Dengue Fever among Renal Transplant Recipients: A Series of 10 Cases in a Tropical Country

Silvana Daher Costa,* Geraldo Bezerra da Silva Jr., Camilla Neves Jacinto, Lorena Vasconcelos Mesquita Martiniano, Yago Sucupira Amaral, Fernando Jose Villar Nogueira Paes, Maria Luiza De Mattos Brito Oliveira Sales, Ronaldo de Matos Esmeraldo, and Elizabeth De Francesco Daher

Post-Graduation Program in Medical Sciences, Department of Internal Medicine, School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil; Division of Renal Transplantation, Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil; Post-Graduation Program in Collective Health, School of Medicine, Health Sciences Center, University of Fortaleza, Fortaleza, Ceará, Brazil

Abstract. This is a case series of 10 consecutive renal allograft recipients, followed at a tertiary hospital in northeast Brazil, with a confirmed diagnosis of dengue. Five of the patients needed hospitalization. Half of them were males and age ranged from 19 to 60 years with a median of 38.2 years. They had been transplanted for a mean of 5 days to 166 months. Four patients developed dengue hemorrhagic fever (DHF). All patients had myalgia and headache. All of them, except one, had fever. Positive dengue serology (IgM) was found in all patients. No patient died. Dengue is an important infectious disease that can affect renal transplant recipients, mainly in endemic areas. Its presentation seems to be similar to that seen in immunocompetent patients.

Dengue is one of the most important tropical diseases worldwide.¹ Almost 40% of the world's population lives now at risk of contracting dengue. Dengue is endemic in tropical and subtropical regions, such as Brazil, the Caribbean, and southeast Asian countries. Dengue occurs both as an endemic disease and as epidemic outbreaks.²

Symptomatic human infections may range from mild disease, flu-like syndrome, sometimes associated with rash (dengue fever [DF]) to a more severe form of the disease associated with plasma leakage, thrombocytopenia, hemorrhage (dengue hemorrhagic fever [DHF]), and/or shock (dengue shock syndrome [DSS]).^{1–5}

Kidney transplant patients that live in endemic zones or who travel to an endemic zone might be affected by this disease, similar to the general population. Previous studies suggest that dengue infection is mild in renal transplant recipients, with good recovery, and that the disease does not affect allograft function.⁶ Dengue can also be transmitted to the recipients from the donor, and even patients who have severe complications, such as hemorrhage, usually have good recovery.⁷ The objective of this article is to describe the clinical manifestations and renal involvement in cases of dengue in renal transplant patients.

A case series of 10 consecutive renal allograft recipients with confirmed diagnosis of dengue is described. All patients were followed at the General Hospital of Fortaleza, northeast of Brazil, and had a dengue diagnosis in the period between May 2001 and January 2014. The epidemiological and clinical data from these patients are described.

Dengue diagnosis was based on clinical and laboratory findings, including antibodies, by using a commercial immunoglobulin M (IgM) capture enzyme-linked immunosorbent assay (ELISA). This study protocol was approved by the Ethical Committee of the School of Medicine, Federal University of Ceará, Brazil.

Ten renal allograft recipients with confirmed dengue viral infection were evaluated in our kidney transplant unit in the study period. Five of them needed hospitalization.

Clinical characteristics of these patients are summarized in Table 1. Half of them were males and their age ranged from 19 to 60 years, with a median of 38.2 years. They had been transplanted for a mean of 5 days to 166 months. Two patients (Patients 1 and 5) developed dengue infection within 1 week of renal transplant and had the most severe complications. Eight patients had received a first renal allograft, one (Patient 9) had received a second renal allograft, and 1 (Patient 6) a third renal allograft; they were recipients of seven living and three deceased donors. Three patients received basiliximab (Patients 1, 5, and 8), one received daclizumab (Patient 7), and one received thymoglobulin (Patient 9) as induction therapy. One patient (Patient 6) received intravenous immunoglobulin (IVIG) 6 months before infection for graft dysfunction. Immunosuppression at the time of the dengue episode consisted of cyclosporine (Cya; $N = 5$), tacrolimus (Tac; $N = 5$), mycophenolate mofetil (MMF; $N = 5$), prednisone (Pred; $N = 8$), sirolimus (Srl; $N = 1$), mycophenolate sodium (MFY; $N = 4$), and deflazacort (Dfz; $N = 1$).

Four patients (Patients 1, 2, 5, and 6) developed DHF. Of these, Patients 1 and 5 had dengue within 1 week of transplantation and both developed disseminated intravascular coagulation (DIC), complicated with perigraft hematoma that needed surgery; Patient 5 needed a nephrectomy because of uncontrolled bleeding. The histopathological analysis showed type II-A acute cellular rejection and severe acute tubular necrosis. One patient (Patient 6) had chronic allograft nephropathy before dengue infection and lost the graft during the course of the disease.

All cases occurred between April and September, and May was the month with the highest incidence.

All patients had myalgia and headache. All of them, except one (Patient 10) had fever. Four patients (Patients 1, 4, 7, and 9) had arthralgia and two had retro-orbital pain (Patients 3 and 7) or rash (Patients 4 and 8). Hypoalbuminemia was present in three patients (Patients 1, 4, and 5). Bleeding manifestations were present only in the four DHF cases. One patient needed mechanical ventilation (Patient 1). Positive dengue serology (IgM) was found in all patients. No patient died.

Other complications were present, such as anemia (Patients 1, 5, and 6), thrombocytopenia (Patients 1, 2, 4, 5, 6, 7, and 10) with minimum platelet count ranging from 15,300/mm³ to 99,000/mm³, neutropenia ($< 1,500/\text{mm}^3$) in five cases (Patients 1, 2, 5, 6, and 7), and elevated levels of alanine aminotransferase

*Address correspondence to Silvana Daher Costa, Department of Internal Medicine, School of Medicine, Federal University of Ceará, Rua Vicente Linhares, 1198, CEP: 60135-270, Fortaleza, Ceará, Brazil. E-mail: silvanadaher1@hotmail.com

TABLE 1
Clinical characteristics of renal transplant patients with dengue fever

Variables/patients	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Age (years)	43	36	35	24	19	19	46	40	38	61
Gender	F	M	F	M	F	F	M	F	M	M
Renal disease	Alport	UN	UN	UN	UN	FN	FN	SLE	FN	SAH
Previous transplant	No	No	No	No	No	Yes	No	No	Yes	No
Donor	LNRD	LNRD	LNRD	LNRD	LNRD	DD	LNRD	LNRD	DD	DD
Tx age	5 days	79 months	47 months	42 months	4 days	11 months	48 months	48 months	21 months	166 months
Immunosuppression	Cya/Pred/MMF	Cya/Pred/MMF	Cya/Pred/MMF	Cya/Pred/Srl	Cya/Pred/MMF	Tac/Pred/Myf	Tac/MMF	Tac/Pred/MMf	Tac/Pred/MMf	Tac/Dfz/Mfy
Significant history	Basiliximab	None	None	None	Basiliximab	IVIg	Daclizumab	Basiliximab	Thymo	None
Type of dengue	DHF	DHF	DF	DF	DHF	DHF	DF	DF	DF	DF
Month of infection	May	August	September	July	May	April	May	August	July	May

Cya = cyclosporine; DD = deceased donor; DF = dengue fever; Dfz = deflazacort; DHF = dengue hemorrhagic fever; FN = familial nephropathy; IVIG* = immunoglobulin, used 6 months before infection for graft dysfunction; LNRD = living non-related donor; LRD = living related donor; MMF = mycophenolate mofetil; Myf = mycophenolate sodium; Pred = prednisone; SAH = systemic arterial hypertension; SLE = systemic lupus erythematosus; Srl = sirolimus; Tac = tacrolimus; Thymo = thymoglobulin; UN = unknown.

(ALT) and aspartate aminotransferase (AST) (Patients 1, 2, 4, 5, and 6). None of the patients had albuminuria and complement component 3 (C3) levels measured. Hematuria was seen in five patients (Patients 1, 2, 5, 6, and 8); Patients 1 and 5 had macrohematuria.

Renal function showed slight worsening during the dengue infection, but returned to basal levels after recovery in eight patients (80%). Three patients needed renal replacement therapy (Patients 1, 5, and 6), two (Patients 5 and 6) lost their grafts, and one (Patient 1) needed dialysis for 3 weeks and had full recovery of graft function. Patient 2 lost the graft 3 months after the dengue episode and this loss was unrelated to the previous dengue episode. Renal allograft biopsy was performed for Patient 1 and disclosed moderate to severe acute tubular necrosis.

Dengue is currently a human viral mosquito-borne infection of utmost importance worldwide, which should be included in the differential diagnosis of transplanted patients with fever. The time of dengue symptom onset after transplant varies. Our patients had been transplanted for a mean of 5 days to 166 months. The occurrence of DHF in the early postoperative period caused potential danger to our patients, similar to cases reported before.^{5,7} In our study, the two patients with DHF in the first week after transplantation had thrombocytopenia, platelet dysfunction, and coagulopathy resulting in profuse bleeding around the graft, leading to circulatory collapse that required hematoma drainage, and one lost the graft, demonstrating the severity of the infection in the early posttransplant period. The other one needed dialysis for 3 weeks before renal function recovery. Proper fluid replacement and early recognition of bleeding with effective control are essential for a favorable outcome in patients with DHF. Basic renal disease, previous transplant history, or type of donor does not seem to affect the incidence or morbidity of dengue infection among renal recipients. All patients reported in this article underwent transplantation during a dengue epidemic, but this information was not available to us before transplantation. Immediately postoperatively, the risk of hemorrhage from dengue is compounded by the risk of postoperative bleeding. Some patients had a dengue focus detected at their homes. Moreover, some patients were in the incubation period at the time of transplantation. When dengue occurs in the first 4 weeks of transplantation, the risk of hemorrhage is higher because of a higher risk of surgical wound bleeding.

Renal transplantation patients treated with multiple immunosuppressive agents should be less likely to develop the severe form of dengue infection.^{2,8} This could be explained by the concept of cytokine, antibody-dependent enhancement, and T-cell-mediated process with activation of the immune response. In this case series, we had six patients with DF and four with DHF, but dengue asymptomatic infection had a high prevalence, and the real incidence in this population was unknown. In accordance with literature,² immunosuppression did not seem to affect the outcome of our patients. Two patients received basiliximab as induction therapy, but there was no reported risk of developing severe forms of dengue after using this drug.

Clinical presentation and the course of the disease in immunosuppressed patients is similar to that seen in immunocompetent patients,² except for a longer period of illness.⁸ In this study, the main clinical signs and symptoms were myalgia and headache (100%), fever (90%), arthralgia (40%), bleeding manifestation

(30%), retro-orbital pain, and rash and ascites (20%). Compared with the general population, the frequency is quite similar, except for arthralgia and retro-orbital pain, which is less frequent in transplanted patients. Arthralgia may be less frequent because of corticosteroid use. Other laboratory findings commonly associated with dengue include leukopenia, anemia, thrombocytopenia, hypoalbuminemia, and increased levels of liver enzymes.⁹ Liver involvement is a common finding during dengue infection. Bleeding, when occurs, results from thrombocytopenia, platelet dysfunction, and increased fibrinolysis. In this study, thrombocytopenia was present in 70% of cases, leukopenia in 50%, elevated ALT/AST in 50%, hypoalbuminemia in 40%, and anemia in 30%.

Renal function was not permanently affected by the infection. As the increase in serum creatinine was mild and transient in some cases, it was likely caused by dehydration or factors associated with infection rather than by a direct effect of the dengue virus on the kidney.² Long-term renal function was not affected in patients who did not lose their grafts. Eight of our patients had mild increase in creatinine that returned to basal levels after recovery. Three patients needed dialysis. Two of them had DHF in the first week after transplant and the other one had chronic allograft nephropathy before dengue infection.

The morbidity and mortality rates can be reduced by optimal supportive care. In this study, no patient died, even those that had received strong immunosuppressive therapy. A previous study reported three renal transplant recipients that died because of DSS, and they had received antithymocyte immunoglobulin as acute rejection prophylaxis.³

In summary, dengue is an important infectious disease in endemic areas that can affect renal transplant recipients and its presentation seem to be similar to that seen in immunocompetent patients. There is no specific therapy or vaccine for dengue. Management is supportive, with correction of hypovolemia and coagulation abnormalities. Physicians should raise the suspicion of dengue in all transplanted patients living in or returning from endemic areas presenting with acute febrile illness.

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Authors' addresses: Silvana Daher Costa, Lorena Vasconcelos Mesquita Martiniano, Yago Sucupira Amaral, and Elizabeth De Francesco Daher, Post-Graduation Program in Medical Sciences,

Department of Internal Medicine, School of Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil, E-mails: silvanadaher1@hotmail.com, lorena_vasconcelos@hotmail.com, yagoamaral@msn.com, and ef.daher@uol.com.br. Geraldo Bezerra da Silva Jr., Master in Collective Health, School of Medicine, University of Fortaleza, Fortaleza, Brazil, E-mail: geraldobezerrajr@yahoo.com.br. Camilla Neves Jacinto, Department of Internal Medicine, Federal University of Ceará, Fortaleza, Ceará, Brazil, E-mail: millinhaneves@hotmail.com. Fernando Jose Villar Nogueira Paes, Maria Luiza De Mattos Brito Oliveira Sales, and Ronaldo de Matos Esmeraldo, Division of Renal Transplantation, Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil, E-mails: fjpaes@gmail.com, marialuizasales@yahoo.com.br, and ronaldoesmeraldo@yahoo.com.br.

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