

## A Case of Immune Complex Mediated Acute Kidney Injury Occurring in the First Few Days of Dengue Fever

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### Abstract

Dengue is an important viral illness in endemic regions, with recent yearly outbreaks in Northern India. Acute kidney injury in dengue is seen usually in presence of shock and hemolysis. Direct immune mediated acute kidney injury is uncommon in dengue and usually presents late. We describe a young male with anuria and azotemia within first few days of illness, requiring hemodialysis. His low complement levels and response to corticosteroids suggest the possibility of immune complex mediated acute kidney injury, which may relate to severity of renal injury in dengue. It is important to suspect and recognize it early.

### Introduction

Dengue fever, caused by dengue virus (an RNA flavivirus) is currently the most important human viral mosquito-borne infection of public health significance. Up to 50-100 million infections are now estimated to occur annually in over 100 endemic countries, putting almost half of the world's population at risk.

It has been known to be endemic in India. Northern region of the country experienced nine major outbreaks between 1967 and 2008. Subsequently there have been outbreaks every year. In 2011, an estimated 16821 cases were detected all over India, with 112 deaths.

Renal injury comprising proteinuria, azotemia, glomerulonephritis, acute kidney injury and haemolytic uremic syndrome has been reported in dengue patients. To date, all dengue hemorrhagic fever-induced acute kidney injury described cases have occurred in association with shock, haemolysis or rhabdomyolysis.

However, reports of acute kidney injury manifesting without these predisposing factors have been rare [1]. We describe here a case of Dengue hemorrhagic fever presenting with acute kidney injury requiring hemodialysis, where the renal injury manifested within the first few days of onset of illness without hypotension, intravascular hemolysis or other predisposing factors.

### Case Report

Previously healthy 30 years male was referred from a local hospital with history of high grade fever with chills and body aches for 6 days and hematuria followed by anuria for one day. He was not taking any nephrotoxic drug and did not have hypotension at any time. Laboratory tests at the referring hospital (3<sup>rd</sup> day of illness) revealed platelets count of 36000/mm<sup>3</sup> and serum creatinine was 4.3 mg/dl. He was conscious and vitals were stable. Systemic examination was unremarkable except for icterus and over extremities. Laboratory tests disclosed hemoglobin 10.4 g/dl, WBC count 3100/cu mm, platelets count 8,000/cu mm, serum creatinine 6.11 mg/dl, blood urea 126 mg/dl, serum potassium 4.8 mEq/l, aspartate aminotransferase 7433 UI/l, alanine aminotransferase 5558 UI/l, total bilirubin 3.2 mg/dl, albumin 3.1 g/dl. Urinalysis showed microscopic hematuria, proteinuria and was negative for myoglobin. An abdominal ultrasound showed normal sized kidneys. Echocardiogram showed mild pericardial effusion. Chest X-ray was normal. Blood and urinary cultures were negative. Serology for HIV, hepatitis B and C was negative. Serology (IgM antibodies, ELISA) against dengue virus was positive. DIC profile was negative and C3 level was 54 mg/dl (NR: 90-180).

He was managed on the lines of dengue hemorrhagic fever in view of the ongoing endemic of dengue. Patient was transfused 2 units of platelet concentrates. In view of anuria, azotemia and rapid onset of the disease, a possibility of post-infectious acute glomerulonephritis with possible crescents was kept. He was taken up for hemodialysis and was maintained on daily hemodialysis and empirically put on steroids, starting with 3 days pulse of methylprednisolone after sending the sample for C3 level. Kidney biopsy could not be performed because of thrombocytopenia.

On 12<sup>th</sup> day of admission, he had hypotension and sudden fall in saturation for which he required mechanical ventilation. He had fall in hemoglobin and hematocrit. Chest X-ray showed diffuse ground glass opacities and possibility of acute lung injury due to diffuse alveolar hemorrhage was kept. ANCA and Anti GBM antibody (IFA) titer were sent which came out to be negative. Repeat DIC profile was also negative.

Patient was managed conservatively with blood transfusion, mechanical ventilation and supportive therapy. Patient remained oliguric for around 3 weeks, on hemodialysis (10 sessions). He gradually recovered with improving urine output and renal functions, and was weaned off from ventilator over next 2 weeks. At the time of discharge, his platelets count was normal and serum creatinine was 1.5 mg/dl. On follow up 3 weeks later, he was asymptomatic and serum creatinine was 0.7 mg/dl.

### Discussion

Proteinuria and abnormal urine sediment are the most common renal manifestations observed in patients with dengue fever. Usually acute kidney injury occurs when there is extensive capillary leak, shock, and disseminated intravascular coagulation, leading to ischemia and

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multiple organ dysfunctions. In some patients, acute tubular necrosis associated with interstitial edema and mononuclear cell infiltration may lead to acute kidney injury.

Various mechanisms are implicated in the pathogenesis of acute kidney injury associated with viral infections. These include the direct cytopathic effects of viral proteins on glomerular and tubular cells, in-situ immune mediated mechanisms involving viral antigens bound to glomerular structures, injury due to circulating immune complexes composed of viral antigens and host anti-viral antibodies and injury due to various inflammatory mediators released in response to glomerular or tubular cytopathic effects [2].

It is not clear whether the virus causes direct damage by invasion of the kidneys. When Dengue virus 2 was injected intraperitoneally in adult mice, proliferative glomerular lesions without urinary abnormalities developed by the second week and immune complex deposition was demonstrable in the glomeruli by the third week of infection [3]. Recent studies using immunohistochemistry techniques have established the presence of viral antigens in kidney tubules of patients with serologically or virologically confirmed dengue infection. Histopathology has demonstrated the presence of IgG, IgM, and C3 deposition in the glomeruli and focal thickening of the glomerular basement membrane, with hypertrophy of mesangial cells at the sites of immune complex deposition in patients with renal insufficiency and dengue fever [4].

It has been hypothesized that Dengue virus infection elicits an immune response to viral antigens and results in the formation of circulating immune complexes, which subsequently get deposited in the glomeruli. Immune complex mediated glomerulonephritis associated with dengue haemorrhagic fever has been reported earlier, immune complex deposits in these cases consisted predominantly of IgG, IgM and C3 and deposited in the mesangium in a coarse granular pattern [5].

The patient developed acute lung injury, possibly diffuse alveolar hemorrhage (sudden fall in hemoglobin and hematocrit, diffuse

ground glass opacities on chest X-ray) in the 3<sup>rd</sup> week of illness. A negative ANCA and negative anti glomerular basement membrane antibody titre rule out the possibility of an ANCA associated small vessel vasculitis, Wegner's glomerulonephritis and Goodpasture's syndrome as the cause of diffuse alveolar hemorrhage. The low serum complement levels suggest the acute lung injury too might be due to immune complex deposits in the alveolar walls.

The low complement levels and response of renal dysfunction on initiation of corticosteroids in our case point towards a possible immune complex mediated acute glomerulonephritis as the cause of renal injury in our case. Development of acute lung injury in the form of diffuse alveolar hemorrhage and its recovery within the same framework of management further suggest a common immune mediated etiology. A renal biopsy however would have added to our wisdom but it could not be done because of severe thrombocytopenia.

In conclusion we have presented a case of acute kidney injury requiring hemodialysis related to dengue fever without any evidence of hypovolemia, hypotension, sepsis, or rhabdomyolysis. We attribute the kidney failure to immune complex mediated acute kidney injury. This phenomenon may be under-recognized and contribute to the severity of renal injury in the setting of dengue infection.

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