INTRODUCTION

Dengue fever is one of the most important and common mosquito-borne viral infection that can cause significant human morbidity and mortality. It has become a major public health problem especially in an endemic area such as Malaysia. In Malaysia, about 5000 cases been reported each year since 1990s and the number of incidence has been increasing tremendously for the past 10 years [1]. The spectrum of disease is varies ranging from asymptomatic to undifferentiated fever to a severe form of dengue infections with or without organ impairment that can lead to fatalities [2,3]. As the number of dengue viral infection (DVI) is dramatically increasing, atypical presentations have been reported throughout the years involving all systems which may include polyneuropathies, fulminant hepatic failure, myocarditis, pulmonary haemorrhage, spontaneous splenic rupture and lymph nodes infarction [4]. The postulated pathophysiology of dengue infection is focusing on the endothelium as the target of the immunopathological mechanism that interferes with the vascular permeability and coagulation cascade thus explained the systemic involvements [5].

The incidence of renal involvement in DVI is uncommon ranging form 0.3% to 13.3% [6,7]. It mainly manifests as shock induced acute tubular necrosis, rhabdomyolysis related sepsis or as a part of haemolytic uremic syndrome (HUS) and rarely immune mediated injury [4,7]. The viral aetiology of HUS is rare and the real incidence is still unknown [8]. HUS is an acute clinical syndrome characterized by the pentad of microangiopathic haemolytic anaemia, thrombocytopenia, rapid progression of renal failure, neurological abnormalities and high grade fever, which is rare [9]. When the manifestation of acute renal failure is more dominant, this may represent HUS rather than “classical” thrombotic thrombocytopenic purpura (TTP) with prominent neurological abnormalities. Hence, we reported a case of acute renal failure with hypertensive emergency as a part of HUS associated with DVI.

CASE PRESENTATION

We described a previously healthy 25 year-old man who was first presented to University Kebangsaan Malaysia Medical Centre (UKMMC) with 4 days history of high grade fever, myalgia, and arthralgia. He had no history of bleeding tendency, seizures, abdominal pain or diarrhoea. He stays in dengue endemic area with a history of recent fogging in the neighbourhood and is not on any medication. On presentation, he had a temperature of 38°C, blood pressure of 140/90 mmHg with no postural drop with a pulse rate of 101 beats per minute. He was not tachypneic and his peripheral perfusion was good with no bleeding tendency. Respiratory and abdominal examinations were unremarkable with no evidence of effusion or ascites. The
Initial blood investigations showed a haemoglobin level of 13.5 g/dL, total white count of 10.2 x 10^9/L, haematocrit of 38.8% and platelet count of 120 x 10^9/L. His renal profile was deranged with urea 8.5 mmol/L, creatinine 270 umol/L and potassium of 2.8 mmol/L. Dengue serology IgM and IgG were positive.

He was hospitalized and received intravenous normal saline solution and anti-pyrexia. The fever subsided after 24 hours of admission and platelet count was improving. He maintained a good urine output which was more than 0.5 mls/kg/hour. However, his systolic blood pressure was ranging from 150 to 170 mmHg. His serum creatinine remained the same during this admission. Renal ultrasound showed normal kidney size. Urinalysis revealed protein 3+ and blood 2+ with isomorphic red blood cells (RBC). Urine chemistry revealed 4.3g proteinuria over 24 hours with serum albumin of 32g/L. He was started with oral Diltiazem 30mg thrice daily and oral Prazosin 1 mg twice daily. He was discharged well after 6 days admission and was scheduled for a renal biopsy.

Nine days after discharge, he presented to the Emergency Department with hypertensive emergency and acute kidney injury. He had recurrent vomiting associated with epigastric pain. There were no fever, diarrhea, bleeding tendency or any neurological symptoms. He denied taking analgesic, any herbal or recreational drugs. In the emergency room, he was tachypneic with a respiratory rate of 22 breaths per minutes, dehydrated, and pale. There was no oedema in the extremities or bleeding tendency. The blood pressure was 205/144 mmHg, heart rate of 103 beats per minute and afebrile. No other abnormalities were found on the physical examinations and no facial or cutaneous appearance to suggest scleroderma.

Blood investigations revealed anemia, (hemoglobin level 8.7 g/dL, normocytic normochromic), high reticulocytes count and thrombocytopenia, with a platelet count of 71 x 10^9/L. Blood urea increased to 24.6 mmol/L and the serum creatinine level was 964 umol/L. Estimated glomerular filtration rate was 6.14 mL/min/1.73m2. Other than hyponatremia at 131 mmol/L on presentation, other electrolytes were within normal range. Urinalysis showed 3+ proteinuria and 4+ of blood. The Coombs test was negative. Full blood picture (FBP) revealed normochromic normocytic cells with presence of microspherocytes, polychromasia and fragmented cells, with thrombocytopenia (platelet of 15-20/high power field) consistent with microangiopathic haemolytic anemia (MAHA).

Chest radiograph showed cardiomegaly with alveolar infiltration in both lower zones. Cardiac assessment on echocardiogram showed good ejection fraction with minimal pericardial effusion less than 1 cm at posterior wall. Serologic test for anti-nuclear antibody (ANA), double-stranded-DNA (dsDNA) and both anti-nuclear cytoplasmic antigen (p-ANCA and c-ANCA) were negative with normal complement (C3 and C4) level. Serial blood cultures were no growth. Leptospira serology was negative. The diagnosis of hemolytic uremic syndrome with hypertensive emergency due to recent dengue infection was made. It was supported by histological findings of severe thrombotic microangiopathy on renal biopsy - Figure 1.

Discussion

Dengue is one of the most common mosquito-borne viral infections that associated with significant morbidity and mortality [3]. They can present in various ways and atypical manifestations are uncommon [4]. Lack of awareness of atypical manifestation of DVI will potentially lead to devastating complications. Haemolytic uraemic syndrome (HUS) is one of the rare renal manifestations [10]. HUS were postulated as a result of widespread microscopical clot formation, thrombi in the arterioles and capillaries of the organs including brain and kidneys, called thrombotic microangiopathic (TMA) [11]. Endothelial injury is the main pathological mechanism in HUS and the same process was thought to happen in DVI [12-14].

The commonest form of HUS is related to Escherichia Coli (E.Coli) infection-producing Shiga toxin that associated with diarrhea, especially in children. However about 5-10% of cases are related to dysregulation of complement pathway and this is called as atypical HUS (aHUS) [15]. In aHUS, the cell damage is a direct result from excessive complement activation on the cell membranes due to uncontrolled activation of alternative complement pathway. These may be due to mutations in complement regulatory proteins (Factor H, Factor I or membrane co-factor protein) that commonly seen as genetically inherited or occasionally due to acquired neutralizing autoantibody inhibitors of these complement system components [16].

Our case is rare and unique as he fulfil the clinical diagnosis of HUS. He presented with MAHA, thrombocytopenia and acute renal failure with marked decreased in eGFR as a sign of organ failure which potentially triggered by DVI that he had 2 weeks prior to this presentation. His deterioration in renal function was proven histologically as TMA from the renal biopsy as the cause of the organ failure. There was no identified neurological or gastrointestinal involvement with negative other infective screening.

From the literature review, cases of dengue fever-induced HUS is rarely been reported and only limited case reports are available. Wiersinga et al reported the first similar clinical
condition of HUS following dengue infection in 48 years old man after 21 days of dengue exposure that proven histologically as TMA from the renal biopsy [10]. While another two reported cases from the paediatric group of patients with HUS following dengue infection that occurred as early as 4 days post dengue infection [17] and up to 12 days [18].

Pathophysiology of acute renal failure following viral illness are difficult to establish. In certain clinical condition such as dengue shock syndrome (DSS), acute tubular necrosis can be one of the causes of deterioration in renal function. It may also be a manifestation of rhabdomyolysis or a diagnosis of HUS and immune mediated renal injury should be considered. Thus, a renal biopsy is worth doing as histological diagnosis can help to differentiate the aetiology of the renal impairment and lead us to appropriate diagnosis and management. In HUS, few histological characteristics have been observed including glomerular thrombosis, endocapillary swelling and various amounts of endocapillary hypercellularity [19]. The described histological findings were seen in our patient. Thus, the findings may further support the diagnosis of HUS.

Thrombotic thrombocytopenic purpura (TTP) is also another entity of TMA. Since the clinical course of this disease (related to neurological and renal disorder), almost similar and overlapping, thus evaluation of a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS 13) activity can provide a supportive clinical evidence of different mechanisms of TMA. ADAMTS 13 is an enzymes that cleaves von Willebrand factor (vWF), a large protein involved in blood clotting, into smaller pieces. The presence of inhibitory autoantibodies that result in a severe deficiency of this enzyme can lead to HUS, however, the mechanism still remains unclear [20].

ADAMTS 13 deficiency is defined when the level is less than 10% of the protease activity. The sensitivity of severe ADAMTS 13 deficiency causing HUS is up to 78%, however, the specificity is still controversial [21]. Rossi et al has first described a case of neutralizing autoantibody against ADAMTS 13 that developed in the course of dengue infection resulting in TMA [8]. This autoantibody was spontaneously disappeared within four months as the dengue infection resolved. For those with ADAMTS 13 activity, more than 10 percent on presentation rarely cause relapse disease, however, the clinical importance of ADAMTS 13 activity during remission is still unknown [22]. Concerning the value of evaluating ADAMTS 13 activity for initial diagnosis and treatment choices is still uncertain as this test is not easily available in all centre and yet the aggressive initial treatment need to be initiated to save a life.

In general, HUS is a medical emergency. Treatment in HUS is mainly supportive care and the outcome for most patients who have diarrhoeal associated HUS is favorable between 65%-85% [23]. Patients with suspected HUS ideally admitted to a center with the capability of performing plasma exchange, as it is believed have benefit in the treatment process, mainly based on the published report in children [24,25]. Utilization of plasma exchange as part of management in TTP and aHUS are well described [26-28]. Despite major improvement in survival for those treated with plasma exchange therapy, overall mortality from this clinical condition is in the range of 10%-25% after initiation of treatment [11].

Atypical HUS has a poorer outcome and it was estimated about 33%-40% patient died or progressed to end-stage renal failure (ESRF) after the first clinical diagnosis of aHUS [16]. However, only 5-10% cases are related to this dysregulation of complement pathway [15]. In aHUS, the cell damage is a direct result from excessive complement activation on the cell membranes due to uncontrolled activation of alternative pathway. These may be due to a mutation in complement regulatory proteins (Factor H, Factor I or membrane co-factor protein) that commonly seen as genetically inherited or occasionally due to acquired neutralizing autoantibody inhibitors of these complement system components [16].

Our patient received 4 cycles of plasma exchange with intermittent haemodialysis during the acute episode however he ended up with ESRF that requires him for life long dialysis. Hence, we report this case for its scarcity of the dengue complication that causes significant morbidity and aims to provide an exposure to the clinician about the clinical entity of this rare complication of dengue fever as early diagnosis can prompt an early treatment which can improve the outcome. There is no known exact mechanism which can explain the above manifestations in dengue. It is likely driven by endothelial injury caused by the invasion of the dengue virus [5]. It was also postulated that it may be associated with acquired autoantibody to ADAMTS 13 enzyme leading to reduced activity or by amplifying of the immune response leading to overwhelming cytokines release that stimulates complements activation [8]. Unfortunately not many centres are capable of measuring ADAMTS 13 activity or even genetic testing in Malaysia, includes UKMMC. Detection of dengue virus in the renal biopsy specimens may help to confirm the association of dengue virus with the renal damage. Based on the temporal timeframe manifestation, we hypothesize the probable link between the previous infection with dengue virus and the subsequent development HUS in this patient as one of the rare manifestation of DVI.

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REFERENCES


