Paediatrica Indonesiana

VOLUME 44 March - April • 2004 NUMBER 3-4

Case Report

D+ hemolytic uremic syndrome

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Hemolytic uremic syndrome (HUS) is characterized by anemia microangiopathy, thrombocytopenia, and acute renal failure, predominantly occurs in children younger than 4 years of age. It is the most common cause of acute renal failure in children.[1,2] HUS is divided into two categories, the epidemic type which is accompanied by enteritis (D+HUS) and the sporadic type which is not accompanied by enteritis (D-HUS). The pathogenesis is unknown, but available evidence strongly suggests endothelial cell damage in the organs.

In the United States, an estimate of 0.3-10 cases of HUS occurred per 100,000 children. The incidence increases during the summer and early fall. Out-breaks of diarrhea followed by HUS have been reported in institutions, boarding schools, and daycare centers. In Indonesia, seasonal variation is not observed.[3,4]

The management of patient is primarily supportive and designed to reserve the renal failure and to control hypertension (when it exists).

The major improvement in HUS depends on careful management of fluid and electrolytes, and early initiation of dialysis to correct fluid overload or severe electrolyte imbalances.[5-7]

Report of the case

A 10 month-old Balinese female baby was referred by a pediatrician from Makassar (South Sulawesi) with the diagnosis of hemolytic uremic syndrome on October 24, 2002. History of the disease was taken from her mother, the chief complaint was pale, which has been observed by her mother since 5 days before admission, and looked worsen since 4 days before admission. She had low grade fever and vomit since 7 days before admission, the vomit contained food and water that she consumed and no blood was found. She had diarrhea since 6 days before admission. The stool was watery, looked brownish and contained mucous with blood.

Reddish urine appeared 5 days before admission, and on the next day the color of urine became yellowish, but the urine volume and frequency of urination continued to decrease, and she did not pass any urine for 15 hours. She had edema at lower extremities and face since 2 days before admission.

Before admission she was hospitalized in Baubau and Makasar, with the diagnosis of malaria and treated with suldox, primaquin, blood transfusion and cefotaxim. No similar history were found among family members. She was born spontaneously and vigorously with the birth weight of 3600 gram. Her growth and development were normal. The family lives in a small town with high endemic of malaria, and her parents were medical doctors who has a private practice in their own house. Two days before the patient got ill, her mother had a bloody diarrhea patient visiting their house.

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On the time of admission, she looked irritable. The pulse rate was 132 times per minute, regular, the blood pressure was 110/60 mmHg, the respiration rate was 36 times per minute, regular, axillar body temperature was 36.5°C. The body weight was 12 kg, height was 75 cm, she was well-nourished. No abnormality was found in head examination, except the conjungtiva looked pale. There was no neck stiffness. The chest was symmetric. The breath sound was normal and there was no abnormality of the heart sound on the auscultation. The abdominal examination showed distended belly on inspection. On palpation, the liver and the spleen were not palpable. Bowel movement was normal. Both extremities were warm and not pale. Power, tonus, and reflexes were normal, pitting edema was found at the lower extremities. There was no enlargement of the axillaries, inguinal and cervical lymph nodes. The skin looked pale.

Laboratory findings from Stella Maris Hospital Makassar revealed the leukocyte count was 22,000/uL, the hemoglobin level was 5.83 g/dL, the hematocrite was 20%, and the platelet count was 92,000/uL. Total plasma protein was 5.97 g/dL, albumin was 3.03 g/dL, creatinine was 6.35 mg/dL, ureum was 201 mg/dL, total cholesterol was 156.1mg/dl, kalium was 5.68 mmol/L, natrium was 138.6 mmol/L, and calcium was 9.3 mg/dl. The laboratory results of urine revealed pH 8.0, leukocyte was 25/mL, erythrocyte was 250/mL, urine sediment showed full of erythrocyte. Blood smear test done in Pomasi clinic, Bau-Bau, on October 22, 2002, showed the erythrocyte was hypochrome, acanthosis, anisocytosis with tear drop cells, schistocyte cells, and burr cells. Leukocytosis and thrombocytopenia were also found.

The laboratory findings on October 25, 2002 (one day after admission) revealed the leukocytes count was 19,540/uL, the hemoglobin level was 5.1 g/dl, the hematocrite was 15.3%, and the platelet count was 280,000/uL. Ureum was 200 mg/dl and creatinine was 7 mg/dl. Blood smear test was done on October 25, 2002 revealed erythrocyte hypochrome, anisocytosis, minimal tear drop cells, helmet cells, leukocytosis with shift to the left and normal platelets. Based on these finding the diagnosis of D+ hemolytic uremic syndrome was established.

The treatment given consisted of furosemide 12 mg, 3 times/day per oral, blood transfusion with packed red cells of 335 cc, low protein diet (protein 1.5mg/kg/day), monitoring vital signs and fluid balance. On November 2, 2002 the peritoneal dialysis was planned due to worsening of renal function. Peritoneal dialysis was performed on November 3, 2002 with Perisol liquid, heparin 1000 IU, datorbyn 15 mg/6 hours, with indwelling time of 45 minutes.

After peritoneal dialysis, the patient was alert and in good condition. The renal function test became better with serum retaining 2.8 and the patient discharged on November 7, 2002 (13 days of hospitalization), all medication was stopped. The patient was advised for further follow-up at the outpatient clinic.

Discussion

HUS is classified into an epidemic/endemic (prodromal) type and sporadic (non-prodromal) type. The epidemic type is more common and accompanied by enteritis (D+HUS), while the sporadic type is not accompanied by enteritis (D-HUS). The etiology and prognosis differ between the D+ and D- types. The etiology of D+HUS has been strongly linked to toxin-producing strain of *Escherichia coli* (O157:H7).[1,2,5] Race and gender are not predisposing factors. A number of other microorganisms have been implicated in the pathogenesis of post diarrhea HUS, especially enterohemorrhagic *E. coli* and, in some area, *Shigella dysentriae* type I. The sporadic form of HUS (also called atypical HUS) is rare in childhood. This type has a worse prognosis, more likely to relapse, not preceded by diarrhea, may be associated with a family history of HUS disease, certain chemotherapy drugs, oral contraceptives, bone marrow transplantation, and vasculitis.[1,7-9]

In our case, the patient got prior enteritis, so this case was classified as diarrhea associated (D+ HUS), but the feces culture showed no growth of pathogenic bacteria.

Pathogenesis of D+HUS is associated with an infection by verocytotoxin (VT) or Shiga-like toxin produced by *E. coli* O157: H7, *Shigella dysentriae* type 1, *E. coli* O26: H11, and other infectious agents.[10] At least three different toxins are designated as VT-1, VT-2 and VT-2c. The toxin binds, invades, and destroys colonic mucosal epithelial cells, resulting in bloody diarrhea. After entering the systemic circulation, the toxin

attaches to a glycosphingolipid membrane receptor (glabotriacylceramide) on endothelial cells (especially in the kidney). The endothelial cells are swollen and injured. In the process, certain endothelial products are released (e.g. von Willebrand factor, platelet aggregating factor, plasminogen activator-1), and platelet/fibrin thrombi form in these injured areas. In addition, the kidney, pancreas, brain and other organs may be injured.[7-10]

The circulating red blood cells that are forced through these occluded vessels are deformed and fragmented, which produce the characteristic schistocytes, tear drop cells, burr cells, and helmet cells. These fragmented red cells are removed by the reticuloendothelial system, resulting in hemolytic anemia (thus it is called microangiopathic hemolytic anemia).[1,5,11]

In our case, microangiopathic hemolytic anemia was shown in blood smear before transfusion, and after transfusion we found normal erithrocytes.[1,2,11]

Thrombocytopenia is believed to be present as the result of the combination of platelet destruction, increased consumption, sequestration in the liver and spleen, and intrarenal aggregation.[1,5] Platelets are damaged as they pass through the affected glomerular capillaries. Remaining platelets circulate in the degranulated form and show impaired aggregation. Abnormalities of antiplatelet aggregating agents (e.g. prostaglandin I_2 (PGI_2), platelet aggregating agents [thromboxane A_2 (TXA_2)] and von Willebrand factor (vWF) multimers, are also important factors that contribute to thrombocytopenia.[7,9] In our case the laboratory results showed thrombocytopenia.

The clinical picture of HUS is a previously healthy child who develops abdominal pain and diarrhea, followed shortly by bloody diarrhea. There may be fever. Within 5 to 7 days, the patient exhibits sign of anemia (e.g. pallor with or without jaundice) and sign of thrombocytopenia (e.g. petechiae). Other signs may include hepatomegaly, hypertension, oligouria, and CNS symptoms (e.g. drowsiness, personality changes), and more severe gastrointestinal manifestations, such as intussusception or gangrenous bowel. Splenomegaly is not a consistent finding, and bleeding (other than bloody diarrhea) is rare. Anuria usually occurs within a few days. At this time, other clinical manifestations may appear, such as coma, hemiparesis, cranial nerve dysfunction, cerebral infarct, seizures, pancreatic insufficiency, and death.[1,11,12] In our case the patient looked severely pale on admission with no urination, edema, and the patient had a history of bloody diarrhea and fever 7 days before admission.

Hematological laboratory findings of HUS are anemia characterized as normochrome-normocytic with an elevated reticulocyte count. The blood smear reveals fragmented cells (helmet cells, burr cells, tear drops cells, schistocytes) and polychromatophilia. Platelets are damaged as they pass through the affected glomerular capillaries.[1,5,11] In our case, the blood smear showed a consistent results which supported the diagnosis.

Renal involvement in HUS can vary from mild to severe. Children, in whom the renal involvement is mild, have only microscopic hematuria, minimal proteinuria, and normal urine output. Some may have an increased urine volume. Severe involvement is characterized by anuria, widespread renal cortical necrosis and irreversible anuric renal failure. Most affected children have the features between these two extremes.[12] Majority of patients (60%) experience oliguria that last in an average of 1 week. Almost 50% were anuric for an average of 3 days. If there is oliguria, it can continue for weeks. All patient have hematuria and proteinuria unless being anuric. Red blood cell casts are frequently found if carefully sought.[1,5,12] In our case, reddish urine appeared 5 days before admission, in the next days the color of urine became yellowish but the volume and frequency of urination were decreased and she had anuria for 15 hours.

Renal dysfunction is indicated by elevated creatinine and blood urea nitrogen (BUN). A variety of fluid and electrolyte imbalances occur because of the reduced renal function, hemolysis, and tissue catabolism. These include hyponatremia, hyperkalemia from reduced glomerular filtration rate, hemolysis, tissue catabolism, hyperphosphatemia and hypocalcemia. Fluid overload is common and can lead to edema and cardiac failure.[12,13] In our case, creatinine increased, but the electrolyte was normal.

The management of patients with D+HUS is primarily supportive and designed to reserve the renal failure and to control the hypertension (when it exists). Red blood cells are infused for symptomatic anemia. Platelet transfusion is rarely needed because a generalized bleeding diathesis is not common, and theoretically platelet infusion could contribute to a microthrombosis. However, platelet transfusion may

be indicated prior to surgical procedures, such as catheter placement for hemodialysis or peritoneal dialysis. Other therapies, including antiplatelet drugs, intravenous immune globulin, anticoagulants, thrombolytic agents, prostacyclin, and corticosteroids, have not been found beneficial.[1,5,10]

The principles of fluid management and electrolyte imbalances in D+HUS and D-HUS are similar. Imbalances must be corrected, the fluid and electrolyte status of patient must be monitored constantly. Nutrition support to achieve normal calorie intake is very important and can be administered intravenously, orally, or by feeding tube. Peritoneal dialysis or hemodialysis should be considered when fluid and electrolyte imbalances cannot be corrected by fluid replacement or when fluid overload compromise cardiac or pulmonary functions. Multiple or large volume transfusion of packed red blood cells may lead to pulmonary edema and congestive heart failure, with dialysis required to remove excess plasma volume during the transfusion. As a general principle, when the BUN exceeds 100 mg/dL (35.7 mmol/L) dialysis should be considered, even in the absence of fluid and electrolyte imbalances. In our case, the patient received lasix 12 mg, 3 times/day orally, blood transfusion of PRC 335 cc, diet of low protein (1.5 mg/kg bw/day) and monitoring of vital signs and fluid balance. On November 2, 2002 the peritoneal dialysis was planned due to worsening of the renal function. Peritoneal dialysis was done on November 3, 2002 with perisol liquid, heparin 1000 IU, datorbyn 15 mg/6 hours and indwelling time of 45 minutes.

The major improvement or prognosis of HUS depends on careful management of fluid and electrolytes and early initiation of dialysis to correct fluid overload or severe electrolyte imbalances. The overall prognosis for D+HUS is better than for D-HUS. The early mortality rate is about 5% and another 5% for patients who develop acute renal failure and anuria that require life long dialysis. The long-term prognosis is more problematic. Long-term complications include proteinuria, reduced glomerular filtration rate, hypertension, and late development of end stage renal disease (ESRD). Many patients in long-term studies experienced initial complete recovery, but the complications developed years later. ESRD develops in approximately 10% to 15% of the patients in 15 to 25 years follow up studies. Accordingly, children who have D+HUS should be followed up for many years, even if the initial recovery appears to be complete. Long- term prognosis can be predicted by renal biopsy performed during the initial illness. Children who have patchy renal cortical necrosis are more likely to develop ESRD or chronic renal failure.[3,10,15] In our case the prognosis of our patient was good.

In summary, D+ hemolytic uremic syndrome (D+HUS) was diagnosed in our case by his clinical feature and laboratory results. The patient was treated with peritoneal dialysis, but discharged form the hospital in a good condition. All medication was stopped, and their parents were advised to follow up the patient in the outpatient clinic.

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