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Case Report

Hemolytic uremic syndrome and hypertensive crisis post dengue hemorrhagic fever: a case report

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Hemolytic-uremic syndrome (HUS) clinically manifests as acute renal failure, hemolytic anemia and thrombocytopenia. Acute renal failure with oliguria, hypertension, and proteinuria usually develops in affected patients.[1,2] In children under 15 years of age, typical HUS occurs at a rate of 0.91 cases per 100,000 population.[3] The initial onset of this disease usually happens in children below 3 years of age. Incidence is similar in boys and girls. Seasonal variation occurs, with HUS peaking in the summer and fall. In young children, spontaneous recovery is common. In adults, the probability of recovery is low when HUS is associated with severe hypertension.[2]

Damage to endothelial cells is the primary event in the pathogenesis of HUS. This damage can occur as a result of dengue virus infection. Deficiency of factor H, membrane cofactor protein, or factor I results in excessive complement deposition, which promotes the development of microthrombi in the kidneys and other tissues. The cardinal lesion is composed of arteriolar and capillary microthrombi (thrombotic microangiopathy [TMA]) and red blood cell (RBC) fragmentation.[4-6]

HUS is mostly associated with *E.coli* 0157:H7 and classified into 2 main categories, depending on its association with Shiga-like toxin. Shiga-like toxin–associated HUS (Stx-HUS) is the classic, typical, primary or epidemic form of HUS. One-fourth of patients present without diarrhea (denoted as D-HUS). Most cases of D+HUS occur in epidemics, and are associated with contaminated food or water, swimming in contaminated water, contact with cattle, contaminated environments or person to person transmission. Acute renal failure occurs in 55-70% of patients, but as many as 70-85% of patients recover renal function.[1] Hypertensive crisis with blood pressure 50% higher than the 95th percentile for age, height, and gender, is a complication of acute renal failure due to HUS.[7,8] Viral etiologies for HUS (atypical HUS), such as Portillo, Coxsackie, influenza, Epstein Barr, rotavirus, and dengue are rare (incidence rate <0.3%).[4]

Supportive care is the mainstay of HUS therapy. Dialysis and renal transplantation are performed when necessary. The role of antimicrobial agents in the treatment of HUS is controversial. There is little evidence that antibiotics are beneficial. Furthermore, indirect evidence suggests that antimicrobials may be dangerous in many cases of *E.coli* O157:H7. There is also controversy on the benefits of therapy with fresh frozen plasma transfusion, glucocorticoids, heparin, thrombolytic agents, and prostacyclin.[1,9] Despite treatment, approximately 5% of children with HUS

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die of the disease and 10% have severe chronic renal impairment.[9-14]

We present a case of atypical HUS with acute renal failure and hypertensive crisis following a dengue fever infection. Supportive therapy resulted in a good outcome, without need for hemodialysis.

Case Report

An 8-year-old boy was referred to a government hospital with a 12 day history of sudden, high, continuous fever and vomiting 1-2 times daily. He had no history of seizures, shivering, cough, sneezing, diarrhea, purpuric rash or other bleeding. During first 4 days of fever, he went to a private hospital for blood tests which showed haemoglobin (Hb) of 13.2 g/dl, leukocytes 2,700/µL, platelet count 116,000/µL, and negative Widal test. He refused hospitalization. On the 7th day of fever, he had petechiae and abdominal pain. Blood tests showed a secondary dengue fever infection (positive dengue IgG and IgM), so he was hospitalized. He received intravenous Ringer's lactate solution, amoxicillin injection, dexamethasone injection, paracetamol, lanzoprazole, ondansetron, and multivitamins. Amoxicillin was changed to ceftriaxone injection on the second day of hospitalization. His platelet count decreased to 47,000/µL, followed by a slow increase. On the fourth day of hospitalization, he had vomiting, oliguria, and hypertension (130/90 mmHg). His laboratory results were Hb 8.2 g/dl and platelet count 76,000/µL. Renal sonography suggested glomerulonephritis. His pediatrician changed ceftriaxone to amoxicillin injection again, and gave him IV vitamin C 1x100 mg, IV furosemide, and captopril 2x12.5 mg. On the fifth day of hospitalization, blood gas analysis (BGA) showed pH 7.47, pO_2 106, pCO_2 26, BE -5, HCO_3 18.2, and FiO_2 21%. Blood tests showed Hb 6.6 g/dl, leukocytes 13,500/µL, hematocrit (Ht) 19%, platelet count 95,000 /µL, and blood smears revealed schistocytes and Burr cells. The pediatrician diagnosed HUS and recommended hemodialysis, therefore, he was referred to Dr. Kariadi Hospital due to his government insurance coverage (Jamkesda Kodya Semarang).

In the emergency room, he had an ill appearance, flushed skin, anemia, mild edema in the lower extremities, good nutrition, and no petechiae. BP was 150/120 mmHg, respiratory rate (RR) 28x/min, and heart rate (HR) 86x/min. Lung auscultation revealed crackles and his liver was palpated 1/3-1/3 with a sharp border. Laboratory results revealed anemia (Hb 6.5 g/dl with normal RDW and erythrocyte index), leukocytosis (19,500/µL), and thrombocytopenia (75,000/µL). Blood urea was 171 mg/dl and serum creatinine was 4.49 mg/dl (GFR: 14.9 ml/minute/1.73 m^2), hypocalcemia at 1.89 mmol/l, hyponatremia at 135 mmol/l, serum total protein 4.3 g/dl, hypoalbuminemia at 2.1 g/dl (↓), and hyperuricemia at 11.2 mg/dl. Urinalysis showed 3+ proteinuria, 3-5 granular casts/HPF, and 2-6 RBC/ HPF. Electrocardiogram showed normal sinus rhythm. BGA showed pH 7.46, pO_2 107, pCO_2 26, HCO_3 18.2, BE -5.5, $AaDO_2$ 10.3, FiO_2 21%, PO_2/FiO_2 509. Chest X–ray showed edema in both lungs, with a pleural effusion index (PEI) of 18%. Ophthamologic examination revealed no hypertensive retinopathy, but he had myopia V OD 2/60, V OS 1/60, corrected with glasses of OD -10, OS -10. He diuresed at a rate of 0.3 ml cc/kg/min on day 1, increasing to normal diuresis by day 4 (>1 cc/kg/min).

The patient was assessed as having HUS with hypertensive crisis and was given supportive therapy, along with intravenous furosemide, ceftriaxone, calcium gluconate, ranitidine, sublingual nifedipine, roborantia, captopril, and allopurinol. After four days, his blood pressure returned towards normal (110/90 mmHg), his extremity edema disappeared, his lungs were clear and his liver was no longer palpable. He received PRBC transfusion on day two, but no platelet concentrate, and his post-transfusion Hb was 14 mg/dl with platelet count 81,000/µL. His discharge diagnosis was HUS with hypertension (95th–99th percentile) and severe myopia.

On his first follow-up visit (6 days following discharge), he had a desquamative post-drug eruption, and was treated with urederm twice a day. By the end of six weeks, the dermatitis had improved and his blood pressure had returned to normal (100/70 mmHg), so the captopril was stopped. Laboratory findings revealed Hb 12.6 g/dl, leukocytes 10,200/µL, platelet count 471,000/µL, urea 49 mg/dl, creatinine 0.6 mg/dl, with normal electrolytes and urinalysis.

Discussion

This patient exhibited the triad signs of HUS:[5,6] (1) hemolytic anemia, in that he had a severely decreased Hb level along with hemolysis [Burr cells, schistocytes] potentially triggered by dengue fever [IgG and IgM-positive] and perhaps a nonspecific bacterial infection [leukocytosis, but no clear infection focus], (2) thrombocytopenia, and (3) acute renal failure, with oliguria, azotemia [increased urea, creatinine], and decreased GFR. The pathogenesis of HUS is unknown. Damage to endothelial cells occurring mostly in the renal arterioles and glomerular capillaries are central lesions in the pathogenesis of HUS. Proinflammatory and prothrombotic events, as well as changes in the coagulation system, along with dysfunctional endothelial cells may result in organ damage. Endothelial cell damage may be caused by lipopolysaccharide (LPS) originating from *E.Coli/Shigella*. LPS in circulation will stimulate monocytes to release interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF-α), which will activate the coagulation cascade producing fibrin. Bacterial toxin-stimulated damage causes endothelial cells to release Von Willebrand Factor (vWF) and react with thrombocytes to increase aggregation/adhesion and accelerated-thrombofibrin formation in arterioles and glomerular capillaries.[10-14] Thrombocytopenia is a primary manifestation in HUS, possibly caused by peripheral destruction of thrombocytes. Endothelial cell destruction is followed by fibrin formation inside arterioles and capillaries, causing narrowed lumen, decreased GFR, oliguria, azotemia, and disturbances in other biochemical processes in the body.[7] Narrowed arterioles and glomerular capillaries may also be caused by increased endothelin levels in plasma. Endothelin is produced by endothelial cells and functions as a vasoconstrictor affecting blood flow in kidneys, GFR, and blood pressure (BP). Fibrin, formed on endothelial cells inside the microvascular kidney, destroys erythrocytes through a microangiopathic process as they move across the vessels. Hemolysis typically occurs suddenly, marked by a Hb level as low as 4 g/dl. Examination showed increased reticulocytes, with usually negative direct and indirect Coombs tests. By microscopic immunofluorescence, fibrin, fibronectin, IgM and C_3 on capillary walls, as well as mesangium and subendothelial space can be observed.

The pathogenic links between viral infection and concomitant renal dysfunction are often difficult to establish. HUS caused by dengue fever infection is rare, except in dengue shock syndrome (DSS) which induces acute tubular necrosis. Various signs of acute tubular necrosis include IgG, IgM and/or C_3 deposition and thickening of the glomerular basement membrane. Acute renal failure and multiple organ failure may also be a manifestation of rhabdomyolysis. The role of immune complex in development of renal failure in dengue infection is still unclear. Wiwanitkit in Gulati et al discovered the diameter of dengue virus–immunoglobulin complex to be much smaller than the diameter of the glomerulus. Thus he postulated that the immune complex can be entrapped only if a previous glomerular lesion caused narrowing of the glomerular diameter. He concluded that the immune complex did not play a significant role in pathogenesis of renal failure in dengue infection.[15]

Renal failure due to HUS was described in an isolated case report where renal biopsy revealed thrombotic microangiopathy with glomerular and arteriolar microthrombi. Electron microscopy demonstrated the presence of microtubuloreticular structures, suggesting a viral infection. Acute renal failure could be partly mediated by the tubular damage, which in turn could be mediated by the direct cytopathic effect of viral proteins and cytokine-induced injury.[12] Renal biopsy was not performed on our patient.

In our subject, we found hemolytic anemia with Hb 6.5 g/dl (with schistocytes and Burr cells), thrombocytopenia (platelet count reached 75,000/μL), and normal coagulation (PT, PTT), but with increased fibrinogen (including increased acute reactive protein such as CRP), positive dengue IgG and IgM, azotemia (serum urea 171 mg/dl and serum creatinine 4.49 mg/dl), decreased GFR, proteinuria, granular casts in urine, and normal potassium. Hyperuricemia was due to acute renal failure, dehydration, and cell damage. Leukocytosis was present, but no bacteria was cultured from the blood. Stool culture was also unproductive.

Biopsy may be used to establish an HUS diagnosis, however, we did not perform a renal biopsy.

Peripheral smears for schistocytes and thrombocytopenia are similarly important for HUS diagnosis. The characteristic HUS pathologic findings are occlusive lesions of the arterioles and small arteries, as well as subsequent tissue microinfarctions.[1,5] A fully developed vascular lesion consists of an amorphous-appearing, hyaline-like, thrombi-containing platelet aggregation and a small amount of fibrin that partially or fully occludes the involved small vessels (see images below).

Glomerular thrombotic microangiopathic lesions and cortical necrosis are the most frequent histologic findings in Stx-HUS, whereas arterial thrombotic microangiopathic lesions are the most frequent features in non – Stx-HUS.[5]

HUS is a self-limiting disease with spontaneous recovery, although strict monitoring and treatment of symptoms are important. Because HUS has highly variable clinical symptoms**,** supportive therapy (good nutrition, anti-hypertensive drugs, strict monitoring of fluid and electrolytes) is important for good outcomes. In our case, we gave supportive therapy (fluid and electrolyte balance, uremic diet for nutrition, PRBC transfusion for hemolytic anemia, and anti-hypertensive drugs with furosemide, captopril and nifedipine).

In a previous meta-analysis, higher risk of HUS was not associated with antibiotic administration.[18] Our patient was given amoxicillin and ceftriaxone.

Indications for hemodialysis are clinical and laboratory in nature. Clinical indications include uremic syndrome (vomiting, seizure, unconciousness), fluid overload (evidenced by cardiac failure, pulmonary edema, and/or hypertension), and metabolic acidosis (Kussmaul). Laboratory indications include urea $\geq$ 200 mg/dl, creatinine $\geq$ 15 mg/dl, hyperkalemia (K+ $\geq$ 7), and $HCO_3 \leq$ 12 meq/l. Hemodialysis may improve HUS prognosis.[7] Our patient did not receive hemodialysis, since he did not meet the above criteria, and his azotemia was improving with no evidence of uremic syndrome. Based on available literature, patient management without dialysis is appropriate when the patient is passing urine (non-anuric), and the acid-base balance, serum electrolyte concentrations and fluid balance can be managed without dialysis.[13]

One complication of HUS is hypertension due to fluid overload or increased renin associated with renal vascular disturbance.[1] Hypertension is defined as average systolic and /or diastolic BP >95th percentile for gender, age and height on > 3 occasions.[16]

Hypertensive crisis (BP > 50% above the 95th percentile for age; practical definition for children > 6 years old: BP systole $\geq$ 180 mmHg or diastole $\geq$ 120 mmHg or any stage of hypertension with encephalopathy, cardiac failure, or papilledema) is different from hypertensive urgency and emergency. Hypertensive urgency is defined as severe hypertension without evidence of end-organ involvement. Hypertensive emergency is defined as hypertension associated with end-organ dysfunction (brain, heart, eye, or kidney).[17]

Acute hypertension in our case may be secondary to the HUS, with no target organ damage. In addition, fundoscopy revealed no hemorrhages, infarcts or papilledema.

Nifedipine, (a calcium channel blocker reducing peripheral vascular resistance but not affecting cardiac output) was administered sublingually to our patient. The nifedipine dosage for his hypertensive crisis was sublingual at 0.1 mg/kg, increased by 0.1 mg/kg every 5 minutes (for the first 30 minutes), with a maximal dose of 10 mg/dose. The effect was rapid -- within 10 minutes. The patient also showed good response to IV furosemide. Furosemide dose was 2 x 1 mg/kg IV before he was switched to oral furosemide after improvement.[18]

ACE inhibitors (captopril 0.3-2 mg/kg every 8-12 h) was given to maintain blood pressure and to reduce proteinuria.

Patients with D$^-$ HUS typically have frequent relapses and a higher risk of progression to end-stage renal disease (ESRD),[1] but our patient's prognosis was good since he responded well to supportive therapy (without hemodialysis) and achieved normal BP without prolonged use of anti-hypertensive drugs. He had normal urea and creatinine, and no further complications.

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