Case Report

SPONTANEOUS REMISSION OF NEPHROTIC SYNDROME IN HUS-TTP

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ABSTRACT

We report a three-year-old girl with thrombotic microangiopathy, severe encephalopathy and nephrotic syndrome. She presented with encephalopathy, oliguria and edema with laboratory findings of thrombocytopenia, anemia, heavy proteinuria, and elevated liver enzymes and blood urea nitrogen. The encephalopathy lasted for 7 days where as the nephrotic syndrome lasted for over a month. Hemolytic uremic syndrome (HUS) - thrombotic thrombocytopenic purpura (TTP) with severe neurological involvement and nephrotic syndrome that improved without any sequelae was discussed.

Key Words: HUS-TTP, Encephalopathy, Central nervous system involvement, Nephrotic syndrome

INTRODUCTION

Hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are thrombotic microangiopathy syndromes and are now increasingly referred to as HUS-TTP syndrome (1). CNS involvement occurs in 20-50 % of patients with HUS and has been reported to predispose renal sequelae like hypertension or chronic renal damage (2,3). Patients with HUS nephrotic syndrome usually indicate a severe renal involvement and proteinuria may persist for years ending in renal failure (4). Although there is no definite therapy for nephrotic proteinuria in HUS, aggressive treatment with plasma exchange, corticosteroid therapy or ACE inhibitors have been reported (5-7).

We report, a 3-year-old girl with thrombotic microangiopathy who developed severe encephalopathy and nephrotic syndrome, recovering after supportive medical treatment.

CASE REPORT

A three-year-old girl was admitted to our hospital for lethargy and irritability. Her medical history was uneventful, no allergies or drug use. She was the first child of unconsanguineus parents

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without any history of familial renal disease or hypertension. Nine days prior to her admission she had 39°C fever lasting for 4 days followed by abdominal pain, dysuria, and edema of the limbs. Intramuscular ceftriaxone was given by her pediatrician for urinary tract infection. The fever and abdominal pain was resolved in two days, but because of lethargy, irritability and decrease in urine output she was brought to the hospital. On physical examination, paleness of the skin, edema, several purpuric, ecchymotic lesions on the trunk and limbs and excessive bleeding at the site of injections were noted. Her blood pressure was 120/60 mm Hg and Glasgow coma scale was 7. In our Pediatric Intensive Care Unit (ICU) specimens of blood, urine, stool and cerebrospinal fluid were obtained for culture and ceftriaxone was continued. Urine analysis showed hematuria, proteinuria and hyaline casts. Her hematological laboratory findings were; Hb: 5 g/dl, Hct: 21 %, white blood cell count: 29000/mm^3, platelet count: 24000 / mm^3, blood urea nitrogen (BUN): 51 mg/dl, creatinine: 0.8 mg/dl, serum elecrolytes were normal but liver enzymes were high (alanine aminotransferase: 186 U/L, aspartate aminotransferase: 327 U/L). Serum albumin level was 1.9 g/dl. The diagnosis of HUS was made based on hemolytic anemia [haemoglobin 8 g/dl dropping to 5 g/dl, a low haptoglobin level (25 mg/dl), increased lactate dehydrogenase (1438 U/L) and bilirubin levels (6.6 mg/dl), negative direct Coombs test], thrombocytopenia (24 000 / mm^3) and acute nephropathy (oliguria, hematuria, proteinuria and mild azotemia). She had generalized tonic seizures without any abnormal neurologic finding except papilledema. Culture tests were negative. The further laboratory investigations revealed normal amylase level, normal complement 3 level, negative tests for antinuclear antibody, antineutrophilic-cytoplasmic antibody, anticardiolipin antibody, anti-double-stranded DNA, VDRL, negative viral serology of Hepatitis A, Hepatitis B, Hepatitis C, Cytomegalovirus, Ebstein Barr virus and negative streptococcal and other bacterial cultures. Cerebral edema was documented on cranial computed tomography and mannitol was started in addition to furosemide. Intravenous fluids were restricted to replace only urine output and insensible losses. An electroencephalogram showed irregular generalized spike-wave discharges. Seizures were controlled by phenobarbital. She required mechanical ventilation support for three days. On the seventh day, she was aware of environmental stimuli, she could maintain verbal contact. No neurologic deficiencies were detected subsequently. On the eighth day, thrombocytopenia and elevated liver enzymes returned to normal and she began to perform daily activities. Peripheral edema disappeared within two days followed by polyuria (6 ml/kg/hr). She was given fresh frozen plasma for 4 days,human albumin for 6 days, 3 units of platelets and 1 unit of packed red blood cells within the first week. To confirm the diagnosis of HUS with these continuing nephrotic markers as heavy proteinuria (140 mg/m2/hr), hypoalbuminemia (2.5 g/dl), hyperlipidemia (cholesterol: 284 mg/dl) a renal biopsy was performed on the 20^{th} day of admission. The biopsy specimen contained 34 glomeruli, one of which showed global sclerosis, another one of which showed mesengiolysis, duplication of the glomerular basement membrane and occasional mononuclear leukocytes. Hyperplastic vascular changes and a thrombotic lesion in one capillary loop was reported. Immune fluorescein examination showed only one (+) linear deposition of Ig M. Ig G, Ig A, complement 3, complement 4 and fibrinogen deposits were negative. Electron microscopic examination showed swollen endothelial cells and obliteration in some of the capillaries. The histologic picture revealed thrombotic microangiopathy and was consistent with a diagnosis of HUS-TTP. There was no evidence of vasculitis or any other form of glomerulonephritis. On the 28th day physical and neurological examinations were normal as well as the electroencephalography and cranial magnetic resonance images. Anticonvulsive medication was stopped and the child was discharged. Spontaneous remission of nephrotic syndrome was observed in 60 days. The patient has been followed up for 18 months without any renal or neurological problem.

DISCUSSION

The differential diagnosis of thrombotic microangiopathy syndromes HUS and TTP is difficult and sometimes impossible due to the wide spectrum of the disease (1). Sudden onset of hemolytic anemia, thrombocytopenia, and

acute renal failure account the classic triad of HUS but multisystem involvement including the gastrointestines, liver, pancreas and CNS may develop. Neurologic manifestations which had been attributed to TTP including irritability, lethargy, deep coma, and seizures as well as focal neurological signs such as hemiparesis occur in 20-50 % of patients with HUS (2). The underlying pathology of encephalopathy and other neurologic manifestations have been related to either metabolic derangements including severe azotemia, hyponatremia, and hypocalcemia or microangiopathic changes of cerebral microvasculature resulting in altered microvascular hemodynamics (2). Autopsy results and neuroradiological findings revealed that thrombotic microangiopathies, generalized edema, petechial hemorrhages, and large-vessel strokes are the most commonly detected findings in patients with HUS (8).

Our patient had a severe cerebral edema confirmed by cranial computed tomography which lasted for 3 days, however the encephalopathy lasted for 4 more days. Lack of typical imaging changes after the third day and the absence of metabolic abnormalities did not allow us to clarify the possible causes leading to the neurological symptoms. Though CNS involvement has been accepted as a predictive factor for poor prognosis in children with HUS[2], some reports have demonstrated that these patients may display an excellent outcome (8). Similarly, our case improved without any sequelae despite severe and long lasting coma.

It has been reported that patients with CNS involvement are prone to renal sequelae such as residual hypertension, chronic renal damage and reduced glomerular filtration rate (3). Nephropathy in HUS usually presents with acute renal failure. Different forms of glomerulonephritis have also been reported, including poststreptococcal glomerulonephritis, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis and Ig A nephropathy (5,6,9). Secondary membrano proliferative glomerulonephritis due to HUS in a 6 year old girl, improving with plasma exchange has been reported (5). Another study by Kimura et al demonstrated a case of thrombotic microangiopathy accompanied by glomerular subendothelial dense deposits who rapidly ameliorated with corticosteroid therapy (6). Recently, the relationship of free radical-mediated injury to HUS or nephrotic syndrome was discussed that excessive generation of free radicals lead to oxidant injury of cell membrane lipids and cause the damage of endothelium and red cells (10, 11). Our patient developed hypoalbuminemia, hyperlipidemia and heavy proteinuria during the first week of the illness. The nephrotic state persisted for 8 weeks. Biopsy findings were in favour of mild form of thrombotic microangiopathy which may have been ameliorated by our supportive management. Subendothelial deposits or membranoproliferative changes were not present. Spontaneous remission was observed in 60 days without any specific treatment for nephrotic syndrome. HUS patients with nephrotic presentation usually end in renal failure requiring dialysis therapy. To our surprise despite the clinical and laboratory findings of nephrotic state with oliguria our patient did not require dialysis therapy.

We conclude that good supportive care with seizure control, avoidance of overhydration, respiratory support, close monitoring of hematologic, renal and vital parameters are the key points in the treatment of HUS-TTP, even with a severe central nervous system involvement, and the nephrotic state may spontaneously undergo remission. Careful and close nephrological and neurological follow up is required.

REFERENCES

1. *Remuzzi G, Ruggenenti P. The hemolytic uremic syndrome. Kidney Int 1995;48:2-19.*
2. *Bale JF, Brasher C, Siegler RL. CNS manifestations of the hemolytic uremic syndrome: relationship to metabolic alterations and prognosis. Am J Dis Child 1980;134:869-872.*
3. *Sheth KJ, Swick HM, Haworth N. Neurological involvement in hemolytic-uremic syndrome. Ann Neurol 1986;19:90-93.*
4. *Milford DV, White RHR, Taylor CM. Prognostic significance of proteinuria one year after diarrhea-associated hemolytic-uremic syndrome. J Pediatr 1991;118:191-194.*
5. *Jha V, Murthy MS, Kohli HS, et al. Secondary*

membranoproliferative glomerulonephritis due to hemolytic uremic syndrome: an unusual presentation. Ren Fail 1998;20:845-850.

6. *Kimura M, Fujigaki Y, Ohtake T, Furuya R, Hishida A, Kaneko E. A patient with thrombotic microangiopathy accompanied by glomerular subendothelial electron dense deposits. Am J Nephrol 1998;18:155-159.*
7. *Moghal NE, Ferreira MA, Howie AJ, Milford DV, Raafat F, Taylor CM. The late histologic findings in diarrhea-associated hemolytic uremic syndrome. J Pediatr 1998;133:220-223.*
8. *Barnett NDP, Kaplan AM, Bernes SM, Cohen ML. Hemolytic uremic syndrome with particular involvement of basal ganglia and favorable outcome. Pediatr Neurol 1995;12:155-158.*
9. *Morita S, Sakai T, Okamoto N, et al. Hemolytic uremic syndrome associated with immunoglobulin A nephropathy: A case report and review of cases of hemolytic uremic syndrome with glomerular disease. Inter Med 1999;38:495-499.*
10. *O'regan S, Chesney RW, Kaplan BS, Drummond KN. Red cell membrane phospholipid abnormalities in the hemolytic uremic syndrome. Clin Nephrol 1981;15:14-17.*
11. *Pedreza Chaverri J, Arevalo AE, Hernandez Pando R, Larriva Sahd J. Effect of dietary antioxidants on puromycin aminonucleoside nephrotic syndrome. Int J Biochem Cell Biol 1995;27:683-691.*