

# Severe dengue in the early postoperative period after kidney transplantation: two case reports from Hospital Geral de Fortaleza

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## ABSTRACT

Dengue is an arbovirolosis that ranges from an asymptomatic presentation to a more severe disease, which is characterized by a vascular leakage syndrome where abdominal pain is a major symptom. Transplant recipients are immunosuppressed and are less likely to develop a severe form of the disease because of a reduction in immune-mediated responses that trigger plasma extravasation events. Herein, we report two cases of severe dengue in the early postoperative period of two kidney transplant recipients. Considering the severity of the cases, we emphasize the importance of dengue screening immediately before transplantation in areas endemic for the disease.

**Keywords:** Dengue hemorrhagic fever. Kidney transplant. Postoperative.

## INTRODUCTION

Dengue is an arbovirus infection caused by a member of the *Flaviviridae* family and has four known serotypes: dengue virus type 1 (DEN-1), dengue virus type 2 (DEN-2), dengue virus type 3 (DEN-3) and dengue virus type 4 (DEN-4)<sup>(1)</sup> (2). The disease involves alternate cycles in humans and *Aedes* mosquitoes, especially *Aedes aegypti* and *Aedes albopictus*<sup>(2)</sup>, and is classified as dengue without warning signals, dengue with warning signals, and severe dengue. The latter can be characterized by a severe vascular leakage syndrome, severe bleeding, or severe organ impairment<sup>(3)</sup>. Among these symptoms, abdominal pain is the most common predictor of a more severe clinical condition; however, pain intensity is not related to disease severity<sup>(4)</sup>. Mucosal and gastrointestinal bleeding may also occur, typically with more intensity in the most serious cases. In such cases, evidence suggests that vascular damage occurs both by endothelial cell dysfunction and by a break in the endothelial barrier. However, these events are secondary both to the viral antigens and to the immuneresponse of the host<sup>(5)</sup> (6).

Importantly, the incidence of dengue appears to be increasing in Brazil. In the first quarter of 2015, more than 460,000 cases of dengue have been recorded. During the same period, 10,407 individuals were affected by dengue in the State of Ceará, which higher than in 2014, when 4,047 dengue cases were reported during all the year<sup>(7)</sup>. Although there is a lower chance of severe dengue in immunocompromised individuals, such as those undergoing a transplant, it may manifest as a very serious clinical condition in these individuals compared to the majority of immunocompetent patients<sup>(6)</sup>.

Unfortunately, little information about this topic is available in the literature. Therefore, we report herein two cases of severe dengue in the early postoperative period of two kidney transplant recipients.

## CASE REPORT

### Case 1

A 15 year-old boy with chronic kidney disease because of nephrocalcinosis underwent a kidney transplant in March 2015. The patient was previously healthy and in preoperative tests, his hemoglobin level was 8.6g/dL, packed cell volume was 25%, platelet count was 113,800/mm<sup>3</sup>, urea level was 114mg/dL, serum creatinine level was 10.2mg/dL, potassium level was 5.9mEq/L, and activated partial thromboplastin time was 40.1s.

The kidney transplant was uneventful and the renal graft became functional immediately. The patient was afebrile until the third postoperative day when he developed a fever

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that peaked at 39.1°C, increased serum creatinine levels, and decreased diuresis. Furthermore, the hemoglobin levels, and leukocyte and platelet counts were 6.0g/dL, 1,148/mm<sup>3</sup>, and 72,570/mm<sup>3</sup>, respectively. We started antibiotic therapy with Tazocin (Pfizer, US) and indicated a graft biopsy to check for rejection.

The patient remained afebrile, but started to present with abdominal pain and ascites. An abdominal ultrasound scan showed free fluid in the abdominal cavity and absence of hydronephrosis in the allograft. The biopsy revealed Banff grade 3 moderate acute tubular necrosis, and was negative for the complement degradation product dismissing the possibility of graft rejection. Dengue virus type 2 was isolated from a blood sample collected on the fourth postoperative day and high titers of immunoglobulin M (IgM) were detected from samples collected on the sixth postoperative day.

Abdominal pain persisted and abdominal surgery was performed on the 26<sup>th</sup> postoperative day, revealing active bleeding at the graft site. Three hours after the surgery, the hemoglobin levels decreased further and the patient displayed hemodynamic instability culminating in heart stoppage, which was reversed in 40 min. Afterward, 700mL of hematic secretion was drained from the left hemithorax; norepinephrine and desmopressin were administered at the maximum doses; and six packed red blood cell, two fresh frozen plasma, six cryoprecipitate, and one platelet concentrate transfusions were performed. However, there was little improvement in the hemodynamic status and during hemodialysis, the patient experienced further hemodynamic instability and suffered from a cardiac arrest, which was not reversed with resuscitation maneuvers.

### Case 2

A 21 year-old man with chronic kidney disease of unknown etiology underwent a kidney transplant in March 2015. He was previously healthy and in preoperative tests, his hemoglobin level was 12.7g/dL, packed cell volume was 41%, platelet count was 76,100/mm<sup>3</sup>, leukocyte count was 14,400/mm<sup>3</sup>, urea level was 57mg/dL, serum creatinine level was 5.5mg/dL, and potassium level was 4.8mEq/L.

The kidney transplant was uneventful. Hemodialysis was performed postoperatively, and meropenem and teicoplanin treatment was initiated because the donor was receiving antimicrobial therapy. The patient was afebrile, able to urinate, and reported pain at the surgical wound site until the third postoperative day when he presented with fever that peaked at 38.5°C, decreased diuresis, and abdominal pain associated with vomiting and diarrhea. He developed pancytopenia (4.9g/dL hemoglobin, 1,209/mm<sup>3</sup> leukocytes, 17,410/mm<sup>3</sup> platelets), and anuria after his renal function worsened. Abdominal computed tomography revealed fluid in the perirenal site and preserved renal parenchyma. Three surgeries were required for hemostasis.

The patient required several transfusions of packed red blood cells, platelet concentrates, and fresh frozen plasma. Dengue virus was isolated from a blood sample collected on the sixth postoperative day and high IgM titers were detected samples collected on the 11<sup>th</sup> postoperative day. Meropenem and teicoplanin

were administered for 13 days. Thenceforth, the hematimetric findings showed improvement, the renal graft function increased, and abdominal symptoms ameliorated, resulting in the patient being discharged on the 27<sup>th</sup> postoperative day.

## DISCUSSION

In contrast to milder forms of the disease, in severe dengue, the levels of many cellular mediators of the innate and adaptive immune systems are elevated, leading to changes in the endothelial barrier, which is composed of endothelial cells, smooth muscle cells, extracellular matrix, basement membrane, and other components. There is some evidence that changes in the complement system that culminate in the formation of immune complexes favor such events<sup>(5)</sup>. While changes in endothelial cells are studied most extensively, immune mediators of the adaptive response are produced chiefly by T cells.

Patients undergoing transplantations are immunosuppressed and have a reduced T cell-mediated immune response, which is responsible for releasing cytokines that trigger structural changes in the blood vessels under normal conditions. These events lead to plasma extravasation and favor hemorrhagic manifestations<sup>(9)(10)</sup>.

Even in countries where dengue is endemic, there is a paucity of reports regarding transplant recipients<sup>(10)</sup>; one case was reported in 2005 in Asia<sup>(8)</sup> and another the following year in Brazil<sup>(9)</sup>. The majority of the reported cases of dengue after transplantation have culminated in allograft survival<sup>(10)</sup>. However, the initial diagnosis in Case 1 and in Case 2 was hyperacute graft rejection. Nevertheless, at the time of the transplants and early manifestation of the disease, the number of dengue cases in Brazil was close to 60,000<sup>(7)</sup>, more than double the number in the previous year. In such a context, the possibility of dengue fever takes on an added importance.

Batista et al.<sup>(11)</sup>, in a retrospective analysis of 1,754 transplants, found only two cases of dengue, including one with hemorrhagic features. More recently, Nasim et al.<sup>(6)</sup> studied 258 renal transplant patients with positive serology for dengue, wherein only 4% presented with severe disease. Other authors<sup>(12)</sup> reported a case with a clinical profile similar to ours, but with a less severe presentation of dengue.

In our cases, there was no history of dengue in the donors. In contrast, Li-Sher et al.<sup>(8)</sup> reported a case where the donor had a significant dengue infection six months before the transplant. However, after reviewing the social context of the recipients, we discovered dengue fever in family members.

Hemorrhagic dengue in the initial days following a transplant is a severe condition without a specific therapy for treating it. Treatment is based on intensive clinical care<sup>(8)</sup>. In our cases, the patients demonstrated exacerbated signs of bleeding even at the graft site. Surgery was indicated only after all conservative measures for achieving hemostasis and hematoma drainage were exhausted and especially because of intractable pain.

These two cases show us the great importance of including severe dengue in the differential diagnosis of hyperacute

renal graft rejection or even in the context of possible viral infection because Brazil is endemic for this arbovirolosis. Moreover, a complete anamnesis seeking any history of dengue in the patient or his/her social circle is required to reinforce diagnostic suspicions. Therefore, in endemic periods, rapid screening tests should be performed in patients immediately before transplantation. Furthermore, research on drugs that hinder changes in the endothelial barrier must progress from experimental animal studies to clinical trials so that better treatment is available.

## REFERENCES

- Holmes EC, Twiddy SS. The origin, emergence and evolutionary genetics of dengue virus. *Infect Genet Evol* 2003; 3:19-28.
- Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 1998; 11:480-496.
- World Health Organization (WHO). Dengue: guidelines for diagnosis, treatment, prevention and control - New edition. Geneva: WHO; 2009. p. 1-147.
- Wong JGX, Gan VC, Ng E-L, Leo Y-S, Chan S-P, Choo R, et al. Self-reported pain intensity with the Numeric Reporting Scale in Adult Dengue. *PLOS One* 2014; 9:1-6.
- Srikiatkachorn A, Kelley JF. Endothelial cells in dengue hemorrhagic fever. *Antivir Res* 2014; 109:160-170.
- Nasim A, Anis S, Baqi S, Akhtar SF, Baig-Ansari N. Clinical presentation and outcome of dengue viral infection in live-related renal transplant recipients in Karachi, Pakistan. *Transpl Infect Dis* 2013; 15:516-525.
- Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico. Volume 46. número 11. Brasília: Ministério da Saúde; 2015; p. 1-7.
- Tan FL, Loh DL, Prabhakaran K, Tambyah PA, Yap HK. Dengue haemorrhagic fever after living donor renal transplantation. *Nephrol Dial Transplant* 2005; 20:447-448.
- Garcia JH, Rocha TD, Viana CF, Gonçalves BP, Girão ES, Vasconcelos JB, et al. Dengue shock syndrome in a liver transplant recipient. *Transplantation* 2006; 82:850-851.
- Weerakkody RM, Palangasinghe DR, Dalpatadu KP, Rankothkumbura JP, Cassim MR, Karunanayake P. Dengue fever in a liver-transplanted patient: a case report. *J Med Case Rep* 2014; 8:378.
- Batista MV, Pierrotti LC, Abdala E, Clemente WT, Girão ES, Rosa DR, et al. Endemic and opportunistic infections in Brazilian solid organ transplant recipients. *Trop Med Int Health* 2011; 16:1134-1142.
- Tangnararatchakit K, Tirapanich W, Tapaneya-Olarn W, Sumethkul V, Sirachainan N, Watcharananan S, et al. Severe non febrile dengue infection in an adolescent after postoperative kidney transplantation: A case report. *Transplant Proc* 2012; 44:303-306.