

Case Report

Early manifestation of severe plasma leakage with fluid overload and early acute kidney injury and liver injury in dengue haemorrhagic fever and lessons learnt from using N-acetylcysteine and CRRT: a Case Report

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Key words: Dengue haemorrhagic fever, early fluid overload, acute kidney injury, CRRT

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Introduction

Dengue is an endemic tropical disease found in Sri Lanka with a high mortality. It is caused by a Flavivirus, transmitted by the vectors *Aedes aegypti* and *Aedes albopictus* [1]. The usual clinical picture is an acute febrile illness associated with either spontaneous or inducible haemorrhagic manifestations lasting for 02 to 07 days which may be complicated by a spectrum of clinical entities including dengue haemorrhagic fever (DHF) and dengue shock [2].

There are three recognized clinical phases of the disease, where the initial febrile phase lasts for 02 to 07 days followed by the critical or the leaking phase and convalescent phase thereafter [2]. The hallmark of the critical phase, which usually begins on the 5th or 6th day of the illness and lasts for a maximum of 48 hours, is extravascular plasma leakage which can be complicated by shock as well as problems due to excessive fluid in extravascular compartments [2]. After the critical phase, the fluids extravasated during the critical phase are reabsorbed into the intravascular compartment. If excessive volumes are administered during the critical phase, the huge amount of reabsorbed fluids in the convalescent phase may lead to pulmonary oedema, heart failure, and death. Therefore, careful fluid administration during the critical phase is pivotal to prevent or minimize fluid overload-related complications in the convalescent phase [2].

In addition to complications related to plasma leakage, specific organ dysfunction involving the kidneys, liver, heart, and central nervous system is observed in patients with dengue [3]. Acute kidney injury (AKI) in dengue is a well-known, but poorly studied, entity. Histopathological evidence is lacking due to the inability to obtain kidney biopsies due to the high risk of bleeding. AKI is observed later in the course of the disease,

usually after 5 days of illness, which may be because of plasma leakage leading to prerenal failure. The occurrence of oliguric renal failure adds to the challenges in patients with DHF because urine cannot be used as a means of getting rid of the massive amount of fluid that is reabsorbed into the vascular compartment during the convalescent phase. Continuous renal replacement therapy (CRRT) has been successfully used in DHF patients with oliguric renal failure as a prophylactic strategy [4]. Acute liver injury is a known complication of dengue and may range from slight elevation of the liver enzymes to acute fulminant liver failure.

This patient had evidence of both acute kidney injury and liver failure, as well as early extravascular fluid overload on presentation on the 04th day of the illness which is not a common scenario in clinical practice. Her acute liver failure was successfully treated with IV N-acetylcysteine. She was also subjected to CRRT to manage the concomitant extravascular fluid overload and circulatory collapse on a background of oliguric acute kidney injury.

Case Presentation

Our patient was a previously healthy, 27-year-old, unmarried female residing in Colombo. She had no history of any kidney-related disease or symptoms of chronic kidney disease such as swelling, frothy urine, reduction in urine output or uraemic symptoms. There was no family history of such. She had first experienced an acute febrile illness with high fever, retro-orbital headache, arthralgia and myalgia. Full blood count on the 2nd day showed; white cell count 3.8×10^9 /L, haemoglobin 12.6 g/dL, platelet count 128×10^9 /L with positive dengue NS1 antigen. On the 3rd day of illness, the patient experienced vomiting and 5 to 6 episodes of loose stools. She was admitted to the National Hospital of Sri Lanka on the 4th day of illness due to difficulty in breathing and abdominal pain. The patient did not have overt bleeding manifestations on admission. Examination revealed an elevated temperature, pulse rate of 140 beats/minute, blood pressure of 120/70 mmHg with no postural drop and a normal jugular venous pressure. There was right upper quadrant abdominal tenderness and right-sided moderate pleural effusion. Oxygen saturation on room air was 70%. The differential diagnosis for this presentation included leptospirosis, hepatitis viral infection, COVID-19 and systemic lupus erythematosus. These were excluded by relevant laboratory investigations. The patient was admitted to the general medical ward and critical phase monitoring was started according to the national guidelines of dengue management [2]. Her initial investigations results were as follows.

Table 1: Investigations

Investigation	Results (normal Range)
WBC	9.3×10^9 /L (4 - 11×10^9 /L)
Neutrophils	55.3 % (40 - 60%)
Lymphocytes	34.7% (20 - 40%)
Haemoglobin	8.4 g/dL (12 - 15.5 g/dL)
Haematocrit	38% (35.5 - 44.9%)
Platelet count	18×10^9 /L (150 - 450×10^9 /L)
ESR	15 mm in 1 st hour (0 -29 mm)
CRP	23 mg/dL (<6 mg/dL)

AST	2220 IU/L (10 – 40 IU/L)	
ALT	1115 IU/L (7 -56 IU/L)	
Total bilirubin	4.1 mg/dL (0.1 – 1.2 mg/dL)	
Direct bilirubin	2.5 mg/dL (< 0.3 mg/dL)	
Serum total protein	5.4 g/dL (6 – 8.3 g/dL)	
Serum Albumin	3 g/dL (3.4 – 5.4 g/dL)	
Serum total cholesterol	64 mg/dL (<200 mg/dL)	
Serum Triglycerides	217 mg/dL (<150 mg/dL)	
Urine protein creatinine ratio (UPCR)	Not available	
Serum creatinine	1.86 mg/dL (0.7 -1.3 mg/dL)	
Serum sodium	127 mmol/L (135 -145 mmol/L)	
Serum potassium	4.7 mmol/L (3.5 -5.5 mmol/L)	
Urine full report	Albumin +++, pus cells 4-6/hpf, red cells 3-5/hpf, granular casts Specific gravity 1.020	
PT	20.2 seconds (10-14)	
INR	1.54 (<1.1)	
APTT	54.4 seconds (18-32)	
LDH	Not available	
CPK	1849 U/L (26 -192 U/L)	
Corrected calcium	9.1mg/dL (8.5 – 10.2 mg/dL)	
VBG	Before intubation	After intubation (ABG)
pH	7.36 (7.35-7.45)	7.47
PO ₂	27mmHg (75 – 100mmHg)	60mmHg
PCO ₂	27 mmHg (35 – 45 mmHg)	24 mmHg
HCO ₃ ⁻	15 mmol/L (22 -26 mmol/L)	118 mmol/L
Lactate	5.2 mmol /L (0.5 – 1.0 mmol/L)	3.6 mmol/L
Blood picture	Normochromic normocytic red cells with some polychromatic cells, Reactive lymphocytosis with left shifted neutrophils and marked thrombocytopaenia, no evidence of MAHA	
Ultrasound scan of the abdomen	Gall bladder wall oedema, pericholecystic fluids, fluids in the hepatorenal pouch, right sided moderate pleural effusion (depth 5 cm), normal kidney sizes with increased echogenicity, corticomedullary demarcation normal. Kidney sizes - left 10.9 cm, right 9.4 cm, A small amount of free fluids in the peritoneal cavity	
ANA	Negative (Hep2 cell method at a screening dilution of 1:80)	
C3	74 mg/dL (55-120)	
C4	34 mg/dL (20-50)	
Dengue IgM ELISA	Positive	
Leptospirosis MAT	insignificant (highest titre 1:40)	
SARS-Cov rapid antigen	Negative	
SARS-Cov PCR	Negative	
Hepatitis A, B, C serology	Negative	

She had early thrombocytopenia on the 2nd day of the illness. Her platelet count dropped to a minimum of $18\,000 \times 10^9 /L$ on the 4th day and started to rise from the 5th day which suggested exit from the leaking phase. She had a white cell count of $3.8 \times 10^9 /L$ on the 2nd day of the illness which increased from day 5 ($7.4 \times 10^9 /L$) which again denoted recovery from the critical phase. White cell counts increased markedly from the 5th day onwards simultaneously with the onset of secondary sepsis.

The patient was transferred to the ICU on the day of admission due to the increased requirement for oxygen and for close monitoring. Later that day, she underwent emergency endotracheal intubation due to dropping oxygen saturation. Bilateral significant pleural effusions, as well as fine crackles, were observed in both lung fields. Since the patient had clinically significant pleural effusions, it was assumed that the patient had started the critical phase 24 hours earlier. In the initial hours, the patient had adequate urine output ($>1\text{ml/kg/hour}$). Even though the patient had normal blood pressure, there was a persistent tachycardia of $>100\text{-}120$ beats/min in the absence of fever. In addition, the PCV dropped to 25 % after 4 hours. Even though there was no evidence of overt bleeding, she was given a red cell transfusion of 5ml/kg over four hours. PCV increased to 30% after the transfusion with a little improvement of the heart rate.

At 20 hours, the PCV dropped again to 26 with persistent tachycardia which warranted further red cell transfusion. Tachycardia settled after the 2nd blood transfusion. The patient's urine output was satisfactory during the 48 hours of critical phase monitoring. Since the patient had highly elevated hepatic transaminases, N-acetylcysteine IV was started (150mg/kg stat followed by 50mg/kg over 4 hours and 6.25 mg/kg thereafter).

At 32 hours of admission, since the patient continued to have high oxygen demand, significant pleural effusions, pulmonary oedema, and a stable PCV at a low value of around 30%, her fluid intake was reduced to 50-80 ml/hour. The patient was given a total fluid of 2436 ml over the period of the critical phase and produced a total urine output of 1410 ml with a positive balance of 1026 ml. Despite a good urine output, the patient had a rapid rise in serum creatinine and oliguria from the 6th day onwards [Figure 01]. Therefore, the patient underwent a 3-hour low-efficiency haemodialysis on the 6th day of admission, removing an ultrafiltrate of 200ml. After the dialysis, the serum creatinine dropped from 6.75 to 4.6 mg/dL. Subsequently, she underwent haemodialysis on days 08, 09, and 11 removing ultrafiltrates of 2000 mL, 2000 mL, and 1000 mL respectively.

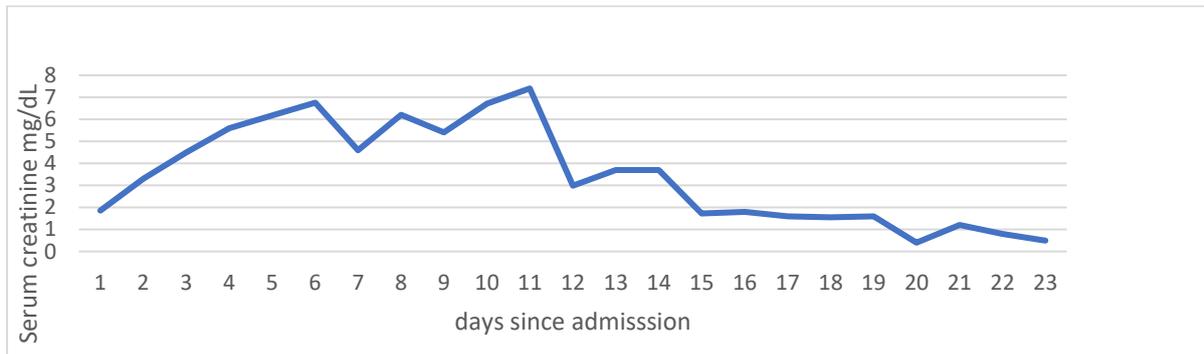


Figure 1: Changes in serum creatinine

The patient continued to have pulmonary oedema, peripheral oedema and bilateral pleural effusions. Since the patient had an adequate urine output with a diuretic response, we attempted to treat the fluid overload with IV frusemide infusion from day 2 to day 6 with dose adjustment according to the pulse pressure, mean arterial pressure (MAP) and degree of pulmonary oedema (dose range 3-15mg/hour). Later, as there was septic shock that needed inotropic support and extravascular fluid overload due to reabsorption during the convalescent phase, the patient was started on continuous renal replacement therapy in CVHD mode from day 12 onwards, to help remove the extra fluids slowly without affecting the haemodynamic status. The CRRT rate was determined by the MAP and the IVC diameter measured ultrasonically. It was assumed that the reabsorbed fluids would increase the mean arterial pressure and the rate of ultrafiltrate was changed accordingly (Figure 2 and 4). However, during the latter part of the CRRT, there was a haemodynamic compromise which necessitated inotropic support. This was probably due to secondary sepsis. CRRT was not escalated and was reduced to achieve a positive fluid balance to maintain adequate tissue perfusion (Figures 2 and 4). Heparin was not used because of the high bleeding risk as evidenced by a high aPTT and thrombocytopenia. The amount of reabsorbed fluid gradually increased which was manifested initially by increasing positive fluid balance and increasing MAP [Figures 2 and 3].

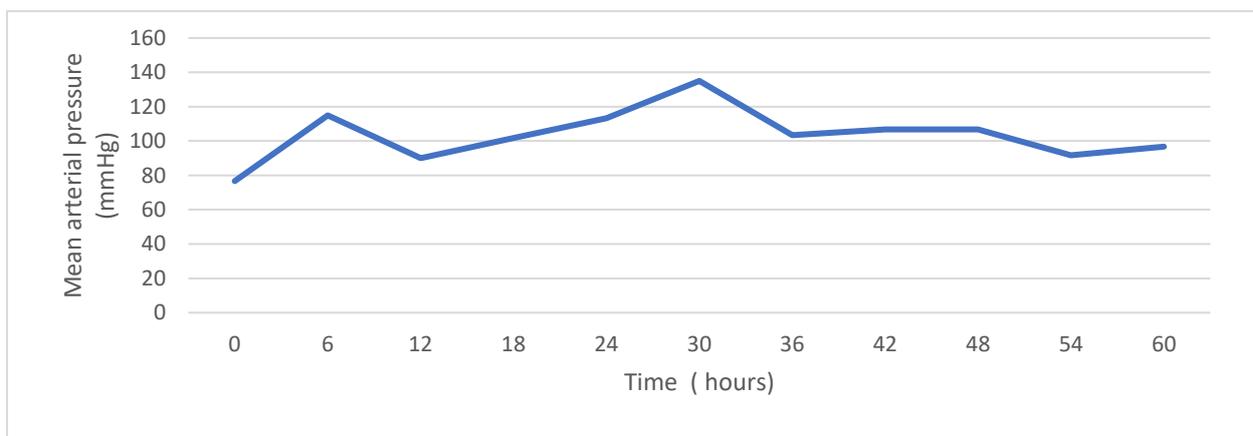


Figure 2: Changes in mean arterial pressure during CRRT

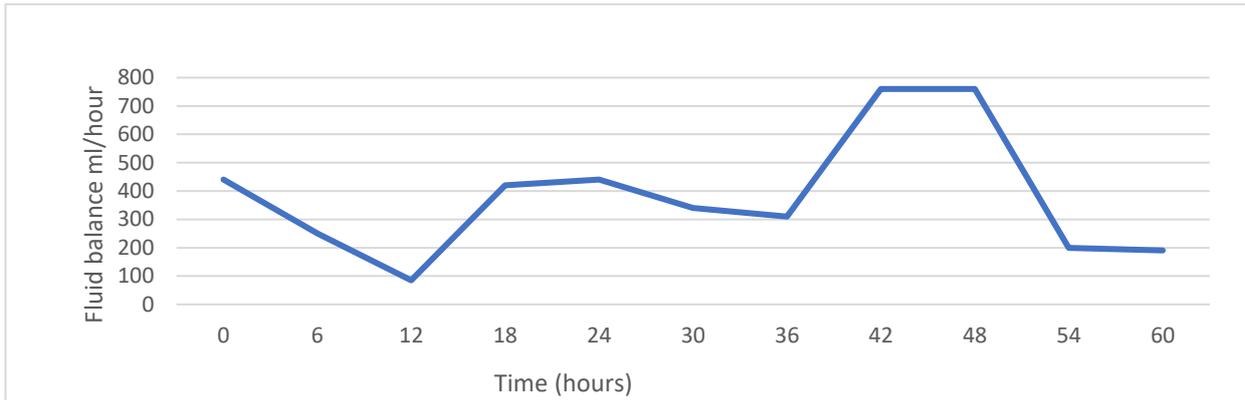


Figure 3: Fluid balance during CRRT

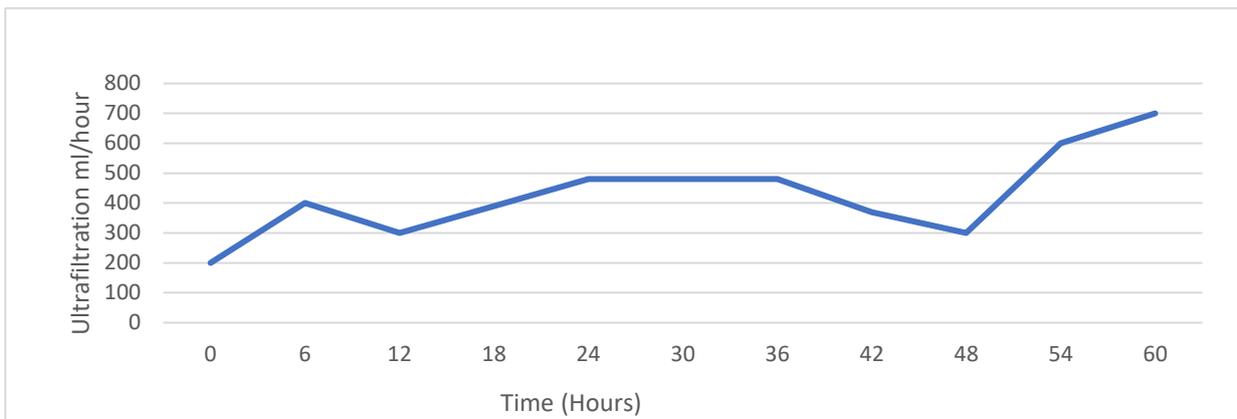


Figure 4: Changes in the rate of ultrafiltrate

Apart from the acute kidney injury, the patient had acute liver injury diagnosed on the 4th day of the illness. She had AST of 2220 IU/L and AST of 1115 IU/L, initially. With N-acetylcysteine treatment, the liver enzymes reduced significantly within 6 days of treatment and returned to normal by 10 days (AST 30 IU/L, ALT 45 IU/L) [Figure [5]].

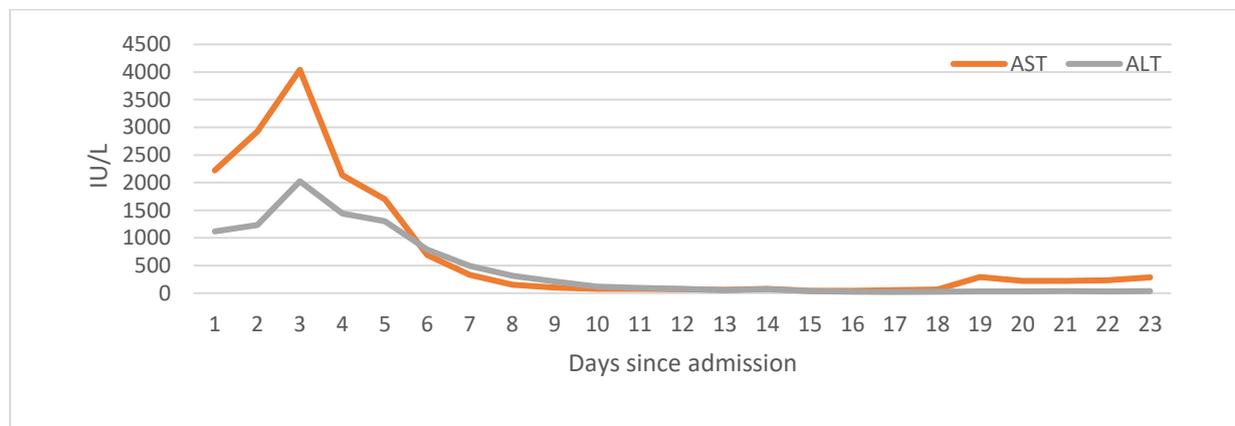


Figure 5: Changes in liver transaminases

During this period, she was treated with an acute liver failure regime including oral metronidazole 400mg 8 hourly and syrup lactulose 30-45 ml 8 hourly for adequate

bowel motions. There were elevated lactate levels on the first day of admission (4.8 mmol/L) which returned to normal on the 3rd day of N-acetylcysteine treatment. EEG showed evidence of encephalopathy. Initially, the patient had a mild prolongation of PT/INR (INR1.4) which was treated with IV vitamin K. During the later days of ICU stay, she had more severe derangements of coagulation due to sepsis and disseminated intravascular coagulation which was diagnosed with thromboelastography and treated with fresh frozen plasma (FFP) and cryoprecipitate.

The patient's ICU stay was complicated with sepsis due to multiple organisms which was treated with IV meropenem, amikacin, and colistin according to the sensitivity pattern. Unfortunately, she developed multiorgan failure and disseminated intravascular coagulation which resulted in death on the 23rd day of admission.

Discussion

Usually in clinical practice, fluid overload occurs late in the convalescent phase of dengue, after 7 to 8 days of illness, in patients who have been given excessive amounts of IV fluids during the critical phase. This patient had loose stools and vomiting on day 3 onwards and was not given any IV fluids before admission but, surprisingly, she had fluid extravasation into the extravascular compartment associated with overload as evidenced by significant pleural effusions, gross ascites, pulmonary oedema and dropping oxygen saturation. There was no lung or cardiac pathology apart from alveolar oedema and pleural effusions reported from the HRCT scan of the chest and the echocardiogram. Therefore, it is an uncommon presentation of DHF with early fluid overload possibly due to extensive early plasma leakage.

The serum creatinine was high on the 4th day of the illness (1.86 mg/dL) and continued to rise which needed haemodialysis. Even with fluid leakage and bleeding, the patient had an adequate urine output during and up to 6 days after the end of the critical phase. Therefore, the patient had non-oliguric acute kidney injury without an increase in serum potassium. Acute kidney injury is commonly seen in patients going into shock due to severe fluid leakage or haemorrhage. In this patient, there was elevated serum creatinine from the 4th day of the admission in the absence of circulatory collapse. The urinalysis revealed +++ protein, 4-6 pus cells and 3-5 red cells per high power field and some granular casts. There are several kidney-related complications identified in dengue viral infection [5], which carry significant morbidity and mortality.

1. Acute kidney injury (AKI)
2. Glomerulonephritis
3. Nephrotic range proteinuria

AKI (defined as a rise of creatinine ≥ 0.3 mg/dl or ≥ 1.5 -2 times elevation from the baseline) was found in 13.3 % of patients with dengue fever in a study from Pakistan [6]. AKI in dengue occurs as a result of the following pathophysiological mechanisms [6].

1. Hypoperfusion
2. Rhabdomyolysis induced acute tubular necrosis (ATN)
3. Haemolytic uraemic syndrome
4. Coagulopathy (as evident by prolonged aPTT)

5. Viral invasion into the kidneys
6. Immune complex deposition
7. Unexplained

There are several important predictors of AKI in patients with dengue viral infection revealed in the Pakistan study [6].

1. Male gender
2. Older age
3. Sepsis
4. DHF/dengue shock syndrome
5. Neurological involvement
6. Prolonged aPTT

Another study from Malaysia found that male gender, multiple organ dysfunction, DHF, late hospital admission, diabetes mellitus, rhabdomyolysis and the use of nephrotoxic medications increase the incidence of AKI in patients with dengue viral infection [7]. This patient had prolonged aPTT from the 4th day of the illness so there may have been a contribution from coagulopathy to the early onset of AKI. Even though the patient did not have dengue shock syndrome during the critical phase, the extensive plasma leakage may have played a role in the pathogenesis of the early AKI. Dengue virus can invade the muscles directly or indirectly leading to the release of myotoxic cytokines (e.g: - TNF) resulting in the release of muscle enzymes and rhabdomyolysis which may cause AKI in dengue [8]. Our patient had elevated CPK levels from the 4th day of the illness though there were no overt features of rhabdomyolysis such as hyperkalaemia and hypocalcaemia. This may also have contributed to the early AKI. Acute glomerulonephritis is an uncommon cause of AKI in patients with dengue viral infection. Self-limited proteinuria is observed in 74% of patients with severe dengue infection and haematuria is found in 12.5% [9]. She had +++ proteins in the urinalysis but, unfortunately, urine protein was not quantified in this patient. Proteinuria may indicate some form of glomerulonephritis which needs to be confirmed with histology. Urine specific gravity ranged from 1.015 to 1.020 in this patient. In patients with AKI in dengue viral infection, a urine specific gravity of > 1.015 suggests pre-renal whereas <1.015 suggests a renal form of AKI [7]. There are only limited data regarding the patterns of glomerulonephritis in dengue. The observed patterns of glomerulonephritis are [9];

1. Mild mesangial proliferation
2. Immune complex deposits (IgM, c3, IgG)
3. Lupus nephritis like pattern
4. IgA nephropathy like pattern
5. Mesangiocapillary glomerulonephritis

Intact kidney function is a very important prerequisite for the successful management of DHF and its complications. During the critical phase urine output is a very important parameter determining the adequacy of tissue perfusion, early identification of shock and for rational adjustment of fluid input. Our patient had an adequate urine output throughout the critical phase even in a background of AKI. During the convalescent phase presence of preserved kidney functions with adequate urine output is of

paramount importance to get rid of the overloaded fluids using diuretics. Therefore, kidney disease in dengue viral infection results in higher morbidity and mortality [7].

CRRT has been used to manage patients with fluid overload and renal failure who recover from the critical phase [4]. When the urine output is reduced and non-diuretic responsive it is challenging to manage a patient with fluid overload particularly when there is haemodynamic compromise. In such situations, CRRT is very useful to get rid of the fluids that cause overload. Fluid is reabsorbed into the circulation during the convalescent phase which may be manifested by increasing diastolic blood pressure, mean arterial pressure, central venous pressure, and inferior vena cava diameter [4]. Therefore, those parameters may be used to decide on the rate of ultrafiltrate removal by CRRT. CRRT can also be used as a preventive measure to minimize fluid overload and related complications in a patient with DHF and renal failure in whom fluid overload is anticipated [4]. In patients with DHF who will experience fluid overload CRRT may be used in the absence of renal impairment as well. This aspect of the behavior of fluid dynamics and ways to adjust the rates of CRRT should be further studied and the results incorporated into dengue management guidelines. In our patient, we believe that if CRRT had been used earlier during the convalescent phase there would have been a better outcome.

Acute liver injury is a known complication of dengue viral infection. The presence of liver injury may increase the severity of plasma leakage particularly in patients with low albumin during the early course of the illness as in this patient [2]. In addition, prolongation of INR >1.3 increases the risk of bleeding. There may be a contribution of paracetamol treatment for fever to the liver derangement as patients often take it prior to hospital admission with no proper records of dosage. NAC is used for the treatment of paracetamol toxicity and has been used for other causes of liver failure such as autoimmune hepatitis, hepatitis B, drug-induced hepatitis and unknown causes of liver failure but there is limited evidence [10,11,5]. In our patient, there was marked improvement of the liver impairment as denoted by transaminases and lactate levels. Therefore, NAC may be a useful drug for the treatment of dengue virus-associated liver failure possibly by reducing oxidative stress, acting as an antiviral agent and reducing the direct viral invasion of the liver and by improving blood flow to the liver [11]. Since dengue-associated liver failure is a challenging clinical entity to manage, particularly in the setting of plasma leakage, the use of NAC should be studied further in future randomized controlled trials [11].

Conclusion

In dengue fever, fluid overload is usually observed during the convalescent phase and after, in patients receiving extra input of fluids during the critical phase. Surprisingly, our patient had clinical as well as radiological evidence of extravascular fluid overload on presentation on the 4th day of the illness. Even though AKI in dengue usually occurs late, with circulatory collapse, this patient had rising creatinine from the 4th day of the illness without evidence of shock.

When patients develop simultaneous overload and oliguric renal failure, it is a challenging task to get rid of the excessive fluids in the intravascular as well as extravascular compartments. In this setup, CRRT is a useful tool that was implemented in our patient. Future studies should investigate the exact dynamics of fluid reabsorption during convalescence and optimization of CRRT for the management and prevention of fluid overload.

Liver injury is a common entity encountered in dengue patients, which can range from mild elevation of liver enzymes to acute fulminant liver failure. Our patient was successfully treated with N-acetylcysteine leading to normalization of AST/ALT/lactate and INR. NAC is recommended for paracetamol-induced liver injury and studies of its efficacy in non-paracetamol-related liver injury are limited. Therefore, future randomized controlled trials should focus on the use of NAC in patients with dengue viral infection-related liver injury.

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