyopathy	Non-ischemic cardiomyopathy	Ischemic cardiomyopathy	Ischemic cardiomyopathy	Non-ischemic cardiomyopathy
<b>Year of HT</b>	1999	2001	2003	2006	1994 2011: re-HT with kidney transplantation
<b>Age at HT</b>	35	37	57	55	50 (1st HT) 68 (2nd HT)
<b>Gender</b>	Male	Male	Male	Male	Female
<b>Immunosuppressive therapy</b>	ATG induction, cyclosporine + azathioprine, Tacrolimus + mycophenolate	ATG induction, cyclosporine + mycophenolate	ATG induction, cyclosporine + mycophenolate	No induction, 2006–2009: cyclosporine + mycophenolate, 2009–2017: everolimus + cyclosporine, Tacrolimus + mycophenolate	ATG induction 1994–1999: cyclosporine + azathioprine, 1999–2005: cyclosporine + mycophenolate, 2005: everolimus + cyclosporine
<b>Risk factors for RCC: Cigarette smoking BMI Hypertension Diabetes mellitus Trichloroethylene exposure</b>	> 20 pack years 20 No No No	> 30 pack years 21 No No No	> 75 pack years 21.7 Yes No No	> 40 pack years 33 Yes No No	None 23 Yes No No
<b>Year of RCC diagnosis</b>	2005 (6 years post-HT)	2007 (6 years post-HT)	2012 (10 years post-HT)	2017 (11 years post-HT)	2016 (22/5 years post 1st/2nd HT, respectively)
<b>Age of at RCC diagnosis</b>	40	43	68	68	72
<b>Classification of kidney tumor</b>	Multifocal papillary	Multifocal papillary	Clear cell	Features of primary papillary	8mm mass, upper pole left kidney, gadolinium enhancement
<b>Surgery</b>	2005 right nephrectomy 2014 Left nephrectomy	2007 bilateral nephrectomy	2012 left nephrectomy	No	No
<b>Dialysis (year)</b>	Yes (2014)	Yes (2007)	No	No	No
<b>Allograft vasculopathy (year)</b>	Yes (2011)	None	Yes (2019)	No	No
<b>Echocardiography (2019)</b>	Normal	Normal	Normal	Normal	Normal
<b>D/R CMV status</b>	Negative/ positive	Missing/ positive	Negative/ positive	Missing/ positive	Negative/ positive

ATG = anti-thymocyte globulin, BMI = body mass index, CMV = cytomegalovirus, D/R = donor/recipient, HT = heart transplantation, RCC = renal cell carcinoma

phenolate. Six years after HT he was diagnosed with multifocal papillary RCC (clinical T1B), and a right nephrectomy was performed. Fifteen years post-HT, a low-grade papillary type tumor was diagnosed in the left kidney, and a radical nephrectomy was performed. The patient then started hemodialysis. Twelve years after HT he developed atherosclerotic coronary disease and underwent stenting of the circumflex artery and subsequently of the left anterior descending artery. Twenty years post-HT preserved function of the transplanted heart was recorded, and the patient underwent kidney transplantation.

The second twin underwent HT in 2001 at the age of 37 years. Post-HT follow-up was uneventful, and he was treated with an immunosuppressive protocol of cyclosporine and myco-

phenolate. Six years later he was diagnosed with bilateral RCC grade 2–3 multifocal papillary type and underwent right laparoscopic nephrectomy and left open radical nephrectomy (clinical multifocal T3), followed by hemodialysis. Fifteen years post-HT, heart function was normal, and normal coronary arteries were demonstrated by catheterization. At 16 years post-HT, he underwent kidney transplantation.

### CASE 3

The patient underwent HT in 2002 due to ischemic cardiomyopathy. Ten years post-HT he was diagnosed with a clinical T1B renal tumor and underwent open partial left nephrectomy. Pathology was RCC clear cell type grade 2 with a negative mar-

gin. The immunosuppressive protocol comprised cyclosporine and mycophenolate, which was later converted to everolimus combined with low dose cyclosporine. Seventeen years post-HT the patient developed one-vessel coronary artery disease and underwent stenting of the right coronary artery, with an outcome of normal heart function and mild renal dysfunction (estimated glomerular filtration rate 70 ml/min/1.73 m<sup>2</sup>). At time of publication, there was no evidence of renal cancer, but the patient has recurrent skin cancer (squamous and basal cell carcinoma).

#### CASE 4

The patient underwent HT in 2006 due to ischemic cardiomyopathy. The immunosuppression regimen initially comprised cyclosporine and mycophenolate. In 2009 it was converted to everolimus combined with cyclosporine. Due to massive proteinuria, the immunosuppression treatment was converted again to tacrolimus combined with mycophenolate in 2017. Eleven years post-HT, a 14 mm primary kidney tumor enhancing renal mass with the radiology features of papillary RCC was diagnosed by magnetic resonance imaging (MRI). During follow-up, renal function was within the normal range. At 13 years post-HT, the patient had normal coronaries with normal heart function.

#### CASE 5

With a background of non-ischemic cardiomyopathy, the patient underwent her first HT in 1994 at age of 50. An immunosuppression regimen comprised of cyclosporine and azathioprine was implemented and subsequently (in 1999) converted to mycophenolate. Due to late graft loss, the patient underwent a re-heart transplant and kidney transplantation in 2011. Since 2005, she has been treated with everolimus combined with cyclosporine. In 2016, a routine ultrasound follow-up revealed an 8 mm mass of the upper pole of the native left kidney. MRI confirmed the mass features of a solid enhancing small renal mass. Seven years post the second HT and kidney transplantation she had normal heart function with normal coronary arteries and normal kidney function.

## DISCUSSION

In this unique case series, we reviewed our experience with the diagnosis, treatment, and long-term follow-up of RCC after HT. To the best of our knowledge, this is the first case series study describing RCC following HT. With the improving outcomes and life expectancy of HT patients, it is of the utmost importance to reach a better understanding of factors that determine the cancer risk of these patients in order to improve their non-cardiac surveillance.

A recent study analyzing the temporal trends of post-HT malignancy in 17,587 HT recipients from the International Society

for Heart and Lung Transplantation registry reported that more than 10% of adult HT recipients developed a de novo malignancy between 1 and 5 years after HT, with non-skin solid cancers affecting 4% of the recipients. The most common of these cancers was prostate cancer (1.3–1.4% of recipients), followed by lung cancer (1–1.1%), colorectal cancer (0.2–0.3%), and breast and renal cancer 0.2% of HT recipients. Renal cancer constituted approximately 5% of the non-skin solid cancers, almost twice the rate in the non-transplant population [8]. In our patient population, the incidence of RCC is expected to increase, parallel to the improved life expectancy of HT patients, because all of our patients presented with RCC more than 5 years post-HT. This expectation is further supported by the findings of a recent large study showing a 53% increased incidence of kidney cancer in the past decade [2].

This case series has important clinical implications:

- Regarding RCC, there is a need for routine renal surveillance, such as kidney ultrasound, which is readily available, has a low cost, no radiation, and has no need for contrast material. In addition, a better quantification of cancer risks might facilitate early diagnosis and tailored follow-up protocols, and thereby potentially improving prognosis.
- RCC is known to be an immunologically active malignancy, and as such the immunosuppressive regimen in patients with RCC is of particular clinical importance especially with the introduction of mTOR inhibitors. These inhibitors are, characterized by anti-proliferative and antiangiogenic effects, which are independently used for treatment of RCC. Immunosuppressive regimens should be further studied with the ultimate aim of minimizing cancer risk.
- Patients who undergo HT, might have additional risk factors for developing malignant diseases, such as smoking and work/environmental exposure. These factors can be potentially identified and managed in order to decrease the risk for malignancy development.
- Detailed studies of cancer following HT might advance our understanding of the carcinogenic process and the role of immune surveillance for several cancer sites and types.

#### LIMITATIONS

There are several limitations to our study. Surveillance for kidney cancer was not routinely undertaken for all patients during the entire follow-up period, probably leading to under diagnosis. Pathology is missing for two patients. Last, this study was limited by being based on a single-center experience.

#### CONCLUSIONS

To the best of our knowledge, this is the first case series study describing kidney tumor following HT. With improved outcomes and life expectancy of HT patients, a better understanding of factors that determine cancer risk is of utmost importance.

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**Capsule****Tumor cells suppress radiation-induced immunity by hijacking caspase 9 signaling**

High-dose radiation activates caspases in tumor cells to produce abundant DNA fragments for DNA sensing in antigen-presenting cells, but the intrinsic DNA sensing in tumor cells after radiation is rather limited. Han et al. demonstrate that irradiated tumor cells hijack caspase 9 signaling to suppress intrinsic DNA sensing. Instead of apoptotic genomic DNA, tumor-derived mitochondrial DNA triggers intrinsic DNA sensing. Specifically, loss of mitochondrial DNA sensing in *Casp9*<sup>-/-</sup> tumors abolishes the enhanced therapeutic effect of radiation. The authors demonstrated that combining emricasan, a pan-caspase

inhibitor, with radiation generates synergistic therapeutic effects. Moreover, loss of CASP9 signaling in tumor cells led to adaptive resistance by upregulating programmed death-ligand 1 (PD-L1) and resulted in tumor relapse. Additional anti-PD-L1 blockade can further overcome this acquired immune resistance. Therefore, combining radiation with a caspase inhibitor and anti-PD-L1 can effectively control tumors by sequentially blocking both intrinsic and extrinsic inhibitory signaling.

*Nature Immunology* 2020; 21: 546

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**Capsule****Use of hydroxychloroquine and chloroquine during the COVID-19 pandemic**

Given the likelihood that shortages will continue in the near term, Yazdany and Kim proposed that manufacturers, clinicians, pharmacies, health systems, and governmental health agencies continue to coordinate an aggressive response to ensure that antimalarial drug use is appropriately managed during the COVID-19 pandemic. First, it is important to prioritize available supply for clinical trials evaluating important questions, such as dosing, prophylaxis, and treatment in COVID-19. Second, treatment interruptions for those with SLE and other rheumatic diseases must be prevented, because lapses in therapy can result in disease flares and strain already stretched health care resources. Third, stakeholders should work together to see whether dispensation of remaining supply to patients with COVID-19 makes sense as evidence rapidly changes. Fourth, clear messages

that reflect the proper interpretations of available data must be disseminated with high frequency to counteract misinformation, including misleading statements or articles with "clickbait" material. Finally, safeguards should be put into place to discourage overutilization by health professionals who are depleting supply by prescribing antimalarials for preexposure prophylaxis. Hoarding by health professionals for themselves and their friends or family is already occurring, but U.S. state governments and pharmacy boards have started to institute strict utilization policies to prevent further HCQ overutilization. Meanwhile, multiple manufacturers have already made critical commitments to initiate or increase production of HCQ.

*Ann Intern Med* 2020; M20-1334

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