

# Hemolytic-Uremic Syndrome Caused by Rotavirus Infection: Case Report

## Rotavirüs Enfeksiyonuna Bağlı Gelişen Hemolitik Üremik Sendrom

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**ABSTRACT** While hemolytic uremic syndrome (HUS) is most commonly associated with *E. coli* 0157-H7 and *Shigella dysenteriae* type 1, it may also occur secondarily to other infection agents. Childhood HUS cases represent the typical form, which is also generally called diarrhea-associated form. A two-year-old male patient was referred from another hospital with complaints of vomiting, bloodless, watery diarrhea and anemia. Fecal sample was found to be positive for rotavirus. Our laboratory results also revealed rotavirus as the cause of the diarrhea. The patient was diagnosed with HUS due to the presence of hemolytic anemia, acute renal failure, and a mildly low platelet level; fresh frozen plasma to the patient was administered for two days and hydration. He exhibited clinical improvement on follow-up. Rotavirus diarrhea-associated HUS has been rarely reported in the literature. Although *E. coli* 0157 strain is the main bacterial etiological agent, either sole or as copathogen, in most cases of HUS, in this specific case rotavirus infection was responsible for the HUS. This case illustrates the importance of suspicion of rotavirus as the sole etiological agent for the diagnosis of HUS.

**Key Words:** Atypical hemolytic uremic syndrome; rotavirus

**ÖZET** Hemolitik üremik sendrom (HÜS) en sık *E. coli* 0157-H7 ve *Shigella dysenteriae* tip 1'e bağlı görülmekle beraber diğer enfeksiyon ajanları ile de beraber görülebilir. Çocukluk çağında görülen HÜS vakaları genellikle diyare bağımlı olarak da isimlendirilen tipik formdur. İki yaşındaki erkek hasta başka bir hastaneden kusma, kansız sulu ishal, anemi şikayeti ile başvurdu. Hastada diare etkeni olarak rotavirüs tespit edilmişti. Bizim laboratuvarımızda da diyare etkeni olarak rotavirüs saptandı. Mikroanjyopatik hemolitik anemi, akut böbrek yetmezliği, hafif trombosit düşüklüğü olması nedeni ile HÜS tanısı konularak iki gün taze donmuş plazma verildi, hidrasyon uygulandı. Takibinde hastanın klinik durumu düzeldi. Rotavirüs diyaresine bağlı HÜS literatürde nadir rapor edilmiştir. *E. coli* 0157 şuşu, tek başına ya da ko-patojen olarak, HÜS vakalarının çoğunda ana bakteriyolojik ajan olmasına rağmen bu vakada spesifik rotavirüs enfeksiyonu HÜS'ten sorumlu idi. Bu vaka HÜS tanısında tek etyolojik ajan olarak rotavirüs enfeksiyonu şüphesinin önemini göstermektedir.

**Anahtar Kelimeler:** Atipik hemolitik üremik sendrom; rotavirüs

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**H**emolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. The typical form is the form secondary to gastrointestinal infections and occurs most commonly due to Shiga toxin-producing *Escherichia coli* (*E. coli*) 0157-H7 and *Shigella dysenteriae* type 1.<sup>1-3</sup> The toxin binds to the specific receptors in the glomerular endothelium, thereby ac-

tivating the clotting cascade and leading to thromboembolism and obstruction in the glomerular microcapillaries. Familial or atypical HUS is associated with congenital deficiency or mutation of the factors including Factor I, membrane cofactor protein and Factor H, the protein regulating the complement activation alternative pathway.<sup>1,2,4-6</sup> Rotavirus (RV) gastroenteritis is the most common cause of diarrhea observed in children under five years of age, particularly in developing countries. The disease is self-limiting. Systemic extraintestinal manifestations are rare.<sup>7,8</sup>

HUS secondary to RV diarrhea has been rarely reported in the literature. In reported cases, rotavirus gastroenteritis was detected together with the *E. coli* 0157 strain.<sup>9,10</sup> We also only detected RV as the cause of diarrhea. Considering that it is rarely observed, we reported a case of hemolytic uremic syndrome following rotavirus diarrhea.

## CASE REPORT

A two-year-old boy was submitted to hospital with diarrhea (not bloody diarrhea) and vomiting for three days in our out-patient clinic. During his follow up in the out-patient clinic his hemoglobin (Hb) value decreased progressively from 13,2 g/dL to 6,4 g/dL, the platelets count decreased from 559.000/uL to 141.000/uL and Blood Urine Nitrogen (BUN) increased progressively from 8 mg/dL to 28 mg/dL. His aspartate transaminase (AST) value increased from 61 U/L to 110 U/L. Faecal sample was positive for Rotavirus antigen with latex agglutination test. His other laboratory findings were normal in his follow up.

He was referred to our emergency department for detected anemia. His physical examination and vital signs were normal in the emergency department. Laboratory findings of the patient were Hb 6.0 g/dL, platelets 179 000/uL, white blood cell count (WBC) 22,400/uL, mean corpuscular volume (MCV) 77 fL, and reticulocyte count 19%. Numerous red cell fragments, spherocytes, polychromasia, basophilic stippling and burr cells were seen in a peripheral blood smear. BUN 22 mg/dL, uric acid 6.6 mg/dL, AST 93 U/L, lactate dehydrogenase (LDH)

1899 U/L and electrolytes were all at normal limits. Prothrombin time 13,5 sec, activated partial thromboplastin time 31,5 sec, D-dimer 2,03 um/mL. Faecal sample was also positive for Rotavirus antigen with a latex agglutination test in our laboratories hospital. Cefixime-tellurite sorbitol MacConkey agar cultures were subcultured on blood agar and screened for *Escherichia coli* 0157 by slide agglutination. *E. coli* 0157 did not grow on the medium. His urine analysis showed 1+ proteinuria and erythrocytes seen in microscopic evaluation. We gave a diagnosis of microangiopathic haemolytic anemia. His Hb values increased to 9,6 g/dL by red cell transfusion. In his follow up, the periferic blood smear still contained findings of hemolysis. The patient was diagnosed with HUS caused by rotavirus infection and given fresh frozen plasma for two days. Hemolysis findings in his peripheral blood smear were regressed after treatment with fresh frozen plasma. His final laboratory findings were Hb 10,1 g/dL, platelets 385 000 /uL, WBC 9800/uL, MCV 83 fL, reticulocyte count 4%, BUN 8 mg/dL, uric acid 2,3 mg/dL, AST 55 U/L, LDH 1398 U/L. He was followed for one week after hospital discharge. His laboratory findings were Hb 11,8 g/dL, platelets 546 000/uL, WBC 11 000/uL, MCV 86 fL, reticulocyte count 1%, peripheral blood smear was normal, BUN 18 mg/dL, uric acid 4,5 mg/dL, and LDH 718 U/L. The patient was monitored for one year and remained healthy. Written informed consent was obtained from the patient's family.

## DISCUSSION

Childhood HUS cases represent the typical form, which is also generally called the diarrhea-associated form. It commonly occurs in children under five years of age. After a mean of two to six days following one to two days of bloody diarrhea, HUS is diagnosed. Our case presented after three days of bloodless, watery diarrhea. Generally, thrombocytopenia and severe anemia exist and Hb was reported below 10 g/dL in 90% of the cases. The serum LDH level is detected to be high with reticulocytosis and hyperbilirubinemia (high indirect bilirubin). Despite the negative direct coombs test, the peripheral smear reveals fragmented erythro-

cytes (schistocytes), and burr or helmet cells (microangiopathic hemolytic anemia findings).<sup>1,11</sup> Our case was observed to have Hb level of 6 g/dL, a reticulocyte count of 19%, a LDH of 1899 U/L with the peripheral smear showing microangiopathic hemolytic anemia findings and mild acute renal failure. Nearly half of the patients diagnosed with HUS require hemodialysis. Seventy-five percent of the cases require platelet transfusion while 25% may exhibit neurologic manifestations (stroke, seizure, coma, etc). Three to five percent of the cases die during the acute phase while 3-5% of them develop end-stage renal failure. The treatment includes hydration, plasma infusion, plasma exchange in severe cases, and rarely, steroid treatment combinations.<sup>1,12,13</sup> Our case was administered a single erythrocyte transfusion and fresh frozen plasma twice and hydration; the patient showed clinical improvement after approximately three days. While hemolytic uremic syndrome is most commonly associated with *E. coli* 0157-H7 and *Shigella dysenteriae* type 1, it may also occur secondarily to other infection agents. Cases secondary to *Streptococcus pneumoniae* and influenza A have also been reported, if rarely, which do not involve gastroenteritis manifestations. In cases not associated with diarrhea, the most common cause of isolated infection was *Streptococcus pneumoniae*. In addition, non-diarrhea associated HUS cases most commonly require hemodialysis and an extended hospital stay.<sup>3</sup>

Similarly, the complication risk is observed to be increased upon detection of RV diarrhea together with *E. coli* 0157-H7. A trial performed in Russia in 2010 investigated the etiologic cause in 70 infants developing HUS between 5 months to 2.5 years of age. In six of the nine cases requiring hemodialysis, rotavirus was detected together with *E. coli* 0157. The coexistence of these two microorganisms was observed to increase the complication risk.<sup>9</sup>

A case reported in 1991 involved the presence of positive RV antigen by the latex agglutination test in a four-year-old female patient with bloody and watery diarrhea. On follow-up, the patient developed HUS and *E. coli* 0157 was isolated. This pa-

tient received peritoneal dialysis for 12 days. RV was re-investigated by electron microscopy and detected to be negative. The RV latex agglutination test was reported to potentially exhibit false reaction and not to be specific to RV.<sup>10</sup> However, this patient had watery but hemorrhagic diarrhea and clinically manifested more severe symptoms.

The latex agglutination (LA) method for RV diagnosis has a sensitivity and specificity of 69% and 100%, respectively.<sup>14</sup> Our patient presented with watery diarrhea, and RV antigen was detected on two separate occasions. However, no other microorganism was detected in the laboratory analyses of fecal and blood samples.

HUS secondary to isolated RV gastroenteritis has not been reported in the literature. This may be due to the mild disease course and spontaneous recovery because all of the cases reported in the literature had a mixed infection and more severe clinical manifestations. Because it is rarely observed, we reported a case of hemolytic uremic syndrome following RV-associated diarrhea. Although the clinical manifestations of HUS and RV are not severe, we believe that care should be taken when treating mixed infections. In such cases, other causes of infection should certainly be investigated, and the patients should be closely monitored.

Rotavirus genotypes varies between geographical areas during a rotavirus seasons. G and P types are the most common causes of rotavirus diseases in humans. The most prevalent types found in Turkey were reported as G4P[8] and G1P[8] in 42.2% and 26.6%, respectively.<sup>15,16</sup>

Although *E. coli* 0157 strain and *Shigella dysenteriae* type 1 are the main bacterial etiological agents, either sole or as copathogens, in most cases of HUS, in this specific case rotavirus infection was detected to be responsible for the HUS. The present case serves as reminder to clinicians that rotavirus can be the sole cause to HUS in children and thereby illustrates the importance of considering rotavirus as the sole etiological agent for the diagnosis and treatment of HUS.

## REFERENCES

- Ruggenenti P, Noris M, Remuzzi G. Thrombotic microangiopathy, hemolytic uremic syndrome, and thrombotic thrombocytopenic purpura. *Kidney Int* 2001;60(3):831-46.
- Proulx F, Wagner E, Toledano B, Decaluwe H, Seidman EG, Rivard GE. Mannan-binding lectin in children with *Escherichia coli* O157:H7 haemorrhagic colitis and haemolytic uraemic syndrome. *Clin Exp Immunol* 2003;133(3):360-3.
- Chen SY, Wu CY, Tsai IJ, Tsau YK, Su YT. Nonenteropathic hemolytic uremic syndrome: the experience of a medical center. *Pediatr Neonatol* 2011;52(2):73-7.
- Allen U, Licht C. Pandemic H1N1 influenza A infection and (atypical) HUS--more than just another trigger? *Pediatr Nephrol* 2011;26(1):3-5.
- Yeniizoral E, Öncül O, Çavuşlu Ö. [Investigation of *Escherichia coli* O157: H7 in fecal samples of patients with diarrhea]. *Turkiye Klinikleri J Med Sci* 2009; 29(6):1398-405.
- Besbas N, Karpman D, Landau D, Loirat C, Proesmans W, Remuzzi G, et al.; European Paediatric Research Group for HUS. A classification of hemolytic uremic syndrome and thrombotic thrombocytopenic purpura and related disorders. *Kidney Int* 2006;70(3):423-31.
- Sarıçoban Ercan H, Özen AO, Bakar F, Karatepe HÖ, Berber M, Gülcan EM, et al. [Prognostic factors in rotavirus and adenovirus gastroenteritis: Which tests are predictive?] *Turkiye Klinikleri J Pediatr* 2011;20(4):267-74.
- Hung LC, Wong SL, Chan LG, Rosli R, Ng AN, Bresee JS. Epidemiology and strain characterization of rotavirus diarrhea in Malaysia. *Int J Infect Dis* 2006;10(6):470-4.
- Dolgikh TI, Kaftyreva LA, Voïtovich MA, Podkolzin AT, Galileïskaia SB, Lazareva LI. [Verotoxin as a major laboratory criterion for *Escherichia coli* O157-induced enteric infection complicated by hemolytic uremic syndrome in infants in the Omsk region]. *Klin Lab Diagn* 2010;(8):52-3.
- Bendall RP, Gray JJ. Haemorrhagic colitis and haemolytic-uraemic syndrome: false positive reaction with a rotavirus latex agglutination test. *J Clin Pathol* 1991;44(7):609-10.
- Klein PJ, Bulla M, Newman RA, Müller P, Uhlenbruck G, Schaefer HE, et al. Thomsen-Friedenreich antigen in haemolytic-uraemic syndrome. *Lancet* 1977;2(8046):1024-5.
- Mead PS, Griffin PM. *Escherichia coli* O157:H7. *Lancet* 1998;352(9135):1207-12.
- Siegler RL. The hemolytic uremic syndrome. *Pediatr Clin North Am* 1995;42(6):1505-29.
- Raboni SM, Nogueira MB, Hakim VM, Torrecilha VT, Lerner H, Tsuchiya LR. Comparison of latex agglutination with enzyme immunoassay for detection of rotavirus in fecal specimens. *Am J Clin Pathol* 2002;117(3):392-4.
- Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. *Rev Med Virol* 2005;15(1):29-56.
- Cataloluk O, Iturriza M, Gray J. Molecular characterization of rotaviruses circulating in the population in Turkey. *Epidemiol Infect* 2005;133(4):673-8.