Advanced native-kidney carcinoma in a heart- and kidney-transplanted patient: a case report

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Abstract

Malignancies are one of the leading causes of death in long-term surviving transplant recipients. Dose and prolonged durations of immunosuppressive regimens are considered the main cause, through a direct oncogenic effect and a renowned interaction on physiological anti-viral and anti-oncogenic immune response. Specific neoplasms are known to occur with different frequencies according to the transplanted organ. As a consequence, imaging screenings have been implemented in many graft surveillance programs, although a wide consensus on the timing and modality has not been concurred. There are little data available in the literature regarding incidence of de-novo malignancies in multi-organ recipients. We report the case of a 66-year-old man who developed a renal mass 10 years after a combined heart–kidney transplant.

Keywords Cancer screening · Immunosuppression · Kidney transplantation · Heart transplantation · Post-transplant malignancy

Introduction

Short and long-term clinical management of transplant recipients (TRs) is a major challenge. Considering the great progress in the reduction of acute rejection incidence and in the treatment of early infective complications, long-term follow-up with careful monitoring for chronic renal dysfunction, graft vasculopathy, and occurrence of neoplasms has

become a central issue for long-term survival and quality of life of TRs. In such a scenario, while deaths related to acute rejection and infectious complications have been decreasing, malignancies seriously jeopardize the life expectancy of transplanted patients [1].

Dose and duration of immunosuppression are thought to be key factors for the increased neoplastic risk in transplanted patients, through a reduced anti-viral immune response, direct oncogenic effects, and a disrupted identification of tumor cells [2, 3].

We report the case of a 66-year-old man with a native-kidney carcinoma diagnosed after 10 years from combined heart and kidney transplantation.

Case report

In 2001, a 52-year-old man with a history of type II diabetes mellitus and hypertension had a myocardial infarction, complicated by cardiogenic shock requiring mechanical ventilation and temporary aortic counterpulsation and acute renal failure. During the hospital stay, percutaneous coronary intervention with stent implantation was performed on the right and the posterior descending coronary artery. At discharge, the left ventricle ejection fraction was 24%.

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In 2005, due to worsening of kidney function, a renal biopsy was performed which revealed an advanced diabetic nephropathy. In the same year, a new hospitalization was required for bronchopneumonia complicated by cardiac shock and acute renal failure that needed a period of hemodialysis. Again, in 2005, an episode of pulmonary edema occurred requiring aortic counterpulsation, blood transfusions, and temporary hemodialysis. In 2006, the patient was enrolled in a combined heart–kidney transplant waiting list.

Combined orthotopic heart transplant and heterotopic kidney transplant were performed in the Cardiac Surgery Department of our Institution in June 2006. Native kidneys were preserved. The induction therapy started with basiliximab and prednisone, in the second post-operative day, thymoglobulins were administered, and from the third post-operative day, a standard therapy was started with tacrolimus and mycophenolate.

The post-operative period was unremarkable and the patient was discharged with a standard triple immunosuppressive maintenance therapy (prednisone 15 mg/qd, tacrolimus 2 mg/bid, and mycophenolate 1000 mg/bid). Post-transplant endomyocardial and renal protocol biopsies, and coronary angiographies were unremarkable.

Clinical follow-up showed no significant complications; cardiac and renal functions were reported as normal up to late 2016 (left ventricle ejection fraction was 64%, serum creatinine 0.76 mg/dL, and estimated GFR was of 105 mL/min/1.73 m²). Only diabetes was not optimally under control, with reported discontinuity of pharmacological treatment and Hb1Ac value of 10.5%; as a consequence, the patient demonstrated cardiovascular complications and diabetic nephropathy also on the kidney graft.

As part of follow-up, an abdominal ultrasound study was required annually, but the patient did not comply between 2010 and 2016. The abdominal ultrasound study performed in November 2016 demonstrated the presence of a mass of the left native kidney. The patient was asymptomatic. A contrast-enhanced abdominal MRI was requested for appropriate definition of the mass and confirmed the presence of a gross exophytic renal mass located at the inferior pole of left kidney (approximately 73 × 62 mm maximum diameters in the axial plane, 70 mm of longitudinal diameter) with vast T2-hypointense core, suggestive for intra-lesional necrosis; after gadolinium administration, the mass showed intense contrast enhancement in the arterial phase, with rapid washout in the following parenchymographic and excretory phases. No abdominal enlarged lymph nodes were noted (Fig. 1a, c–e).

A total-body contrast-enhanced spiral CT scan was performed for staging purposes: the mass showed the same contrastographic features shown at MRI and neither pathologic lymph nodes nor distant metastases were demonstrated (T3aN0M0) (Fig. 1b).

In January 2017, the patient underwent laparoscopic left native nephrectomy and surrenalectomy, without post-operative complications. Pathology of the removed kidney demonstrated a high-grade clear cell renal carcinoma (pT3a; 7.4 × 6.8 × 6.0 cm), without intra-lesional necrosis or neoplastic vessel invasion, but with perirenal fat local infiltration (Fig. 2). The patient was later discharged without post-surgical complications; no further therapy apart from surgery was indicated. Immunosuppressive therapy was maintained, but changed by reducing tacrolimus trough levels. The tacrolimus-based immunosuppressive treatment was maintained because of the patient's anti-donor specific antibodies serum presence.

Discussion

Transplantation is the gold standard treatment for end-stage organ failure. In the last decades, great progress has been achieved in clinical management of transplanted patients, with a significant reduction of acute rejection [4], and infective complications. Despite this, long-term survival remains uncertain because of occurrence of graft vasculopathy, late antibody mediated rejection, and the risks related to chronic exposure to immunosuppressive therapy [5, 6].

In our case, the patient positivity for anti-donor specific antibodies serum increased significantly the risk for chronic graft failure and consequently suggested the prosecution of a triple immunosuppressive therapy, albeit tacrolimus was later reduced through levels.

Apart from chronic renal disease, a well-known side effect of long-term immunosuppression is the increased risk of malignancies, the main cause of death in long-surviving patients with a functioning graft. When compared to the general population of the same age and sex, the overall oncologic risk in the transplanted population is increased between two and three times, with risk levels comparable to those of non-transplanted subjects 20–30 years older. Such a risk is inversely related to age at transplant, as increased risk to develop a neoplasm is particularly evident in younger subjects [7]. Most common malignancies developed in transplanted patients include non-melanoma skin cancer, lip carcinoma, post-transplant lymphoproliferative diseases, Kaposi sarcoma, and anogenital tract cancers. No effect has been shown on prevalence of breast and prostate cancers [5, 8]. Nonetheless, even considering that overall risk for all-site cancer is similar across different TRs, the incidence of specific cancers is known to vary according to the transplanted organ [5].

In particular, kidney TRs show a three-to-eightfold increased risk to develop a malignancy, mainly non-melanoma skin cancers (particularly squamous cell carcinoma) [9] and lymphoproliferative disorders, especially

Fig. 1 CT and MR imaging of renal mass. **a** T2-weighted TSE sequence shows a gross exophytic left native-kidney mass, with a hyperintense core, suggestive for intra-lesional necrosis; **b** coronal CT scan acquired shows vivid contrast enhancement in the arterial

phase; basal (**c**) and post-contrast (**d–e**) T1-weighted Fat saturated VIBE sequences show contrast enhancement in the arterial phase (**d**), with rapid washout in the following parenchymographic phase (**e**)

Fig. 2 Native-kidney clear cell carcinoma: nests of cells with clear cytoplasm; adjacent thin-walled blood vessels (hematoxylin and eosin stain, microscope objective was $\times 20$)

non-Hodgkin lymphoma [10]. Renal cancer of the native kidney, mainly clear cell and papillary renal cell carcinomas,

has been described previously in the context of a renal transplant, with an incidence quoted as 0.35–3.9% [11]. Acquired renal cystic disease and long-term dialysis are considered to be the main risk factors [12, 13]. However, none of these predisposing factors was evident in this patient.

When considering heart transplantation, tumors are the second long-term cause of mortality after graft vasculopathy [14–16]. Reported cumulative prevalence of malignancies in heart TRs ranges from 2.9% at 1 year to 31.9% at 10 years, being non-melanoma skin cancers and lymphoproliferative disorder the two most common entities [17, 18]. Yet, controversial data are available claiming cancer rates comparable to that of general population [14].

Even though feasibility and complications of combined heart–kidney transplant have been thoroughly studied [19–21], only few data are currently available regarding the risk of malignancies in this particular setting and more generally in multi-organ graft recipients. Whether such a condition modifies risk rates, according to the combination of grafts remains unanswered.

Studies regarding long-term follow-up of combined heart–kidney transplant reported the occurrence of

de-novo malignancies as well, mainly represented by skin cancers and lymphoproliferative diseases but also from solid cancers in up to 25% of cases, even though small samples are available [19, 22, 23].

The increased risk of malignancies in graft recipients implies and suggests a proper planning of screening programs. In our case, a clear cell renal carcinoma was diagnosed 10 years after combined heart–kidney transplant. As reported previously, the patient disregarded the scheduled abdominal ultrasound annual screening; therefore, clinical success in identifying the de-novo malignancy was impossible before 2016.

Many authors claimed the importance of screenings for several neoplastic entities in the transplanted population [24–27], recommending vigorous surveillance programs with long-term follow-up, as malignancies can develop even after more than 10 years from the transplant. Even if importance of screening programs is undoubted in such a context, still, precise guidelines are not yet available, as the medical community has not reached a full consensus.

It has been proposed that the frequency of screening of native kidneys after transplant should be decided considering the presence of renal cysts and the duration of the dialysis [28]. Yet, the Kidney Disease Improving Global Outcomes guidelines do not advise kidney cancer screening after transplantation [29].

Regarding heart graft recipients, routine clinical screening for skin cancer and breast, colon, and prostate cancer is recommended. Renal cell carcinoma has been described in heart transplanted patients and routine abdominal ultrasound examination has been recommended [30].

In addition, it still has to be demonstrated that dedicated and intense screening programs benefits can effectively overweight harms; ecotomography, for instance, may result in overdiagnosis in cases of slow-tumor progression, especially in older patients that would presumably die of another cause. In this context, unnecessary and potentially dangerous procedures or surgeries may be performed [31]. Further studies are needed to determine more accurately the efficacy and benefit/risk ratio of such screenings, their timing and the related costs [32].

To conclude, we believe that, despite the reported risks in certain specific cases, the importance of follow-up diagnostic imaging is crucial in detecting the development of malignancies. The cases where this surveillance is missed for any reason, as the one we are reporting, confirm our thought. In our center, with regard to the risk of solid abdominal malignancies, we propose an annual abdominal US study, together with a list of other diagnostic studies, in line with other centers and the few existing consensus documents [33]. Such an approach proved to be effective in detecting de-novo cancers and promptly guided their management.

Compliance with ethical standards

Conflict of interest All the authors have declared no competing interests.

Human participants and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient included in this article.

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