Metastatic renal cell carcinoma of the native kidney in a renal transplant recipient: Revisiting the era of tyrosine kinase inhibitors – Case report

Daniel Suso-Palau a, b, *, Julián Chavarriaga a, Francisco Usubillaga a, Josué Asprilla c, Lina Micolta b, Marcela Urrego b

a Division of Urology, Clínica Imbanaco – Quirón Salud, Cali, Colombia
b Division of Oncology, Clínica Imbanaco – Quirón Salud, Cali, Colombia
c Division of Pathology, Clínica Imbanaco – Quirón Salud, Cali, Colombia

ARTICLE INFO

Keywords:
Metastasis
Clear cell renal cell carcinoma
Transplant
Kidney

ABSTRACT

Patients who receive solid organ transplants are at higher risk for developing cancer, which is attributable to chronic immune suppression. Less than 8 cases of metastatic RCC (mRCC) have been reported until now. The aim of this article is to present the case of a 77-year-old male with mRCC of the native kidney and discuss treatment options including targeted therapy, which appears to be the treatment of choice, even in the era of immunotherapy.

1. Introduction

Patients who receive solid organ transplants are at higher risk of developing cancer, attributable to chronic immune suppression. Renal cell carcinoma develops in the native kidneys of patients with kidney allografts 10 to 100 times more common than in the general population. In kidney transplant recipient’s immune suppression does not appear to be the primary etiology in the development of Renal cell carcinoma (RCC). In lieu, abnormalities specific to end-stage kidney disease (ESKD) and acquired cystic kidney disease (ACKD) appear to be correlated with RCC development.

Less than 8 metastatic RCC (mRCC) cases have been reported in the literature until now. The first one was by Nakamoto et al., in 1994. No significant developments have been made in the treatment options for these patients, who still represent a significant dilemma. Currently, first line therapy for mRCC in the general population are Immunotherapies (IO) in combination with tyrosine kinase inhibitors (TKI). Regimens such as Pembrolizumab/Axitinib, Nivolumab/Cabozantinib, Nivolumab/Ipilimumab, Lenvantiñib/Pembrolizumab, and Avelumab/Axitinib represent the first choice of treatment for these patients in 2021. The major setback in kidney transplant recipients is that the goal of IO is to restore the ability of the immune system to eliminate cancer cells by either activating the immune system directly or inhibiting mechanisms of suppression by tumours. Most studies assessing IO in combination with TKI excluded patients who had received systemic treatment with either glucocorticoids or other immunosuppressive medications.

This article aims to present the case of a 77-year-old male with mRCC of the native kidney and discuss treatment options in the era of IO.

2. Case presentation

A 77-year-old male with hypertension and chronic kidney disease underwent a kidney transplant of a cadaveric donor in 2003. He has been receiving cyclosporin A with no signs of rejection for 17 years. During his follow-up and 15 years after the allograft transplant, an incidental finding of a heterogenous multilobed, exophytic solid mass in the right native kidney measuring 4.9x3.3 x 4.6 cm was made. Surgery was initially withheld given that the patient presented a myocardial infarction and required surgical intervention and rehabilitation.

In 2020 the patient was re-staged, and a computed chest tomography (CT) showed multiple images of bilateral pulmonary metastates (Fig. 1). The case was presented at a multidisciplinary team meeting (MDT) as an mRCC of the right native kidney with an MSKCC/Motzer and IMDC risk scores, both with 0 points, classifying the patient in favourable risk.

We decided to perform a laparoscopic radical nephrectomy, which the patient underwent without complications. Metastectomy was not

* Corresponding author. Carrera 38 A No. 5A 100, Cali, 76001, Colombia.
E-mail addresses: danielsusopalau@gmail.com (D. Suso-Palau), chavarriagajulian@gmail.com (J. Chavarriaga), franiscousubillaga@imbanaco.com.co (F. Usubillaga), joneasprilla@imbanaco.com.co (J. Asprilla), marcelaurrego@imbanaco.com.co (M. Urrego).

https://doi.org/10.1016/j.eucr.2022.102082
Received 2 March 2022; Received in revised form 31 March 2022; Accepted 10 April 2022
Available online 11 April 2022
2214-4420/© 2022 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
an option for this patient, given that he had bilateral pulmonary metastases. Histopathological analysis, including immunohistochemistry, showed a 4 cm, clear cell RCC with renal sinus fat involvement, nuclear grade WHO/ISUP 3, staged as pT3a (Fig. 2).

The case was discussed in a MDT including the kidney transplant division. We determined the patient benefited from changing immunosuppression from cyclosporin to sirolimus and starting Sunitinib. At ten-month follow-up, the patient developed gastrointestinal symptoms including diarrhea, which required sirolimus and sunitinib dose-adjustment. However, at twelve-month follow-up, continues to have normal allograft function and without clinical or radiographic progression.

3. Discussion

Immunotherapies and antiangiogenic therapies have improved oncologic outcomes and quality of life in patients with mRCC in the general population.\(^1,5\) Renal transplant recipients required chronic immunosuppression, which could be associated with medium- and long-term appearance of malignant lesions and contraindicate the use of IO for the treatment of these malignancies. mRCC in transplanted patients is a rare condition, only reported in a handful of patients in large retrospective series.\(^1,5\) The importance of this paper is to make a critical analysis of the available literature to determine the optimal treatment options for these patients.

Leveridge et al., reported 45 RCC of the native kidney in 39 patients (1.1%) and 8 patients (0.2%) developed in the allograft kidney of a total of 3,568 kidney transplant recipients. Two patients had metastatic disease; 1 of these two patients had asynchronous bilateral disease, which developed 31.5 months after his initial diagnosis, while the other patient had evidence of metastatic disease at diagnosis. No treatment strategies for these two metastatic patients were discussed.\(^1\)

In kidney transplant recipients with malignancies or metastatic disease, interruptions, reductions, or changes in immunosuppressive treatment have been suggested with the risk of immunologic graft loss.\(^1,5\) Antitumoral immunotherapy is theoretically contraindicated for patients receiving immunosuppressive treatment. Nakamoto et al., reported in 1994 discontinuation of cyclosporine A and treatment with interferon-\(\alpha\); the latter has been replaced by TKI in the upcoming years after this study was published.\(^4\) Neuzillet et al., reported the treatment of a patient with mRCC arising in the native kidney, with maximal reduction of the immunosuppressive regimen, IL-2 and interferon-containing immunotherapy.\(^5\) Vegso et al., suggested that TKI and mammalian target of rapamycin (mTOR) inhibitors seem to be promising for treating mRCC in kidney transplanted patients.\(^3\) However, there is still no clear consensus for the treatment of these patients in 2021 (Table 1).

Our rationale to approach this case was that VEGFR-targeted therapy used to be the standard first-line treatment for patients with mRCC based on improvements in progression-free survival (PFS) in phase 3 clinical
trials, including the COMPARZ (Pazopanib vs. Sunitinib) and CABOSUN (Cabozantinib vs. Sunitinib) trials. The VEGF-signalling pathway is upregulated in clear cell RCC due to the inactivation of the VHL tumour suppressor gene, providing a molecular rationale for using VEGF-targeted therapies in this setting.\textsuperscript{1, 3} Most importantly, there is no contraindication, and the aforementioned studies did not exclude patients with immunosuppressive treatment, which would make TKIs the ideal treatment for patients with kidney allografts and mRCC.

In conclusion, mRCC in renal transplanted patients is highly unusual; cytoreductive nephrectomy could be considered an option in patients with favourable and intermediate IMDC risk groups. Subsequent targeted therapy should be discussed with a multidisciplinary team. However, the optimal treatment for mRCC in kidney transplant recipients is not established, and more systematic studies and, ideally clinical trials including transplant patients are needed to bring this field forward. For now, immunotherapy should not be automatically dismissed for transplant patients, although for RCC, the survival benefit may not outweigh the risks.

Consent for publication

The patient in this manuscript has given his full written and verbal consent to publish anonymous photos and clinical and laboratory details of the case.

Funding sources

The authors have no funding sources to declare.

Acknowledgement

We have no acknowledgements to make.

ABBREVIATIONS

\textbf{RCC} = Renal cell carcinoma

\textbf{CT} = Computerized tomography

\textbf{mRCC} = metastatic Renal cell carcinoma

\textbf{TKI} = Tyrosine Kinase inhibitors

\textbf{VEGFR} = Vascular endothelial growth factor receptor

\textbf{IMDC} = International metastatic RCC database

\textbf{MDT} = Multidisciplinary team

\textbf{ESKD} = end-stage kidney disease

\textbf{ACKD} = acquired cystic kidney disease

\textbf{PSI} = Proliferation signal inhibitors

References

1. Leveridge M, Musquera M, Evans A, et al. Renal cell carcinoma in the native and allograft kidneys of renal transplant recipients. \textit{J Urol}. 2011;186(1):219–223.
2. Neuzillet Y, Lay F, Luccioni A, et al. De novo renal cell carcinoma of native kidney in renal transplant recipients. \textit{Cancer}. 2005;103(2):251–257.
3. Vegso G, Toronyi E, Hajdu M, et al. Renal cell carcinoma of the native kidney: a frequent tumour after kidney transplantation with favourable prognosis in case of early diagnosis. \textit{Transplant Proc}. 2011, May;43(No. 4):1261–1263. Elsevier.
4. Nakamoto T, Igawa M, Mitani S, Ueda M, Usui A, Usui T. Metastatic renal cell carcinoma arising in a native kidney of a renal transplant recipient. \textit{J Urol}. 1994;152(3):943–945.
5. Ianhez LE, Lucon M, Nahas WC, et al. Renal cell carcinoma in renal transplant patients. \textit{Urology}. 2007;69(3):462–464.

| Study        | n | Histology     | Treatment                      | Immunosuppression | Antineoplastic                  |
|--------------|---|---------------|-------------------------------|-------------------|---------------------------------|
| Suso-Palau et al. (2021) | 1 | Clear cell - mRCC | Change Cyclosporin to PSI (Sirolimus). | VEGF Inhibitor (Sunitinib) |
| Vegso et al. (2011) | 2 | mRCC | Change Cyclosporin to PSI | VEGF or mTOR Inhibitors |
| Leveridge et al. (2011) | 2 | NR | NR | NR |
| Neuzillet et al. (2005) | 1 | Clear cell - mRCC | Cyclosporin A | IL-2/IFN Immunotherapy + Paliative Radiotherapy (Bone metastases) |
| Nakamoto et al. (1994) | 1 | Clear cell - mRCC | Interruption of cyclosporin A | IFN-α |

mRCC = Metastatic renal cell carcinoma; PSI = Proliferation signal inhibitors; VEGF = Vascular endothelial growth factor; mTOR = Mechanistic target of rapamycin; NR = Not reported; IL-2 = Interleukin-2; IFN = Interferon.