

# Enteric Fever Presenting as Hemolytic Uremic Syndrome

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**Abstract:** Hemolytic uremic syndrome is usually caused by toxigenic strains of *E.coli* or *Shigella*. HUS due to *Salmonella typhi* is a rare presentation. We present a seven year old child with diarrhea followed by microangiopathic hemolytic anemia, acute kidney injury and thrombocytopenia. Blood culture grew salmonella typhi (NARST). Supportive care with antibiotics, fluid and electrolyte management resulted in complete recovery in a week. Our child presented with mild clinical features hence didn't require peritoneal dialyses or blood transfusions.

**Keywords:** HUS, Enteric fever, Salmonella typhi.

## 1. Introduction

Hemolytic-uremic syndrome (HUS) is one of the most common causes of community-acquired acute kidney failure in young children. It is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. Usual infectious causes are Verotoxin-producing *Escherichia coli*, Shiga toxin-producing *Shigella dysenteriae*, Neuraminidase-producing *Streptococcus pneumoniae*, Human immunodeficiency virus. Very rarely it is caused by other organisms. We hereby report a case of HUS due to *Salmonella typhi* which is an uncommon causative organism and review available literature regarding presentation, pathogenesis and management.

## 2. Case Report

Seven year old boy admitted with history of loose stools for 1 week, fever for five days, abdominal pain and vomiting for two days and decreased urine output for one day. He was developmentally normal child studying second standard with no significant past history of medical illness. On general examination he was lethargic, febrile with some dehydration. His weight was 20 kg (25<sup>th</sup> percentile) and height was 120 cm (50<sup>th</sup> percentile). Vitals were within normal limits with no hypertension. On systemic examination hepatomegaly 3cm and soft splenomegaly 1cm below costal margin were the per abdomen findings. Other systems were normal.

He was started on intravenous fluids for some dehydration, parenteral ceftriaxone after sending investigations and cultures. His hemoglobin was 12.0mg/dl, total count was 8,000 with thrombocytopenia of 80,000. He had elevated renal parameters along with dyselectrolytemia. Urea being 125 mg/dl, creatinine 3.6mg/dl, sodium 114meq/L, potassium 2.6meq/L, bicarbonate 13meq/L. In spite of correction for some dehydration his urea and creatinine remained high at 135 and 3.3 meq/L respectively. His urine output was just 1ml/kg/hr. Sonogram suggested bilateral medical renal disease. Fluids were restricted and sodium correction was given with 3% saline.

During hospital stay his hemoglobin dropped to 10 mg/dl and platelets decreased to 39,000. Peripheral smear showed

few fragmented RBC's with thrombocytopenia. Reticulocyte count and LDH were increased to 6% and 794 U/L respectively. Blood culture grew salmonella typhi which was sensitive to cephalosporins and resistant to fluoroquinolones (NARST). A diagnosis of hemolytic uremic syndrome due to salmonella typhi was made. He was managed conservatively with fluid restriction, ceftriaxone and intensive monitoring. He recovered in a week with normal renal and hematological parameters. He was discharged on oral cefixime.

## 3. Discussion

Hemolytic uremic syndrome is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. A confirmed diagnosis of HUS should have onset within three weeks of acute diarrhea or dysentery<sup>1</sup>. It should fulfill the laboratory criteria of anemia with microangiopathic changes and renal injury as evidenced by hematuria, proteinuria, or elevated creatinine level:  $\geq 1.0$  mg/dL in a child <13 years. Our case presented with non-bloody diarrhea for one week and creatinine of 3.6mg/dl along with microangiopathic hemolytic anemia as evidenced by fragmented RBC's in peripheral smear, elevated LDH and reticulocytes. Also there was evidence of consumptive coagulopathy in the form of thrombocytopenia. Our case fitted with the diagnosis of HUS.

The most common cause of HUS due to diarrhea is caused by vero-toxin producing *Escherichia Coli*<sup>2</sup> while in Asia it is more commonly due to shiga toxin of *Shigella dysenteriae* type 1. HUS due to other infections is rarely reported. In our boy, HUS is due to *Salmonella typhi*. HUS is considered a rare complication of *Salmonella typhi*. Less than 40 cases of hemolytic anaemia were associated with typhoid as noticed by Retief and Hofmeyr (1965) in the literature<sup>3</sup>. Since then there have been further case reports usually of single case reports. Lwanga and Wing (1970) reported the first case of acute renal failure after intravascular haemolysis in typhoid fever but the patient was G-6-PD deficient<sup>4</sup>. Most of the cases presented in 1960 to 1970 were G-6-PD deficient. Also it was the era of chloramphenicol causing intensification of hemolysis among G-6-PD deficient. In 1974 Baker et al presented six cases of HUS due to *Salmonella typhi* with normal G-6-PD levels<sup>5</sup>. Out of 73 cases of HUS reported by

AIIMS, India nine cases were due to non typhoidal salmonella<sup>6</sup>. No case was reported by them due to Salmonella typhi. Only case report of HUS due to Salmonella typhi by Chaturvedi et al from India is not available for review<sup>7</sup>. Clearly very few cases have been reported in Asian countries with little scientific literature available in public domain.

Regarding pathogenesis microvascular injury with endothelial cell damage is characteristic of all forms of HUS. In the common form of HUS, Shiga toxin produced by Shigella or the highly homologous Shiga-like verotoxin by E.coli O157:H7 directly cause endothelial cell damage<sup>8</sup>. Shiga toxin can directly activate platelets to promote their aggregation. Capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli, causing a direct decrease in glomerular filtration rate. Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia. Microangiopathic hemolytic anemia results from mechanical damage to red blood cells as they pass through the damaged and thrombotic microvasculature.

Albaqali et al in his reported case HUS due to typhoid found no evidence for immunoglobulin (Ig) M and IgA against the LPS of E coli O157:H7<sup>9</sup>. However anti-S typhi LPS IgM and IgA were strongly positive. In the polymerase chain reaction, DNA from the Stx-producing E coli controls yielded stx1 and stx2 fragments of the expected sizes on agarose gel electrophoresis, whereas no stx1 and stx2 fragments were obtained from the S typhi isolate. He concluded that the inciting toxin may not be stx.

Clinical presentation of HUS can be mild or can progress to a severe, and even fatal, multisystem disease<sup>10</sup>. No presenting features reliably predict the severity of HUS in any given patient. Patients with HUS who appear mildly affected at presentation can rapidly develop severe, multisystem, life-threatening complications. Renal insufficiency can be mild but also can rapidly evolve into severe oliguric or anuric renal failure. Volume overload, hypertension, and severe anemia can all develop soon after onset and together can precipitate heart failure. Most have mild manifestations, with significant irritability, lethargy, and nonspecific encephalopathic features. Severe CNS involvement occurs in  $\leq 20\%$  of cases.

Our child presented with milder clinical features of anaemia 10.0mg/dl, non oliguric renal insufficiency, lethargy with no evidence of volume overload or hypertension. Hence recovered quickly in a span of one week without requiring blood transfusion or renal dialysis. Usually 50% of HUS cases undergo dialyses due to renal insufficiency<sup>12</sup>. Antibiotics and careful management of fluid and electrolyte imbalances especially hyponatremia was all that he needed. Antibiotic therapy to clear the toxigenic organisms can result in increased toxin release, potentially exacerbating the disease, and therefore is not usually recommended in HUS due to Shigella or E.coli<sup>11</sup>. We continued antibiotics in our child without any worsening of HUS features.

## 4. Conclusion

Hemolytic uremic syndrome can be caused rarely by Salmonella typhi. Clinical presentation is similar to HUS caused by E.coli or Shigella. Very few cases have been reported post chloramphenicol antibiotic era. In such cases implicated toxin may not be stx.

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