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CASE REPORT

Acute Tubular Necrosis Associated with Non-Hemorrhagic Dengue Fever: A Case Report

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Dengue fever (DF) is an arthropod-borne viral infection affecting humans. Dengue viruses are transmitted through the bites of the mosquito *Aedes aegypti*. Acute renal failure (ARF) is reported in patients who are affected mainly with Dengue hemorrhagic fever (DHF), which is a severe presentation of the disease. We report the case of a 24-year-old Omani female with no past history of particular medical problems. She was referred to our hospital for the further management of acute renal failure. She had clinical features of DF without DHF. The kidney biopsy showed features of acute tubular necrosis (ATN). She had a complete recovery after 25 days and required three sessions of hemodialysis. We conclude that DF even without DHF may lead to ATN and ARF. Clinicians should be aware of this etiology. Treatment is supportive and may require dialysis. The prognosis could be favorable.

Keywords Dengue fever, acute renal failure, acute tubular necrosis, renal biopsy, hemodialysis

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INTRODUCTION

Dengue fever (DF) is caused by four different serotypes of Dengue viruses. It is transmitted to humans through the bite of the mosquito *Aedes aegypti*.^[1,2] The disease is widely distributed through Africa, Asia, Eastern Australia, and Central and South America,^[1,3] and DF outbreak has been recently reported recently in Saudi Arabia.^[4] The disease occurrence is increasing, probably due to travel and migration.^[1,2,5] DF is usually a self-limited illness with clinical manifestations evoking a common viral illness.^[2] A few patients will likely develop Dengue hemorrhagic fever (DHF), which is a serious and potentially life-threatening disease.^[6–9]

Acute renal failure (ARF) may occur in some patients as well.^[4,10] The true incidence of ARF is not known, as the majority of patients will not seek medical attention or will not have their renal functions investigated. Renal biopsies in these cases are very scarce.

We report the first case in Oman with DF and documented acute tubular necrosis (ATN). She had an excellent recovery.

CASE REPORT

Ms. A.A., a 24-year-old Omani female from the Southern region, was referred to the Department of Nephrology of

the Royal Hospital for further management and investigation of an acute renal failure.

She did not have a history of a particular medical condition. The patient was well until 10 days prior to her admission, when she developed fever with sore throat. She has been to a private general practitioner and diagnosed to have tonsillitis. She was prescribed oral antibiotics and analgesics. The next day she complained of suprapubic pain, dysuria and dark urines. There was a rash over the lips and the periorbital area. She visited the local hospital, and admission was advised. Investigations at that hospital showed deranged renal functions with a serum creatinine of 309 $\mu\text{mol/L}$ (N: 40–90 $\mu\text{mol/L}$), and a serum urea of 15.4 mmol/L (N: 2–6 mmol/L). Liver function tests were also unusual, with total bilirubin of 197 $\mu\text{mol/L}$ (N: 3–17 $\mu\text{mol/L}$) and alanine transaminase (ALT) of 2012 iu/L (N: 10–60 iu/L). The serum albumin was normal at 39.5 g/L (N: 35–50 g/L). She was referred five days later to our center for further management and investigations. There was no history of cough, diarrhea, traveling abroad or contact with sick patients. She worked as a schoolteacher. Upon examination, the patient was conscious and well oriented. She had a moderate built. She was afebrile, her blood pressure was 122/65 mmHg, and her pulse rate was regular at 77 beats/minute. Chest and cardiovascular examinations were unremarkable. The abdominal examination revealed mild tenderness over both flanks and the supra pubic area. Relevant investigations showed a normochromic and normocytic anemia with hemoglobin of 9.7 g/dL (N: 11–16 g/dL). The platelet count was normal at $257 \times 10^9/\text{L}$, and the white blood cells were $9.9 \times 10^9/\text{L}$ (N: $3.6\text{--}11.1 \times 10^9/\text{L}$). Renal function tests were markedly irregular, with a serum creatinine of 1248 $\mu\text{mol/L}$ (N: 40–90 $\mu\text{mol/L}$) and a blood urea of 31.2 mmol/L (N: 2–6 mmol/L). She was hyponatremic at 127 mmol/L . Urine analysis and urine microscopy revealed the presence of epithelial cells, leukocyturia, and hematuria. Proteinuria was +2 on dipstick. Liver function test results were still atypical, though improved, with total bilirubin of 26 $\mu\text{mol/L}$ and ALT 114 iu/L with now mildly low serum albumin at 29 g/L . Coagulation parameters showed a mildly prolonged prothrombin time and activated partial thrombin time. The ESR was 28 mm/h (N: 1–25 mm/h) and the C-reactive protein was mildly elevated at 33.6 units (N: < 5 units). Serology for hepatitis A, hepatitis B, hepatitis C, CMV, and HIV was negative. Hemodialysis was initiated and the supportive treatment was continued. A kidney biopsy was performed. It had shown features suggestive of acute tubular necrosis. She received three sessions of dialysis, after which renal function improved. The coagulation and liver function parameters became normal. Serology using enzyme-linked immuno-sorbent assays (PanBio Dengue Duo ELISA, PanBio Pty Ltd., Brisbane, Australia)

was positive for IgM. She was referred back to her local hospital on the 25th day of her symptoms. Her serum creatinine on discharge was 80 $\mu\text{mol/L}$.

DISCUSSION

Dengue affects approximately 100 million individual yearly.^[1,2] The incidence of the disease is increasing, the geographic distribution is extending, and the number of people at risk is estimated to be around 2.5 billion.^[1,11] These elements make Dengue fever the most important arthropod-born virus at the global level.

Dengue viruses comprise four serotypes and belong to the Flaviviridae family. The vector of the disease is a mosquito of the genus *Aedes* and mainly of the *Aegypti* species. *Aedes albopictus* may also be a vector but with much less efficiency than *Aedes aegypti*. *Aedes aegypti* is widely distributed within the latitude ranging from 45° north to 35°.^[1,11]

The pattern of transmission is usually either epidemic or hyperendemic.^[12,13] Epidemic transmission occurs when a single serotype of the virus is introduced into a region with favorable circumstances for the development of the disease, resulting in a large epidemic.^[1,12] The other pattern of transmission is hyperendemic. This type of transmission occurs in endemic regions with a continuous flow of multiple serotypes of the virus. It usually results in multiple small epidemics in small areas.^[1,13] As far as is known, there have been no documented systematic larval surveys for *Aedes aegypti* and *Aedes albopictus* in urban areas of Oman. However, there are anecdotal reports of wild populations of *Aedes aegypti* in some areas in Oman.^[14] It is noteworthy that another case of DF with renal failure was diagnosed in a patient who spent a few days in the same area. The two cases occurred within two weeks' time. It is possible that the virus was introduced recently to the region, with subsequent development of the disease in few individuals. Nevertheless, the disease was not diagnosed in other patients and the serotype of the virus was not determined. This does not exclude a small epidemic with a low number of affected individuals with a mild form of the disease.

The clinical presentations of the infection are variable and ranges from an asymptomatic infection to a potentially lethal disease.^[6,10,15] Asymptomatic infections occur mostly in children. Symptomatic infections according to the World Health Organization classification fall into three categories: undifferentiated fever, classic Dengue fever, and Dengue hemorrhagic fever.^[16] It is noteworthy that patients with classical Dengue fever may also present some bleeding tendency. Dengue hemorrhagic fever is the severe form of the disease and is characterized by

increased vascular permeability leading to plasma leakage syndrome, severe thrombocytopenia of less than 100,000/mm³, fever, and bleeding tendency. This form may be associated with shock.^[6,15]

Other complicated forms include hepatic failure, neurological manifestations, renal failure, and Reye syndrome.^[6,17]

The patient under discussion presented with classic features of Dengue fever without those of the Dengue hemorrhagic fever. She did not have pleural effusion or acnitis. She did not present any sign of hypotension or shock. She did a full recovery with supportive treatment.

Diagnosis of DF is confirmed by serology and/or viral detection.^[6,15,18] In the case under discussion, the diagnosis was confirmed by serology, which demonstrated the presence of IgM antibodies.

Acute renal failure has been reported in association with Dengue virus infections. Several types of acute renal injury have been reported. These included acute tubular necrosis, which may be associated with interstitial edema and mononuclear infiltration; acute glomerulonephritis; thrombotic microangiopathy; and myoglobinuric renal failure within the context of multiorgan failure.^[4,10,19–22] It is noteworthy that DF may have a benign form in renal transplant recipients.^[23,24] Histopathological diagnosis of the acute renal failure is scarce, and it seems that most of the ATN diagnosis is formulated on clinical grounds. The patient under discussion had a confirmed acute tubular necrosis within the context of DF without DHF. This was the first case in Oman of a confirmed ATN associated with DF.

The case under discussion raises the point of the necessity of renal biopsies within the context of DF. The procedure is not without risks in view of the thrombocytopenia and the bleeding tendency. Nevertheless, it presents also the benefit of confirming the type of the renal injury and the exclusion of other forms of renal injuries such as TMA. It may be indicated in patients in whom the renal functions remain deteriorated in spite of proper fluid management. This case also emphasizes the need of the nephrologists to be aware of this association and to evoke DF as a possible etiology of an unexplained ARF. Similarly, the internist and the infectious disease specialists should aware of the possibility of ARF in patients with DF and assess the renal functions in these patients. It is very probable that ARF within DF is largely under-diagnosed. The detection of early renal function impairment will help to better manage the patients in terms of fluid administration and avoidance of nephrotoxic drugs, as well as to initiate dialysis in proper time.

In conclusion, ATN is associated with DF even without DHF. The clinician should be aware of this association so that early supportive measures can be engaged at the proper time. A kidney biopsy may be indicated in few

cases. This case is also challenging for public health and vector surveillance in Oman.

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