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Case Report

Sonidegib induced rhabdomyolysis in kidney transplant patient: a case report

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Abstract

Kidney transplant recipients (KTR) have a higher risk of developing malignancies compared to the general population, due to the immunosuppressive regimens which can promote the oncogenesis process. The incidence of de novo non-melanoma skin cancer (NMSC) in KTR is greater than in the general population. Basal cell carcinoma (BCC) represents one of the most frequent malignancies in KTR. Sonidegib is a Hedgehog signaling pathway inhibitor approved for the treatment of locally advanced basal-cell carcinoma (LABCC) that following surgery or radiation therapy, or is given to those candidates who are not eligible to surgery or radiation therapy. This paper reports the case of a kidney transplant patient, who developed severe acute kidney injury (AKI) due to rhabdomyolysis (RML) induced by sonidegib therapy which required renal replacement therapy (RRT).

Keywords: Rhabdomyolysis, Recurrent basal cell carcinoma, Kidney transplant recipient, Hedgehog pathway inhibitors, Sonidegib

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Introduction

The overall incidence of non-melanoma skin cancer (NMSC) in kidney transplant recipients (KTR) is nearly 65-100-fold greater compared to the general population (1). In this context, the risk of developing basal cell carcinoma (BCC) increases 10-12 times compared to the age-matched general population (2,3). The prevalence and the incidence of skin cancer is directly correlated with the long-term and the intensity of immunosuppression therapy, which can promote the oncogenesis process by leading to lower immune- mediated tumor surveillance and development of malignant tumors (4,5).

Skin cancers in KTR could be clinically more aggressive and in have worse cancer histopathology than the general population (5). BCCs are generally slow growing and rarely metastasize, and patients who receive appropriate therapy typically have a good prognosis. A minority of patients develop locally advanced basal-cell carcinoma (LABCC) or recurrent BCC, who treatment can be challenging or associated with poorer outcomes (6,7).

Treatment requires a multidisciplinary approach, including surgery and/or radiation therapy and/or topical therapy and/or photodynamic therapy (8).

Mammalian target of rapamycin inhibitors (mTORi), such as everolimus, has been shown to reduce the incidence of BCC in KTR (9).

In the case of LABCC, the standard care and the switch of immunosuppressive therapy to mTORi can be insufficient.

The introduction of sonidegib, targeted therapy for LABCC in the form of hedgehog signalling pathway inhibitors represents one of the greatest successes of translational medicine, and a therapeutic option in patients with LABCC and recurrent BCC including KTR. Sonidegib is used to treat patients affected by LABCC that are not amenable to curative surgery or radiotherapy, or those who are not candidates for surgery or radiation therapy (10,11).

We present a case of kidney transplant patient who developed severe acute kidney injury (AKI) due to rhabdomyolysis (RML) induced by sonidegib therapy.

Case Presentation

The case study is based on a 74-yeasrs-old woman who underwent to kidney transplantation on December 2005 from a deceased donor. Her starting immunosuppression therapy was based on the use of steroids, azathioprine, and tacrolimus. Her medical history included: statin intolerance (muscle spasms) and multiple BCCs, diagnosed in 2012 and 2014. Subsequently, immunosuppressive therapy

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Implication for health policy/practice/research/medical education

Kidney transplant recipients (KTR) have a higher risk of developing malignancies. One of the most frequent malignancies in KTR is represented by BCC. The treatment in certain cases could be challenge as like in cases of locally advanced BCC. Sonidegib represents one of the greatest successes of translational medicine and it represent and therapeutic option in cases of LABCC. The sonidegib use could be complicated by RML. This case report can help to pay more attention to the administration of sonidegib in delicate subject such as KTR.

was modified, azathioprine was switched to m-TORi (everolimus) associated with a low dose of tacrolimus. in addition, the patient was evaluated by a dermatologist and plastic surgeon, and subsequently underwent treatment for BCC (surgery, local chemotherapy, photodynamic therapy). In view of frequent and recurrent episodes of BCCs and LABCC (from 2021 to 2022 there have been nine episodes), the patient started the therapy with sonidegib 200mg once a day from the 14-th of June 2022. Thereafter, the patient undertook routine monitoring of creatinine kinase (CK) and the kidney function, resulting normal until the July 20th when the patient was admitted to the emergency room, after an episode of fever, generalized myalgia, weakness, dark urine and fatigue lasting all day long. The physical evaluation showed normal arterial blood pressure (130/85 mm Hg), normal heart rate (73 bpm) and O_2 saturation (99%), fever (38°C), mental confusion and dehydration; diuresis was preserved.

Laboratory results showed elevated CK (35571UI/L, normal range 5-145 UI/L), elevated lactate dehydrogenase (LDH) (1171 UI/L normal range 84-246 UI/L), elevated inflammatory markers white blood cells (WBC) (11200/mm^3) and C-reactive protein (CRP) (16.6 mg/L), elevated aspartate aminotransferase (AST) (814 UI/L), alanine aminotransferase (ALT) (154 UI/L, normal range 2-32 and 13-56 UI/L respectively) and worsening kidney graft function (creatinine 1.5 mg/dL, baseline value 1.17 mg/dL) (Table1).

The urine test showed the presence of proteinuria at 200 mg/dl. Myocardial necrosis markers were negative and no serum electrolytes alterations were registered.

Electrocardiogram, abdomen echography, and chest radiography did not show any alteration. Intravenous (IV) fluids, urine alkalinization, and diuretics were initiated. CK, myoglobin, AST, ALT, LDH, and urine output were monitored.

The suspicion of sonidegib-induced RML was strongly supported by the mean time of clinical symptoms onset and laboratory alterations after starting therapy, as well as the absence of any other reasons that could explain the elevated CK. Given the known adverse effects of Hedgehog signaling pathway inhibitor use, sonidegib was discontinued immediately (12). Despite the IV hydration at 150/mL/h for almost 48 hours. CK levels continued to rise reaching a level above 160 000 UI/L, on day 2 The serum myoglobin and LDH levels were elevated up to 72 000 mg/mL (normal range 0-76 mg/mL) and 1819 UI/L respectively, associated with the evidence of acute kidney graft injury (serum creatinine 3.1 mg/dL) and worsening of myalgias and muscles spasms (Table 1).

Taking into account the whole picture of the clinical and laboratory data course, we decided to start renal replacement therapy (RRT) in intermittent hemodialysis modality for a total of two sessions, using a high-flux membrane dialyzer in convective technique to remove myoglobin from circulation, with the intent to limit a kidney graft injury induced by myoglobin. We decided to treat with a convective technique and high-flux membrane considering the myoglobin molecule weight (17500 Da) (13).

Given the preserved diuresis and the good hemodynamic status, we continued with hydration, alkalinization and diuretic therapy, which induced a forced diuresis achieving a urine output out of 5L/24 h, guaranteeing a slow but

Table 1. Trend of laboratory data during hospitalization

	D0	D1	D2- HD	D3-HD	D4	D5	D10	D13	D14	D15
WBC (mm^3)	11200	12300	8400	8600	5400	7000	8700	11100	10700	7200
Mgb (mg/mL)		32505	72050	44420	18223	12809	2808	1722	1237	553
Urea	72	96	130	95	74	97	117	92	80	66
sCr (mg/dL)	1.5	2,6	3,1	2.17	2.5	2.6	2.4	2.17	2.07	1.78
UA (mg/mL)		10.1	9.7	5.3	5	3.9	4.8	4.8	4.9	4.8
AST (UI/L)	814	1558	2800	2870	1760	1348	319	135	105	67
ALT (UI/L)	154	282	356	701	501	465	274	183	147	102
CK (UI/L)	35571	77810	160000	126330	59850	39490	5811	2028	1467	970
LDH (UI/L)	1171	1225	1819	1760	1530	1237	792	718	670	535
Na (mmol/L)	137	140	140	140	135	141	144	142	144	142
K (mmol/L)	3.8	3.9	4.7	3.8	3.7	3.6	3.3	3.9	4	3.5

Abbreviations: WBC; White blood cells, Mgb; Myoglobin, sCr; Serum creatinine, UA; Uric acid, AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, CK; Creatinine kinase, LDH; Lactate dehydrogenase, Na; Sodium, K; Potassium, D; day, HD; Hemodialysis.

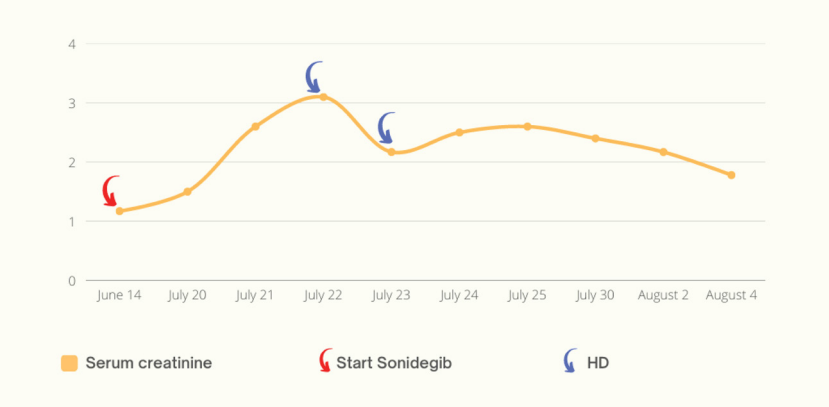

Figure 1. Trend of serum creatinine after initiation of sonidegib therapy on June 14-th, and hemodialysis treatment starting on July 22-th, and subsequent improvement of kidney graft function. Serum creatinine in mg/dL, HD hemodialysis.

progressive reduction of CK (970 UI/L), myoglobin (553 mg/mL), LDH (535 UI/L), AST (67 UI/L) and ALT (102 UI/L) serum levels, amelioration of kidney graft function (creatinine 1.78 mg/dL) and resolution of muscle spasms and myalgia (Figure 1).

The patient was discharged in stable clinical conditions on day 15 without Hedgehog signaling pathway inhibitor treatment and with a big dilemma regarding future LABCC treatment.

Discussion

Sonidegib is a Hedgehog signaling pathway inhibitor, approved for the treatment of adult patients with LABCC who are not eligible for surgery or radiation therapy (10,11). This drug represents an important treatment tool for the category of KTR, who are at high risk of developing malignancies.

Sonidegib use was described in the BOLT trial and its use was associated with many adverse effects like muscle spasms, myalgia, fatigue, elevated serum CK and transaminase levels. The average time for the appearance of elevated CK values was 12.9 weeks (range 2 to 39 weeks) after initiation of sonidegib therapy and the meantime of resolution was 12 days (range 8 to 14 days) (12).

Despite none of the RML cases reported in the BOLT trial were confirmed, it should be considered a severe complication of therapy with sonidegib. Our patient demonstrated a temporary relationship between the exposure to sonidegib and the onset of elevated CK levels, followed by improvement in CK levels after discontinuation of the medication. AKI is one of the most severe complications of RML. Myoglobin can cause renal tubular damage by different mechanisms (14). The prompt recognition and treatment of RML could be the key to preventing AKI. As in our case, medical therapy may not be sufficient to treat RML, and it became necessary to resort to invasive therapy, in our case RRT.

The guidelines suggest against the routine use of RRT in RML- induced AKI. However, there are no recommendations favouring the continuous renal replacement therapy (CRRT) versus intermittent haemodialysis, convection versus diffusion, or medium versus high cut-off membranes for AKI prevention/ treatment (15,16).

Conclusion

Clinicians need to be aware and vigilant about sonidegib-related RML, particularly during the early phase of treatment. The discontinuation of sonidegib therapy, on one hand, allowed the resolution of the RML, but on the other hand, it represents a future challenge regarding LABCC therapy in KTR category.

Authors' contribution

Conceptualization: SM.
Methodology: SF, SM.
Validation: DR.
Formal analysis: SF, SM.
Investigation: SM, SF, LP, MA, MM.
Resources: SM, MT.
Data curation: SM, SF.
Visualization: DR, SM.
Supervision: DR.
Project administration: SM.
Writing–original draft: SM.
Writing–review and editing: SM.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this report. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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