

Retrospective Study

## Dengue in renal transplant recipients: Clinical course and impact on renal function

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## Abstract

### AIM

To present clinical characteristics from renal transplant recipients with dengue fever and its impact on graft function.

### METHODS

We retrospectively evaluated 11 renal transplant recipients

(RTR) with dengue infection confirmed by laboratory test, between January 2007 and July 2012, transplanted in the Renal Transplant Center of Walter Cantídio University Hospital from Federal University of Ceará.

## RESULTS

Positive dengue serology (IgM) was found in all patients. The mean time between transplant and dengue infection was 43 mo. Fever was presented in all patients. Nine patients presented with classical dengue and two (18%) with dengue hemorrhagic fever. All cases had satisfactory evolution with complete recovery of the symptoms. The time for symptom resolution varied from 2 to 20 d, with an average of 9 d. An increase of creatinine after the infection was observed in three (27.2%) patients with no clinically impact on the kidney graft function.

## CONCLUSION

RTR with dengue infection seems to have a clinical presentation and evolution similar to those seen in the general population, with no long-term damage to patient and to the graft.

**Key words:** Kidney; Renal; Transplant; Dengue; Clinical; Brazil

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**Core tip:** Dengue is a viral arthropod-borne disease transmitted by mosquitoes of the genus *Aedes*, mainly *Aedes aegypti*. The kidney is the most transplanted solid organ in the world with approximately 79000 transplants performed annually. Data are lacking on the clinical presentation of dengue in renal transplant recipients. We retrospectively evaluated 11 renal transplant recipients with dengue infection confirmed by laboratory test, between January 2007 to July 2012, transplanted in the Renal Transplant Center of a tertiary hospital in northeast Brazil.

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## INTRODUCTION

Dengue is an arthropod-borne disease caused by a *Flaviviridae* virus transmitted by mosquitoes of the genus *Aedes*, mainly *Aedes aegypti*. Most of dengue cases are asymptomatic, which explains the high number of under diagnosed cases<sup>[1-3]</sup>. Ceará is a hyperendemic state, in 2015; there were 55400 confirmed dengue cases and 72 deaths in Ceará State<sup>[4]</sup>. In the last years,

organ transplant programs have been expanding in Brazil, with increase of specialized centers and number of organ donations. In 2015, 5556 kidney transplants were conducted in the country, of which 264 were in Ceará<sup>[5]</sup>.

Kidney transplant patients who travel to or live in endemic areas are under higher risk of acquiring the disease. However, few dengue cases are reported in this population. Dengue viral infection in the immunosuppressed population may be more severe as compared with immunocompetent hosts, with reports of fatal cases in our environment<sup>[6]</sup>. Conversely, severe dengue infection, which is hypothesized to be the result of the immune-mediated mechanisms, may not occur in transplant recipients who have a muted immune response. Only a few case series of dengue in renal transplant recipients have been reported, with most describing a mild disease<sup>[7-10]</sup>.

The aim of our study was to determine the clinical presentation of dengue in kidney transplant patients and the impact of this disease in patients and allograft outcomes.

## MATERIALS AND METHODS

We retrospectively evaluated dengue in renal transplant patients in the Renal Transplant Center of Walter Cantídio University Hospital (HUWC) from Federal University of Ceará, in Northeast of Brazil. The ethics committee of the institution approved the study. They were diagnosed in the period from January 2007 to July 2012. The inclusion criteria were all kidney transplant patients who had dengue confirmed by laboratory test attended in our center with clinical suspicion. Laboratory diagnosis of dengue was made by IgM enzyme-linked immunosorbent assay (ELISA) using commercially available kits or by polymerase chain reaction (PCR). The HUWC Renal Transplant Center works since 1977; it has performed 1255 transplants, with a mean of 100 transplants per year in the last 5 years, and 95% of the donors are deceased.

Patients were classified according to the World Health Organization (WHO) classification from 1997<sup>[11]</sup>, which was then adopted by the Brazilian Ministry of Health<sup>[12]</sup>. Since 2014, Brazil started adopting the WHO 2009 new classification for dengue<sup>[13]</sup>.

The classic dengue fever (DF) was characterized by a febrile condition that lasts 7 d, followed by at least two unspecific signs and symptoms (headache, malaise, retro-orbital pain, exanthema, myalgia and arthralgia). Dengue hemorrhagic fever (DHF) was characterized by increased vascular permeability leading to a bleeding diathesis or disseminated intravascular coagulation, with at least one of the following signs: Hemorrhagic manifestations, hemoconcentration due to capillary leak, hypoproteinemia, and pleural effusion or ascites. Dengue shock syndrome (DSS) was all severe cases that do not follow the WHO DHF criteria, and when the classical dengue classification is unsatisfactory, presence of one of the following findings characterizes the clinical condition:

**Table 1** Characteristics of kidney transplant patients with dengue diagnosis in the period from January 2007 to July 2012 *n* (%)

Characteristics	<i>n</i> = 11
Age in years-mean (variation)	41.3 (19-61)
Female gender	7 (63.3)
Transplant time in years - mean (variation)	3.6 (1 mo-9 yr)
Deceased donor	9 (82.0)
Thymoglobulin induction	4 (36.6)
Immunosuppressive regimens	
PRED + TAC + MMF	4 (36.3)
PRED + CYA + AZA	2 (18.1)
PRED + TAC + MPS	2 (18.1)
TAC + MMF	1 (9.0)
PRED + AZA + SRL	1 (9.0)
CYA	1 (9.0)
Rejection before dengue	3 (27.2)
Clinical findings	
Fever	11 (100.0)
Myalgia	10 (91.0)
Headache	6 (54.5)
Abdominal pain	3 (27.2)
Bleedings	3 (27.2)
Nauseas and vomiting	2 (18.1)
Postural hypotension	2 (18.1)
Pleural effusions	2 (18.1)
Laboratory outcomes	
Thrombocytopenia	9 (81.8)
Severe Thrombocytopenia (< 50000/mm <sup>3</sup> )	4 (36.6)
Leucopenia	4 (36.6)
Hemoconcentration	4 (36.6)
Transaminases increase (AST;ALT)	7 (63.6)
AST value, mean (variation) UI/L	130 (17-360)
ALT value, mean (variation) UI/L	100 (14-230)
Hospitalization	9 (81.8)
Hospitalization time in d, mean(variation)	14.2 (3-45)
Classification of dengue cases	
Classical dengue	9 (81.8)
DHF	2 (18.1)
Dengue with complication	0

PRED: Prednisone; TAC: Tacrolimus; MMF: Mycophenolate mofetil; CYA: Cyclosporine; AZA: Azathioprine; MPS: Mycophenolate sodium; SRL: Sirolimus; AST: Aminotransferase alanine; ALT: Aminotransferase aspartate; DHF: Dengue hemorrhagic fever.

several changes in the nervous system; cardiorespiratory dysfunction; liver failure; thrombocytopenia equal or lower than 20000/mm<sup>3</sup>; digestive hemorrhage; pleural effusions; global leukocyte count equal or lower than 1000/mm<sup>3</sup>; suspicious dengue case evolving to death.

Software Excel 2010 was used for data tabulation and analysis. Clinical and laboratory data were obtained from the revision of patients' kidney post-transplant ambulatory follow-up forms and medical records.

## RESULTS

Among the 416 medical records of the assessed patients, from January 2007 to July 2012, we found 27 cases with clinical suspicious dengue, with only 11 confirmed through laboratory exams. Among these 11 patients, seven (60%) were female with mean age of 41.3 years old (19 to 61 years old). All patients lived

in an endemic area, in the city of Fortaleza, State of Ceará, Brazil.

All cases were confirmed through the ELISA test for IgM antibody detection. One patient also presented positive polymerase chain reaction (PCR). Two patients received the graft from living donors and other nine were from deceased donors. In three patients, there was graft rejection before dengue diagnosis. The mean time between kidney transplant and dengue infection was of 43 mo. The most used immunosuppressive regimen was the association of tacrolimus, prednisone, and mycophenolate mofetil (36.3%). The immunosuppressive drugs, especially mycophenolate mofetil, had its doses reduced and in some cases and temporarily suspended in severe leucopenia and thrombocytopenia.

The clinical and laboratory characteristics, as well as the patients' evolution, are summarized in Tables 1 to 3. All patients had fever varying from 37.8 °C to 40 °C; headache and myalgia were also present in most cases. Among 11 patients from the study, 9 showed thrombocytopenia, which was seen right in the moment of patient's admission, with absolute mean value of 135390/mm<sup>3</sup>. Only four patients (3, 9, 10 and 11) achieved levels lower than 50000/mm<sup>3</sup>, one of whom (Patient 3) needed platelet transfusion due to level below 10000 and presence of active gastrointestinal bleeding. The lowest mean count of patients' platelets was of 90818/mm<sup>3</sup>. Four patients (36.4%) presented hemoconcentration (hematocrit increase > 20%) throughout the infection. Only four subjects showed light leucopenia, with a mean of leukocytes of 5103/mm<sup>3</sup>. The minimum level of leukocytes had an average of 3898/mm<sup>3</sup>. One patient developed pancytopenia (Patient 9), with severe leukopenia (775 leukocytes) and sepsis secondary to urinary tract infection, and needed critical care support.

Seven patients had increased liver enzymes above three times the reference value of Alanine transaminase (ALT) and Aspartate transaminase (AST). The AST maximum value registered was 360 UI/L, with mean of 130 UI/L, and maximum ALT registered was 230 UI/L, with mean of 100 UI/L. Nine patients had classical dengue and two followed DHF criteria (Patients 7 and 9) through the old WHO classification. Using the most recent classification, we found 3 cases of dengue with warning signs (Patients 1, 3 and 6). Hemoconcentration, blood hypertension, persistent abdominal pain, and pleural effusion were seen in such patients. There were two cases with severe dengue (Patients 7 and 9) due to the presence of postural hypotension and shock.

All cases had satisfactory evolution with complete recovery of the symptoms. The time for symptom resolution varied from 2 to 20 d, with an average of 9 d. Only two patients needed hospitalization, with a mean of hospital stay of 9 d. Among the hospitalized patients, only one (patient 9) was admitted in intensive care unit due to urinary sepsis, not directly associated with dengue infection.

**Table 2 Clinical and kidney graft evolution of 11 kidney transplant patients with dengue *n* (%)**

Characteristics	<i>n</i> = 11
Resolution of symptoms	11 (100)
Death	0
Time for resolution of symptoms in d, mean (variation)	9 (2-20)
Creatinine before dengue, mean (variation)	1.35 mg/dL (0.8-2.2)
Increase of creatinine > 20% and < 50% of baseline	3 (27.2)
Increase of creatinine > 50% of baseline	3 (27.2)
Creatinine after dengue, mean (variation) mg/dL	1.1 (0.8-1.7)
Creatinine 1 mo after dengue, mean (variation) mg/dL	1.3 (0.8-1.8)

With regard to kidney function, the mean creatinine value of patients at admission time was 1.35 mg/dL (0.8 to 2.2 mg/dL). The mean creatinine value at infection time was of 2.5 mg/dL, and the maximum creatinine value presented was 10 mg/dL, which was seen in Patient 7, who developed acute kidney failure with the need of transitory dialytic support. After the infection, values varied from 0.85 to 1.75 mg/dL with an average value of 1.33 mg/dL. An increase of creatinine after the infectious condition was observed in three (27.2%) patients. Nevertheless, there was no clinically significant impact on the kidney graft function, which returned to the baseline creatinine in almost all patients after 1 mo of symptom resolution.

## DISCUSSION

In the present study, we found 11 dengue cases in kidney transplant patients throughout almost 6 years, in a single center located at a hyperendemic area. Based on the high number of cases reported in our State in such period<sup>[4]</sup>, we expected a higher number of cases in this specific population. However, it is very difficult to assess the real prevalence of the disease in these patients, since most of the cases present as flu-like syndrome with spontaneous resolution, with high sub-notification. The largest Brazilian casuistic of dengue in kidney transplant patients was reported by Azevedo *et al*<sup>[9]</sup> with 27 cases in 10 years achieved through inquiries sent to 182 renal transplant centers in the country. Comparing to our study, we can see a much more expressive casuistic comprised of 11 cases in only one center, with almost half of the evaluated period. The largest series of cases published until now was conducted by Nasim *et al*<sup>[8]</sup> with 102 cases diagnosed from January 2009 to December 2010, in a kidney transplant center in Karachi, Pakistan, which is a hyperendemic country for the disease. In 2015, Costa *et al* published a dengue series with 10 cases, this article was produced with data from a tertiary hospital in the same city from our own, not surprisingly, it showed similar results<sup>[10]</sup>. After literature review, we found several other series of cases, such as those from Singapore<sup>[14]</sup> (six cases) and India<sup>[7]</sup> (eight cases), among many others. Most of them described dengue as a benign disease in this population.

Dengue asymptomatic infection is commonly seen in Brazil. A serologic survey carried out in the city of Salvador (BA), Brazil, in 1998<sup>[15]</sup>, showed a 69.7% seroprevalence in a sample with 1515 people.

When these data are extended for the city population, 560000 people could have been infected with the virus, which is different from the only 360 cases that were reported in the same period<sup>[15]</sup>.

The mean time of dengue symptoms, especially thrombocytopenia, in our study was of 9 d, which is higher than the general population. This fact was also seen by Nasim *et al*<sup>[8]</sup> with mean thrombocytopenia duration of 11 d compared to 3.6 d in the general population. This longer evolution can be associated with use of immunosuppressive medications and slower viral clearance that is seen in immunocompromised patients. Another important fact of Nasim *et al*<sup>[8]</sup> study was the absence of fever in 20% of their patients. This was mainly seen in subjects using larger immunosuppressive doses, thus concealing a notable manifestation of the disease and making its diagnosis more difficult. This finding has not been seen in our area, in which 100% of our patients had fever.

In our study, thrombocytopenia was found in most of the cases, with only 33.6% in the severe scale. Most of our patients presented the classical form of the disease with only two (18%) evolving to DHF, without any deaths. Comparing with data from the general population in our state, we observed a 0.2% incidence of DHF in the year of 2013, which is much lower than that seen in our study. This can be justified by the small size of our analyzed population and by the non-inclusion of other 16 suspected cases without confirmation. Similarly, Azevedo *et al*<sup>[9]</sup> reported only 1 DHF case among the 27 dengue cases. However, in their sample, one patient died, corresponding to a 3.7% mortality, which is similar to ours. Nassim *et al*<sup>[8]</sup> also noticed an 11% incidence of DHF (12 cases among the 102 reported ones).

Several hypotheses attribute the severe forms of the disease to an immunopathological process mediated by T cells and interleukins<sup>[16]</sup>.

The immunosuppressive drugs given to transplant patients may modify both cellular and humoral immune system, which possible explain a more benign clinical evolution of dengue seeing in this population<sup>[17]</sup>.

Table 3 Characteristics of kidney transplant patients diagnosed with dengue, from January 2007 to July 2012

	Patient										
	1	2	3	4	5	6	7	8	9	10	11
Age	52	58	58	61	31	41	25	32	41	19	36
Gender	Female	Male	Male	Female	Female	Male	Male	Female	Female	Female	Female
Pre-Tx baseline diseases	CGN	CGN+HN	FSG	DN	MG	IN	FSG	SEL	HN	BWT	DN
Tx period until dengue	1 yr	10 mo	1 mo	4 mo and a half	3 yr	3 yr and 6 mo	7 yr	2 yr and a half	5 yr	7 yr and 8 mo	9 yr
Kind of donor	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Deceased	Alive	Deceased	Alive	Deceased
Induction	Thymoglobulin + methylprednisolone	Basiliximab + methylprednisolone	Thymoglobulin + methylprednisolone	Thymoglobulin + methylprednisolone	Thymoglobulin + methylprednisolone	Basiliximab + methylprednisolone	Methylprednisolone	Basiliximab + methylprednisolone	Methylprednisolone	Methylprednisolone	Methylprednisolone
IMS drugs on use (during dengue period)	T + M + P	P + C + A	T + M + P	T + M	T + M + P	P + C + A	T + M + P	T + M + P	T + M + P	P + A + S	C
Dengue symptoms	Fever, myalgia, headache	Fever, myalgia	Fever, myalgia, abdominal pain, bleedings (enterorrhagia)	Fever, myalgia, headache	Fever, headache, abdominal pain	Fever, myalgia	Fever, myalgia, headache, hypotension, postural hypotension	Fever, myalgia, headache, vomiting, abdominal pain	Fever, myalgia, hypotension, postural hypotension	Fever, myalgia, headache	Fever, myalgia, vomiting
Bleeding	No	No	Yes	No	No	No	Yes	No	Yes	No	No
Dengue diagnosis	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup> and serum PCR	IgM <sup>+</sup>	IgM <sup>+</sup>	IgM <sup>+</sup>
Hemoconcentration	Yes	No	No	No	No	Yes	Yes	No	Yes	No	No
Pleural effusions	Yes	No	No	No	No	No	No	No	Yes	No	No
Hospitalization time	3 d	None	15 d	8 d	13 d	None	1 mo and a half	4 d	20 d (ICU)	10 d	10 d
Evolution	Symptom resolution in 3 d	Symptom resolution in 20 d	Symptom resolution in 15 d	Symptom resolution in 8 d	Symptom resolution in 5 d	Symptom resolution in 6 d	Symptom resolution in 16 d	Symptom resolution in 2 d	Symptom resolution in 5 d	Symptom resolution in 10 d	Symptom resolution in 8 d
Baseline creatinine before dengue	1	1.1	2	1.1	2.2	0.85	1.4	1.45	1.6	1.25	1
Maximum creatinine throughout dengue	2	1.2	2	1.1	2.2	1	10	1.8	3.3	2.1	1.4
Creatinine immediately after dengue	1	1.175	1.5	1.1	1.75	0.85	1.6	1.55	1.5	1.5	1.2
Creatinine 1 mo after dengue	0.9	1.2	1.7	0.8	1.7	0.8	1.8	1.5	1.8	1.6	1

Tx: Transplant; IMS: Immunosuppressive; PCR: Polymerase chain reaction; ICU: Intensive care unit; CGN: Chronic glomerulonephritis; HN: Hypertensive nephropathy; DN: Diabetic nephropathy; FSG: Focal segmental glomerulo-sclerosis; EL: Systemic erythematous Lupus; MG: Mesangiocapillary glomerulonephritis; IN: IgA nephropathy; BWT: Bilateral Wilms Tumor; T: Tacrolimus; M: Mycophenolate; P: Prednisone; C: Cyclosporine; A: Azathioprine; S: Sirolimus.



In agreement with other studies, even though a higher percentage of severe forms of the disease have been found, we observed in our cases that dengue tends to follow the usual course of the disease. Thus, we must pay attention to thrombocytopenia, even if no fever is seen in this group of patients, since it could be dengue virus infection with sub-clinical presentation.

In our study, we could not find any information about previous dengue infection in these subjects, neither through medical record nor laboratory exams, like the detection of IgG antibodies. It is also important to notice that in some patients who live in endemic areas, there is a persistence of IgM, which makes it even harder to diagnose acute infection<sup>[9]</sup>.

Nasim *et al*<sup>[8]</sup> demonstrated that 25% of the severe cases seen were in primary infections, which can be associated with the immunosuppression given to these patients that predisposes more severe clinical conditions. Azevedo *et al*<sup>[9]</sup> also found a higher mortality (3.7%) than that of the general population, associated with clinical conditions of secondary bacteremia with sepsis.

Azevedo *et al*<sup>[9]</sup> also showed a transitory dysfunction of the kidney graft in the course of dengue. After using the level of serum creatinine as an assessment of the kidney function, we also found in our sample an increase of the mean value of creatinine level from 1.35 to 2.5 mg/dL in the infectious period. Although one of our patients reached creatinine levels of 10 mg/dL, with the need of dialytic support, the baseline creatinine levels were completely re-defined, thus no damage was seen in grafts at medium or long term in both studies. Recovery of all our patients was satisfactory with a mean value of 1.1 mg/dL in the post-infectious period. This standard behavior might not be due to the direct lesion of the virus in the kidney parenchyma, because there has not a study yet that proves this fact; however, this might happen due to factors associated with dehydration/hypovolemia caused by capillary leakage, vomiting, or bleedings<sup>[18]</sup>.

Prasad *et al*<sup>[7]</sup> also pointed out the transitory dysfunction of the kidney graft with complete recovery after infection in kidney transplant patients that did not evolve to death. However, Nasim *et al*<sup>[8]</sup> found a 66.7% rate of kidney graft dysfunction, which was higher in patients who already had some degree of impairment. Both the percentage of increase in the serum creatinine level and the duration of return rate to baseline of kidney function were higher in subjects that developed the severe forms of dengue. In our study, we found the same behavior with regard to the temporary dysfunction of the kidney graft in the infectious period.

The present study had several limitations and potential bias. This was a retrospective series of cases with data collected through a review of medical records, without follow-up of the patients by the investigator. In addition, many patients with suspicion of the disease were not included in the study due to lack of laboratory confirmation with high rate of sub-diagnosis.

The renal transplant recipients with dengue infection

have a clinical presentation and evolution similar to those seen in the general population. Due to the lack of serological surveys in this population and non-performance of routine serological screenings in asymptomatic patients, we do not know the real prevalence of the disease in these patients. Thus, assessing the impact on disease morbidity and mortality on these patients, based on our series of cases, was not possible.

Nonetheless, as seen here and in other studies, development of most of the cases seemed benign without evidence of higher mortality. Likewise, renal function is generally well preserved, with transitory graft dysfunction seen in most of the patients, without negative impact lifelong. It is very clear that dengue hypothesis should always be in the differential diagnosis of fever and thrombocytopenia or leucopenia in kidney transplant patients who lived or were from endemic areas.

Hence, new studies with better design and a larger amount of patients are needed to find the dengue impact on kidney transplant patients.

## COMMENTS

### Background

Dengue is an arthropod-borne disease caused by a *Flaviviridae* virus transmitted by mosquitoes of the genus *Aedes*, mainly *Aedes aegypti*. Most of dengue cases are asymptomatic. However the immunosuppressive drugs given to renal transplant patients may modify both cellular and humoral immune system, thus, modifying the disease characteristics and prognosis.

### Research frontiers

Dengue fever is endemic in most tropical areas, the kidney is the most transplanted solid organ in the world. Data on renal transplant recipients with dengue fever is limited. This case series is important to update the clinical experience.

### Innovations and breakthroughs

This is a well-documented case series of Brazilian renal transplant recipients with dengue fever and serves as an update of previous published cases.

### Applications

This study concluded that renal transplant recipients with dengue infection have a clinical presentation and evolution similar to those seen in the general population and should be managed as regular patients.

### Terminology

RTR: Renal transplant recipients; DF: Classic dengue fever; ELISA: Enzyme-linked immunosorbent assay; PCR: Polymerase chain reaction; DHF: Dengue hemorrhagic fever; DSS: Dengue shock syndrome.

### Peer-review

A very informative case series of post kidney transplant recipients who developed dengue fever. Basically they were managed as regular patients and had similar outcomes.

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