

# Development of Hemolytic Uremic Syndrome in Renal Transplant Recipient due to Typhoid Fever: A Case Report and Brief Summary of the Literature

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## ABSTRACT

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. Typhoid fever caused by *Salmonella typhi*, a systemic infectious disease that can affect several organs, is rarely encountered in clinical practice. Due to developments in the food industry, endemic typhoid fever as a result of *Salmonella* bacteremia has been reduced. However, it can have a high mortality and morbidity if left untreated, especially in high-risk groups. Presently described is the case of a 31-year-old kidney transplant patient who presented with diarrhea, a skin rash, macroscopic hematuria, oliguria, microangiopathic hemolytic anemia, and *Salmonella typhi* cultivated in blood cultures. To our knowledge, this is the first case of HUS due to typhoid fever in a renal transplant recipient to be reported in the literature.

## INTRODUCTION

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The most common cause of HUS is Shiga toxin-producing *Escherichia coli* (STEC). Traditionally, HUS has been divided into diarrhea-positive and diar-

rhea-negative HUS. The former, also referred to as typical HUS, primarily resulted from STEC infections, and less frequently from *Shigella dysenteriae* type I infection. All other causes of HUS were referred to as atypical HUS or were assigned to the diarrhea-negative HUS category, even though some patients with non-STEC HUS presented with diarrhea.<sup>[1]</sup>

*Salmonella* can cause bacteremia, or, rarely, HUS, in renal transplant recipients. Due to developments in the food industry, endemic typhoid fever as a result of *Salmonella* bacteremia has not been seen in recent years as it had been previously. Nonetheless, it can lead to morbidity and mortality, especially in immunocompromised patients. The present report describes a unique case of typhoid fever that caused HUS in a renal transplant recipient. To the best of our knowledge, this is the first such case in the literature.

## CASE REPORT

A 31-year-old male patient was admitted to the hospital with a high fever, diarrhea, macroscopic hematuria, oliguria, dysuria, nausea, and fatigue. Four years earlier his mother had been a donor for a renal transplantation, due to chronic kidney disease (unknown etiology). The patient was admitted due to concern about losing the transplanted kidney. At the time, he was taking tacrolimus 1x1 mg, mycophenolate mofetil 2x1 g, and prednisolone 5 mg. He was hospitalized in the nephrology clinic with the diagnosis of pyelonephritis, gastroenteritis, and acute kidney injury (allograft rejection). A physical examination revealed a maculopapular rash that was a few millimeters wide in size at the upper section of the abdomen, which faded on pressure (rose spots) and splenomegaly. The patient's vital signs were recorded as a body temperature of 39°C, a heart rate of 82 beats/minute, and a blood pressure of 150/90 mm/Hg. Other system examinations were normal.

Laboratory test results were as follows: white blood cell count: 23,050/mm<sup>3</sup> (polymorphonuclear leukocytes 84%, lymphocytes 8%), hemoglobin: 12.1 mg/dL (decreased from 15 mg/dL) hematocrit: 34% (decreased from 43.4%) platelet count: 104,000/mm<sup>3</sup> (previously 289,000/mm<sup>3</sup>), creatinine: 6.51 mg/dL (baseline creatinine 2 mg/dL), blood urea nitrogen: 61 mg/dL, and lactate dehydrogenase: 780 IU/L. Urinalysis revealed 584 erythrocytes and 747 leukocytes per high power field. A peripheral blood smear revealed fragmented erythrocytes (acanthocytes, schistocytes, poikilocytosis), which were considered signs of microangiopathic hemolytic anemia, leukocytosis dominated by PNL, not enough platelets, and platelet clumps bulged and individual.

The patient had bradycardia, gastroenteritis, rose spots, fever, splenomegaly, and was prediagnosed with typhoid fever. Broad-spectrum antibiotic treatment was initiated for this immunocompromised patient. Stool microscopy revealed no erythrocytes and few leukocytes; stool cultures were negative. The patient had sterile pyuria; the 24-hour urine volume recorded was 100 mL. A renal biopsy was planned to exclude allograft dysfunction, but was refused by the patient. Polyomavirus DNA and cytomegalovirus DNA were negative causes of allograft dys-

function. On the fifth day of hospitalization, *Salmonella typhi* was isolated from both blood cultures. Antibiotherapy treatment was replaced with imipenem. No growth was observed in repeated blood cultures, and the diarrhea and fever subsided. Antibiotherapy was discontinued after 14 days of treatment. The patient was discharged from the hospital after improvement was seen in his clinical and laboratory results.

## DISCUSSION

*Salmonella* bacteremia is rarely encountered in clinical practice. However, it can lead to high mortality and morbidity if left untreated, especially in high-risk groups. Three clinical patterns of infection are recognized: 1) enteric fever, 2) acute enterocolitis, and 3) bacteremia and focal lesions.

Typhoid fever is a systemic infectious disease, which can affect numerous organs. Complications occur in 10% to 15% of typhoid patients.<sup>[2]</sup> Most frequently, gastrointestinal bleeding and intestinal perforation are seen; renal manifestations are rare, occurring in only 2% to 3% of patients.<sup>[3]</sup> A review of the literature reveals occasional reports of renal manifestations of typhoid fever, including acute, transient, and reversible glomerulonephritis with proteinuria or hematuria,<sup>[4]</sup> immunoglobulin A nephropathy,<sup>[5]</sup> HUS,<sup>[6]</sup> Henoch-Schonlein purpura,<sup>[7]</sup> acute interstitial nephritis,<sup>[8]</sup> and nephrotic syndrome.<sup>[6]</sup>

The term thrombotic microangiopathy (TMA) encompasses different disturbances, usually classified as thrombotic thrombocytopenic purpura (TTP) or HUS. These syndromes are characterized by thrombocytopenia, macroangiopathic hemolytic anemia, neurological deficits, and renal failure. The etiology of TMA may include exotoxins, drug toxicity (cyclosporin, tacrolimus, ticlopidine, clopidogrel, mitomycin), and familial conditions associated with a deficiency of factor H (HUS) or the von Willebrand factor, which can lead to TTP. TMA in renal transplant recipients may reflect de novo conditions, or may represent recurrence in patients diagnosed with TMA as the primary renal disease.<sup>[9]</sup>

Although HUS is associated with various infectious agents, and occasionally *Salmonella* infections, the role of *Salmonella* in the pathogenesis of HUS is uncertain. Besides cell wall lipopolysaccharide of salmonellae as gram (-) microorganism by affecting pyrogenic endotoxin is the cause of symptoms and findings of disease. The presence of endotoxins can lead to the development of HUS: a direct injury to glomerular endothelial cells may indirectly lead to the secretion of cytokines, such as tumor necrosis factor, interleukin-6, and interleukin-8. As a result of the interaction of leukocytes and coagulation, the activation of a platelet cascade and renal vasoconstriction may occur.<sup>[6]</sup>

Basić-Jukić et al.<sup>[9]</sup> presented a case of thrombotic microangiopathy that occurred 3 years after a kidney transplant in which, despite plasma exchange therapy and the discontinuation of cyclosporine, the patient was enrolled in a dialysis program due to deterioration in graft function.<sup>[9]</sup> In our patient, we also considered calcineurin-inhibitor usage as a potential cause of HUS; however, the tacrolimus level in the blood was normal, and the patient responded to intravenous volume replacement and antibiotic therapy. There was no need for dialysis.

Arslan et al.<sup>[10]</sup> investigated diarrhea episodes in 43 patients with a solid organ transplantation. In all, 77% were caused by infectious agents (*Salmonella enteritis* was isolated in only 1 case) and 24% were caused by prescription drug usage, including drugs such as colchicine, mycophenolate mofetil, laxatives, and antibiotics.

Leukopenia is common in *Salmonella* infections; however, in our case, leukocytosis was also observed. The presence of leukocytosis in typhoid fever suggests a complication and should alert practitioners to the possibility of HUS. Baker et al.<sup>[6]</sup> reported that HUS developed in 6 of 48 patients with typhoid infection and concluded that glomerular microangiopathy caused by an endotoxin of *Salmonella typhi* was the pathogenesis. Similarly, Lwanga and Wing reported a case of typhoid fever followed by oliguric renal failure and intravascular hemolysis.

Thirty *Salmonella* bacteremia cases in renal transplant recipients in the literature were reviewed. The causes of salmonellosis in renal transplant recipients were more serious than in non-compromised patients, as 70% were complicated with bacteremia. However, no cases of HUS were observed. Renal transplant recipients have a prolonged carrier state and frequent relapses or recurrences of salmonellosis. Some 45% of the *Salmonella* bacteremia seen in renal transplant recipients is observed after a high dose of methylprednisolone for graft rejection episodes.<sup>[11]</sup>

Chloramphenicol and ampicillin have traditionally been used to treat typhoid fever for many years; however, they are now used less often as a result of multidrug-resistant *Salmonella enterica* serotype *typhi*. Fluoroquinolones have been the first-line choice of drug treatment for typhoid fever, as they are the most effective; however, quinolone-resistant strains have been reported, especially in developing countries, since the 1990s.<sup>[12]</sup>

Since typhoid fever is only transmitted by humans, the incidence of the disease gradually decreases with improved sanitary conditions. A history of travel to endemic regions is important in patients with typhoid fever. In this case, however, our patient had no history of travel to an endemic region. He may have ingested food or water contaminated by fecal or urinary carriers.<sup>[13]</sup>

The urinary tract is the most common source of infection

in renal transplant recipients. Chronic and recurrent urinary tract infections after renal transplantation remain a major challenge, and the most important reason is thought to be structural anomalies. In a study, 19 patients with a urinary tract infection caused by *Salmonella* species were reported to have a chronic disease, such as diabetes mellitus or urological anomalies like nephrolithiasis.<sup>[14]</sup> Mathai et al.<sup>[15]</sup> followed 18 patients with *S. typhi* bacteriuria for 5 years. Fourteen patients had a localized urinary tract infection due to *S. typhi*. Four others had bacteriuria, probably associated with typhoid fever. Only 1 of these patients was a renal transplant recipient.

*Salmonella* can cause bacteremia, or, rarely, HUS, in renal transplant recipients. Before transplantation, recipients and donors should have urine and stool cultures analyzed for evidence of active infection or as a carrier for *Salmonella*. Eradication therapy should be provided if the results of cultures are positive for *Salmonella*. In renal transplant patients who present with symptoms like hematuria, diarrhea, and fever; HUS caused by *Salmonella typhi* bacteremia should be considered in the differential diagnosis with other opportunistic infections. This case report is offered as a supplement to the literature regarding typhoid fever associated with HUS in renal transplant recipients.

#### Informed Consent

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

#### Peer-review

Internally peer-reviewed.

#### Authorship Contributions

Concept: Y.Ö.; Design: Y.Ö.; Data collection &/or processing: Z.E.D.; Analysis and/or interpretation: Y.Ö., M.G.; Literature search: S.T.; Writing: Y.Ö., Y.K.; Critical review: G.Ş.

#### Conflict of Interest

None.

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### Transplante Böbrekte Hemolitik Üremik Sendrom Gelişimi: Tifoid Ateş; Olgu Sunumu Nedeniyle Literatürün Gözden Geçirilmesi

Hemolitik üremik sendrom (HÜS) mikroanjiopatik hemolitik anemi, trombositopeni ve akut böbrek hasarı ile karakterize bir sendromdur. Tifoid ateş ise, klinik pratikte nadir görülen fakat birçok organı etkileyebilen *Salmonella* tifoynun sebep olduğu sistemik bir enfeksiyon hastalığıdır. Gıda teknolojisindeki gelişmeler sonucu geçmiş yıllarda görülen endemiler görülmemekle birlikte immünsistemin baskılandığı durumlarda *Salmonella* bakteriyemisi (tifoid ateş) görülebilmekte ve komplikasyonlara yol açabilmektedir. Tedavisiz kaldığı takdirde özellikle yüksek riskli guruplarda yüksek morbidite ve mortaliteye sebep olabileceği için dikkate değerdir. Biz burada ishal, idrar miktarında azalma ve vücudunda döküntü şikayetiyle başvuran, makroskopik hematürisi, oligürisi, mikroanjiopatik hemolitik anemisi olan ve kan kültürlerinde *Salmonella typhi* üremesi olan 31 yaşında böbrek nakilli hasta sunduk. Literatürde transplante böbrekte tifoid ateşe bağlı olarak gelişen ilk hemolitik üremik sendrom olgusu olması nedeniyle sunuma layık görüldü.

**Anahtar Sözcükler:** Böbrek transplantasyonu; hemolitik üremik sendrom; Salmonella; tifoid ateş.