Dear Editor,

Salmonella infections are observed frequently in the childhood age group and mostly characterized with gastrointestinal findings. Extraintestinal involvement is observed rarely (8%) (1). Renal involvement has been defined in approximately 3% of the patients. Pyelonephritis, cystitis, hemolytic uremic syndrome, acute renal failure and rarely glomerulonephritis have been reported as urinary system involvement (2-4). Hemophagocytic lymphohistiocytosis (HLH) is a condition characterized by fever, pancytopenia, hyperferritinemia, hypertriglyceridemia and hemophagocytosis in the bone marrow (5). Hemophagocytic lymphohistiocytosis may be primary (familial) or may develop secondary to many infectious agents. Salmonella-related HLH has been reported considerably rarely (5, 6). Here, a 13-year old girl who developed both acute glomerulonephritis and hemophagocytic lymphohistiocytosis in relation with Salmonella spp has been reported. Association of glomerulonephritis and HLH in relation with salmonella infection has not been described before in the literature.

A 13-year old female patient presented with the complaints of fever, nausea, vomiting, headache, abdominal pain, malaise and fatigue which had been continuing for four days and was hospitalized for performing investigations and administering treatment. Physical examination findings were as follows: general status: moderate, consciousness: open, body temperature: 39.5°C, pulse rate: 100/min, respiratory rate: 24/min, blood pressure: 95/60 mmHg. Abdominal examination revealed diffuse tenderness. Laboratory findings were as follows: hemoglobin: 128 g/dL, white blood cells: 1700/μL (absolute neutrophil count 1 200/μL), plaletes: 92 000/μL; C-reactive protein: 161 mg/L (distribution 0-5), erythrocyte sedimentation rate: 40 mm/h, blood urea nitrogen: 10 mg/dL, creatinine: 0.47 mg/dL, urinary density: 1025, pH 6.5, protein +3, leukocyte (-); urinary sediment: 10 leukocytes, 214 erythrocytes; spot urinary protein/creatinine ratio: 1.2 mg/mg (normal <0.2). Systemic infection and glomerulonephritis were considered with these findings. Peripheral blood smear revealed shift to the left, plasma cell, toxic granulation and toxic vacuolization. Intravenous ceftriaxon at a dose of 100 mg/kg/day was initiated after blood, urine and stool cultures were obtained. The serum C3 level was found to be low (77 mg/dL; normal 90-180) and C4 level was found to be normal (16 mg/dL; normal 10-40). ANA was found to be negative. In the follow-up, oliguria, edema or hypertension did not develop. Marked megaloblastic changes especially in the myeloid series, plasma cell, marked increase in the number of hystiocytes and a high number of hemofagocytes were observed on bone marrow aspiration biopsy which was performed on the second day of hospitalization because of bicytopenia. The levels of ferritin (774 ng/mL; normal 11-306), LDH (418 U/L) and trygliceride (237 mg/ dL) were found to be increased. On the same day, a reduced hemoglobin level (10.7 g/dL) accompanied with neutropenia and thrombocytopenia in addition to deteriorated general status and fever which exceeded 39°C were observed. Thus, HLH secondary to infection was considered and intravenous immunoglobulin at a dose of 1 g/kg/day was administered for two days. Abdominal and pelvic ultrasonography revealed splenomegaly and multiple lymph nodes the largest one reaching a size of 12 mm in the right lower quadrant. No growth occurred in urine and stool cultures; viral serology (hepatitis viruses, Ebstein Barr virus, TORCH) and Brucella antibodies were found to be negative; Salmonella spp was grown in blood culture. On the third day of treatment, fever subsided, the
hematological values returned to normal and acute phase reactants were decreased. No growth was found in the follow-up blood culture and treatment was completed to 14 days. The serum complement levels were found to be normal before discharge.

Salmonellosis is a condition which is observed commonly worldwide and frequently characterized by gastrointestinal findings. In addition to diarrhea, it may lead to extraintestinal infections including enteric fever, sepsis and rarely aseptic meningitis, hepatitis, cholecystitis, acute abdomen, intestinal perforation, pneumonia, psychosis and ataxia (1, 6-8). Fever, headache, abdominal pain and gastrointestinal complaints including loss of appetite, nausea, vomiting and constipation are observed in the first weeks of typhoid fever related with Salmonella typhi, whereas bradycardia, hepatomegaly, splenomegaly and abdominal tenderness develop in the second week. Presence of fever, abdominal pain and mesenteric lymph nodes in our patient suggested the diagnosis of enteric fever and the diagnosis was confirmed when Salmonella Typhi was grown in blood culture.

Acute glomerulonephritis may be clinical presentation of typhoid fever or may be observed as a late complication. The severity of involvement may range from complete recovery to mortality (2, 3). In one study which compared the patients who did and did not develop glomerulonephritis during the course of salmonella infection, a reduction in the C3 level was found in 86% of the subjects who developed glomerulonephritis, while serum complement levels were found to be normal in the subjects who did not develop glomerulonephritis (9). However, some studies found serum complement levels to be normal in patients with salmonella-related glomerulonephritis. It is thought that immune complex mediated glomerular injury occurs in salmonella-related glomerulonephritis (9). Diffuse proliferative glomerulonephritis has been defined on light microscopic examination of renal biopsy materials and immunoglobulin, C3 and Salmonella Typhi Vi antigens have been detected on immunoflorescent examination. Histopathological examination is not necessary in all patients, but it may be performed in patients with a suspicious diagnosis of glomerulonephritis or in cases where differential diagnosis with IgA nephropathy is required. The clinical and laboratory findings of our patient left no room for doubt in the diagnosis and histopathological examination was not needed, because the clinical findings and serum complement levels returned to normal.

The prognosis of the patients with typhoid fever-related glomerulonephritis is usually favourable. Although mortality has been reported very rarely, complete recovery is mostly observed without sequelae in the long-term. However, it has been reported that the mortality rates reach up to 30%, if patients are not treated. Our patient had a mild clinical picture of glomerulonephritis and did not develop oliguria, hypertension and azotemia. The signs regressed rapidly with early and efficient treatment of infection.

In countries where salmonella infections occur frequently including our country, awareness of extraintestinal complications of the disease is important in terms of early diagnosis and efficient treatment. It was aimed to remind that infectious diseases may cause to renal involvement or renal findings may be caused by systemic infection and to emphasize that early recognition of the findings and taking the necessary precautions decrease the morbidity and mortality rates.

Hemophagocytic lymphohistiocytosis is an inflammatory syndrome characterized by excessive action of macrophages and T lymphocytes (5). Familial HLH is transmitted through autosomal dominant inheritance and is substantially fatal in young children. Secondary HLH is observed during the course of many infections or malignancies. Salmonella is considerably rare among the infectious agents which have been reported (6).

Parenteral ceftiraxone is generally sufficient for microbial elimination in treatment of enteric fever. In acute glomerulonephritis, early diagnosis and close monitoring and ensuring fluid-electrolyte balance may be sufficient to prevent potential negative outcomes. Immunosuppressive drugs including steroid, cyclosporine and etoposide may be required for hemophagocytic lymphohistiocytosis. In our case, early diagnosis and treatment of infection prevented progression of HLH. The clinical and laboratory findings of the patient was controlled with antimicrobial and supportive treatment alone.

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**References**