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Dengue Virus in Kidney Allograft: Implications for Donor Screening and Viral Reservoir

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INTRODUCTION

Dengue is a systemic viral infection transmitted by mosquitoes, capable of causing severe diseases in humans, and presenting significant health, economic, and social challenges.[1,2] The Dengue virus (DENV) is rapidly spreading, putting half of the world's population at risk of infection, with autochthonous transmission observed in Europe and the United States.[3]

There are 4 distinct serotypes of DENV: DENV 1, DENV 2, DENV 3, and DENV 4. Infection with one serotype provides lifelong immunity against that specific serotype (primary infection). However, subsequent infections with a different DENV serotype increase the risk of severe dengue (secondary infection).[4]

The kidneys may act as reservoirs for arbovirus infections. For example, in Zika virus infections, human podocytes, glomerular endothelial cells, and mesangial cells serve as amplification reservoirs, leading to persistent high-level viruria.[5,6] West Nile Virus has been detected in the urine of convalescent patients up to 9 years postinfection.[7] However, limited data are available regarding kidney involvement in Dengue infection.

Since the onset of the Dengue epidemic in Réunion Island (a French overseas department in the Indian Ocean) in 2018, 6 kidney transplant recipients have developed Dengue infection shortly after transplantation.

The objectives of this report were as follows: (i) to describe viral transmission through the kidney allograft using genotyping analysis of donor and recipient samples, (ii) to report the risk of Dengue infection in kidney transplant recipients, (iii) to confirm the kidney's role as a viral reservoir through longitudinal blood and urine reverse transcription polymerase chain reaction (RT-PCR) follow-up, and (iv) to share the adaptations our center had to implement to prevent new infections.

RESULTS

Since the onset of the Dengue epidemic in 2018, a total of 180 kidney transplantations have been performed on Réunion Island. Among this cohort, 6 recipients (R) experienced Dengue infections shortly following transplantation. Notably, 4 recipients contracted Dengue infections from 2 distinct donors (D), with D1 transmitting the infection to R1.1 and R1.2, and D2 to R2.1 and R2.2.

Two additional recipients, R3.1 and R3.2, acquired Dengue infections in the immediate posttransplant period. The mean duration of follow-up post-transplantation was 615 days, ranging from 451 to 918 days.

Donors' characteristics

Patient D1, a 50-year-old male, presented with symptomatic Dengue infection and thrombocytopenia concurrent with traumatic brain injury. Upon admission, blood RT-PCR confirmed Dengue infection with the DENV2 serotype. Thirteen days after admission, he progressed to brain death. Notably, DENV replication was controlled, with 2 consecutive negative results on blood RT-PCR tests obtained respectively at 8 and 12 days postadmission, before organ procurement.

Table 1. Clinical and biological characteristics of the recipients with early dengue after transplantation and their respective donors

Donors			Recipients												
	Dengue Infection (Yes/No)	Serotype		Age (yr)/ Gender	Previous Dengue Infection (Serotype)	CKD Etiology	Dialysis Duration (yr)	DENV Origin, Serotype	Severe Dengue	Lowest Platelet Count (10^9/l)	Thrombocytopenia Duration (d)	ALAT (Normal Value Below 35)	DGF[b] (Days of Dialysis)	Hospitalization Duration (d)
1	Yes	DENV-2	1.1	39/M	No	Unknown	13	Donor 1, DENV-2	No	64	20	144	No	15
			1.2	64/M	No	Unknown	5	Donor 1, DENV-2	No	104	12	41	No	20
2	Yes	DENV-1	2.1	58/M	Yes (DENV-2)	Nephrolithiasis	3	Donor 2, DENV-1	Yes[a]	11	45	3160	Yes (36 d)	56
			2.2	61/M	No	IgA Nephropathy	10	Donor 2, DENV-1	No	32	36	182	No	39
3	No	-	3.1	52/M	Yes (DENV-2)	Unknown	4	Vectorial, DENV-1	No	18	39	76	No	30
			3.2	38/F	No	Focal segmental glomerulosclerosis	5	Vectorial, DENV-1	No	92	7	34	No	14

ALAT, alanine aminotransferase; CKD, chronic kidney disease; DENV, Dengue virus.
[a]Recipient 2.1 experimented hemorrhagic shock requiring multiple transfusions.
[b]Delayed graft function (DGF) was defined as the requirement of dialysis within the first week of transplantation.

D2, a 61-year-old male, succumbed to brain death following a traumatic cerebral hemorrhage within the context of acute alcohol intoxication. Notably, he did not exhibit any clinical or biological manifestations indicative of Dengue infection. The presence of Dengue infection remained undisclosed at the time of organ procurement, which occurred 5 days after admission. Nevertheless, a systematic blood RT-PCR test conducted at that juncture returned a negative result.

Subsequently, retrospective RT-PCR analysis was performed on a blood sample collected at the time of admission. This decision stemmed from the fact that the recipients of the sister kidneys had been diagnosed with Dengue infection, and this retrospective analysis confirmed the presence of Dengue infection with the DENV1 serotype.

Serological testing, as well as blood and urine RT-PCR, conclusively excluded Dengue infection in the case of D3. Detailed characteristics of the donor are provided in Table 1.

Recipients and transplant characteristics

The 6 recipients underwent a first ABO-compatible kidney allograft transplantation. Immunosuppressive therapy included Thymoglobulin as induction therapy, along with mycophenolate mofetil and tacrolimus for maintenance therapy. None of the 6 recipients had received any Dengue vaccine before their kidney transplantations (currently, the French National Authority for Health does not recommend the use of Dengue vaccine). Recipients and transplant characteristics are detailed Table 1.

Between day 5 and day 12 after transplantation, all 6 recipients presented a thrombocytopenia, with platelet counts ranging from 11 to 104 10^9/l concurrent with elevated liver enzymes (alanine aminotransferase levels ranging from 34 to 3160 U/l, for a normal value below 35 U/l).

RT-PCR testing on blood samples conducted on day 10 confirmed Dengue infection for all 6 recipients. A retrospective analysis ruled out Dengue infection at the time of admission.

Five of the 6 recipients displayed either no or mild clinical manifestations of Dengue infection. Specifically, R1.1, R3.1, and R3.2 presented isolated fever between day 8 and day 10 post-transplantation, whereas R1.2 and R2.2 remained clinically asymptomatic.

In the latter cases, the decision to conduct Dengue testing was prompted by the results of a biological assessment and the presence of clinical manifestations in the recipients of their sister kidneys.

R1.1, R1.2, R2.1, R3.1, and R3.2 experienced immediate allograft function recovery, with stable

creatinine levels approximately around 2.0 mg/dl (estimated glomerular filtration rate [eGFR] of 39 ml/min per 1.73 m^2), 2.2 mg/dl (eGFR of 30 ml/min per 1.73 m^2), 2.1 mg/dl (eGFR of 34 ml/min of 1.73 m^2), 1.3 mg/dl (eGFR of 64 ml/min per 1.73 m^2), and 1.4 mg/dl (eGFR of 48 ml/min per 1.73 m^2), respectively.

R2.1 presented with hemorrhagic shock on day 10 post-transplantation, occurring in the context of fever and thrombocytopenia. This required intensive care management, including mechanical ventilation, pressor amines, and substantial blood and platelet transfusions. The kidney allograft displayed a slow recovery after 37 days of dialysis dependence. Renal allograft function ultimately improved, resulting in a serum creatinine level of approximately 2.2 mg/dl (eGFR of 30 ml/min per 1.73 m^2).

Genotyping analysis of the DENV in D1 and D2, as well as R1.1, R1.2, R2.1, and R2.2, confirmed the presence of the same DENV strain in D1, R1.1, and R1.2, whereas a different strain was identified in D2, R2.1, and R2.2.

Primary versus secondary dengue disease

Four recipients (R1.1, R1.2, R2.2, and R3.2) tested negative for Dengue serology at the time of transplantation and subsequently developed primary Dengue disease. Their clinical presentations ranged from mild to asymptomatic.

Conversely, 2 recipients (R2.1 and R3.1) had a history of Dengue infection before kidney transplantation, confirmed by the presence of circulating IgG antibodies on the day of transplantation (both had been previously infected with DENV2). These recipients developed a secondary Dengue infection with DENV1. Their clinical presentations varied, from isolated fever to hemorrhagic shock.

Recipients with secondary Dengue infections exhibited more profound and prolonged thrombocytopenia compared to those with primary Dengue disease. The mean lowest platelet count for secondary Dengue infection recipients was 14.5 10^9/l, whereas it was 73 10^9/l for the primary Dengue disease group. In addition, the mean duration until platelet count normalization was 42 days for recipients with secondary Dengue infection, in contrast to 18.75 days for those with primary Dengue infection (see Table 1 for details).

Dengue infection evolution and serological response

The DENV serological response was concurrent with clinical recovery and the beginning of thrombocytopenia resolution.

The serological response to DENV occurred at a median time of 22.5 days (ranging from 14 to 31 days) post-transplant, characterized initially by temporary IgM antibodies followed by the sustained presence of circulating IgG antibodies. Detectable DENV viremia persisted for a median duration of 42.5 days (ranging from 20 to 65 days) posttransplant (Supplementary Figure S1). This DENV serological response coincided with clinical recovery and marked the onset of thrombocytopenia resolution.

DENV urinary excretion and lymphocyte recovery

As part of their follow-up in the kidney transplantation department, all 6 recipients underwent systematic screening for DENV using RT-PCR in both blood and urine samples during each follow-up appointment, in addition to the standard evaluation for renal transplant patients.

The urinary excretion of DENV persisted for a prolonged period following the resolution of clinical symptoms, normalization of biological parameters, and the disappearance of DENV viremia. The median duration of DENV urinary excretion was 183.5 days, ranging from 11 to 356 days post-transplant. Clearance of DENV from the urine coincided with the recovery of lymphocyte counts.

Notably, 2 patients, R1.1 and R1.2, experienced new episodes of DENV urinary excretion at 608 and 849 days post-transplant, respectively, which occurred 463 and 493 days after the previous detection in urine samples. These episodes occurred shortly after a decline in lymphocyte counts, with no concurrent detection of DENV viremia. The dynamics of DENV urinary detection and lymphocyte counts are illustrated in Figure 1.

DISCUSSION

This report highlights the concerning risk of non-vectorial DENV transmission through kidney allografts following kidney transplantation. In addition, it underscores the kidney's potential role as a viral reservoir in immunocompromised patients. The observed delay between the clearance of DENV in the blood and urine, which coincided with the serological response and an increase in lymphocyte counts, suggests the involvement of cellular immunity in eliminating DENV. However, our findings in patients R1.1 and R1.2 raise the possibility that urinary sterilization may not be permanent, with the potential for recurrences when lymphocyte depletion occurs anew.

The long-term consequences of this prolonged viruria on kidney function remain unknown and necessitate investigation through large-scale population-based

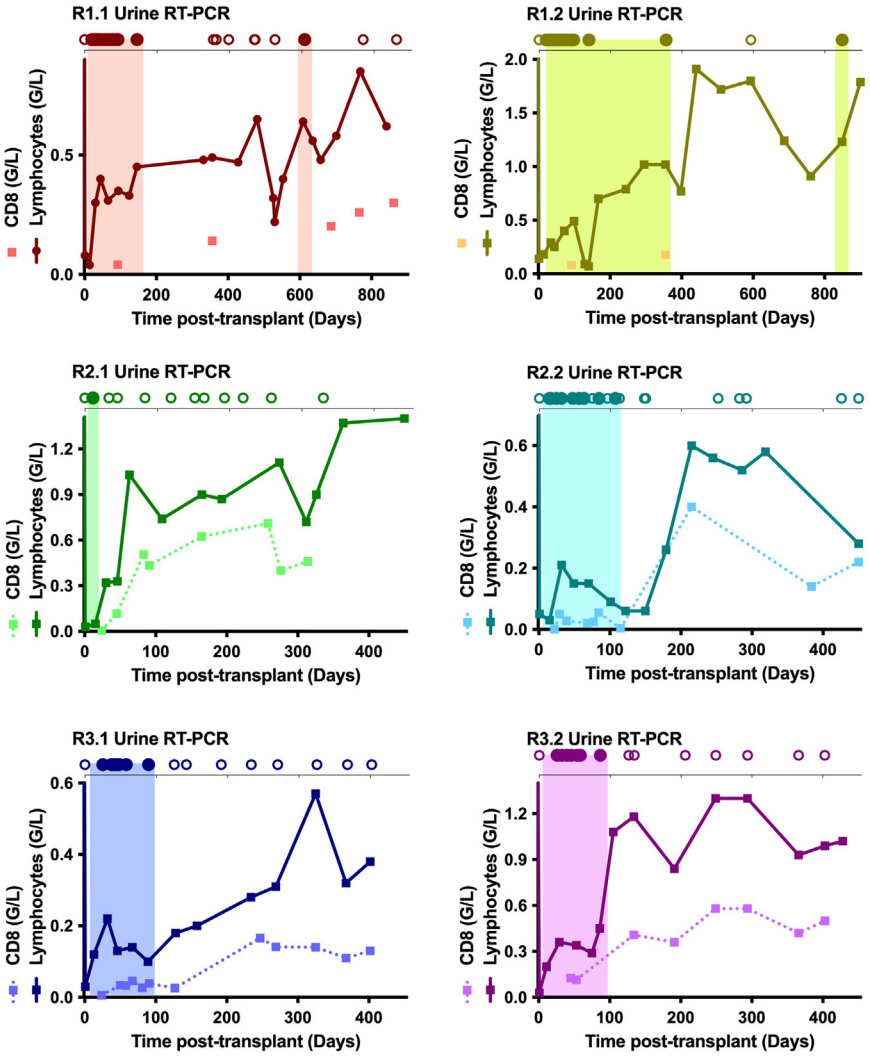

Figure 1. Evolution of urine DENV RT-PCR detection and lymphocytes blood count after transplantation for the 6 recipients. Filled circles represent positive DENV RT-PCR detection; empty circles represent negative dengue detection. Colored areas represent the total duration of DENV detection in urines after transplantation. Continuous lines represent total lymphocytes blood count and dash line total CD8 lymphocytes blood count. CKD, chronic kidney disease; DENV, dengue virus.

studies in endemic regions. Similar to observations in the general population, secondary Dengue infections appear to predispose kidney allograft recipients to more severe manifestations compared to primary infections. Therefore, systematic DENV serology at the time of kidney transplantation may aid in assessing individual risk for kidney transplant recipients in endemic areas.

The existing literature has already reported suspected cases of DENV transmission through kidney transplant allografts.[8–10] We have further substantiated this risk through genotyping analysis in both donors and recipients, along with sequential blood and urine RT-PCR assessments at admission and during follow-up. In response to this risk, our center has adapted its kidney allograft procurement protocol by implementing systematic DENV RT-PCR testing of both blood and urine samples from donors. The detection of DENV in either sample precludes organ procurement.

As Dengue infection continues to emerge as a global health issue, especially among immunocompromised patients, the kidney's potential role as a viral reservoir and the risk of transmission through kidney allografts pose ongoing and evolving challenges for the kidney transplantation community.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Evolution of blood DENV RT-PCR detection and serologic response after transplantation for the 6 recipients. Filled circles represent positive dengue RT-PCR detection; empty circles represent negative dengue detection. Continuous lines represent IgG and dash line

IgM against DENV. DENV, Dengue virus; RT-PCR, reverse transcription polymerase chain reaction.

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