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Case Report

A pediatric case with hemolytic uremic syndrome associated with COVID-19, which progressed to end-stage kidney disease

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ABSTRACT

Background. Hemolytic uremic syndrome (HUS) is a serious cause of acute kidney injury in children. There is a suggestion that coronavirus disease 2019 (COVID-19) may be a trigger for HUS. In this study, we present a pediatric case diagnosed with HUS associated with COVID-19, which progressed to end-stage kidney disease.

Case. A previously healthy 13-year-old girl with fever and vomiting was referred to our hospital. Laboratory investigations revealed direct Coombs-negative hemolytic anemia, thrombocytopenia and renal impairment accompanied by COVID-19 infection. Although anemia and thrombocytopenia showed improvement on the seventh day after admission, the renal impairment persisted. The histopathological findings of a renal biopsy were compatible with both HUS and COVID-19. One month later, the patient had a recurrence of HUS, again testing positive for COVID-19. Kidney function improved with plasma exchange therapy. Eculizumab treatment was recommenced after COVID-19 PCR became negative. Anemia and thrombocytopenia did not recur with eculizumab, while renal impairment persisted. Eculizumab was discontinued after three months when genetic analysis for HUS was negative. Subsequently, the patient was diagnosed with end-stage kidney disease.

Conclusions. COVID-19 can be associated with HUS relapses, leading to chronic kidney disease. Further studies should investigate the mechanism of HUS associated with COVID-19.

Key words: COVID-19, chronic kidney disease, hemolytic uremic syndrome, SARS-CoV-2.

Coronavirus disease 2019 (COVID-19) emerged as a public health problem in 2019. Although COVID-19 primarily affects the lower respiratory tract, it has also been associated with a prothrombotic state that increases the risk of thrombotic microangiopathies such as hemolytic uremic syndrome (HUS).[1] The exact mechanism behind COVID-19 triggering HUS is unknown, although some theories have been proposed.[2] COVID-19 may cause endothelial injury and endotheliitis, leading to HUS. Accordingly, the effect may not be associated only with the direct cytopathic effect of the virus, as the subsequent inflammatory response may also contribute to the development of HUS.[3] Complement activation by COVID-19 is another potential underlying mechanism leading to HUS. The spike protein can directly induce an alternative complement pathway.[4] These findings are supported by the effectiveness of eculizumab (anti-C5 monoclonal antibody) treatment in patients with HUS triggered by COVID-19.[2,5,6]

In the current study, we present a pediatric case diagnosed with HUS associated with COVID-19, which subsequently progressed to end-stage kidney disease.

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Case Report

A previously healthy 13-year-old girl was admitted to the pediatric emergency service of another center with complaints of vomiting and fever for a week. She had pretibial edema and tachycardia. Her anthropometric measurements were within the normal range. Her laboratory results revealed renal failure (urea: 103 mg/dl, creatinine: 6.5 mg/dl) and proteinuria (3.4 g/m^2/d) on admission and mild anemia (Hgb: 10 gr/dl) with a normal platelet count. She underwent hemodialysis and received antibiotic treatment (tazobactam and ceftriaxone).

On the seventh day of hospitalization, she was referred to our center to investigate the etiology of renal failure. On admission, she had fever (38.2°C), tachycardia (124/min) and hypertension (159/100 mmHg). There were no symptoms of diarrhea, respiratory distress, oliguria or hematuria. The patient had periorbital and pretibial edema. Her laboratory results showed Coombs-negative hemolytic anemia and thrombocytopenia accompanied by increased lactate dehydrogenase (LDH) and low haptoglobin levels (Table I). She had renal failure, proteinuria (3+) and hemoglobinuria. Myoglobin and creatine kinase levels were within the normal range. Renal ultrasonography revealed normal kidney length with increased echogenicity. SARS-CoV-2 PCR was positive, so she was hospitalized in the COVID-19 unit. Cyanocobalamin was initiated for vitamin B12 deficiency [Vit B12: 158 (182-820) ng/ml]. Due to hyperparathyroidism [PTH: 700 (12-88) pg/ml] and vitamin D deficiency [Vit D: 12 (>30 μg/L)], 25-OH-D_3 and calcitriol were initiated. Serum homocysteine and urine methylmalonic acid levels were within the normal range. Complement levels, pANCA, cANCA, and anti-glomerular basement membrane antibody levels were within the reference range. Antinuclear antibody was negative. ADAMTS13 activity was normal (94%). Urine output was normal (1.3 ml/kg/hr). She continued hemodialysis due to edema and hypertension. Enalapril, doxazosin, amlodipine and furosemide treatments were initiated gradually for hypertension. On the seventh day of hospitalization, thrombocytopenia and hemolysis improved. Enoxaparin sodium was initiated due to an increased level of D-dimer and COVID-19 positivity. Methylprednisolone was started due to nephrotic syndrome. On the 12th day, COVID-19 PCR was found to be negative, and on the 18th day, the patient underwent renal biopsy, which revealed glomerular capillary obliteration, fibrin thrombi, and glomerular basement membrane duplication on light microscopy, consistent with the histopathological findings of HUS. In addition, tubular epithelial nucleus hypertrophy and an atypical appearance were detected, consistent with COVID-19 histopathological findings (Fig. 1). Thickening of arteriolar walls was observed, but there was no interstitial fibrosis. Immunofluorescence microscopy revealed mild staining with IgM and C3, leading to the diagnosis of HUS associated with COVID-19. Electron microscopy could not be evaluated due to degeneration in the glomeruli. Anti-complement factor H antibody levels were

Table I. Laboratory parameters of the patient.

Parameters (reference values)	On admission	At discharge (28th day)	2 weeks after discharge	Latest control values (six months after transplantation)
Urea (10-38 mg/dl)	103	156	122	19
Creatinine (0.5-0.9 mg/dl)	6.5	6.6	6.4	0.67
Albumin (32-45 g/L)	24	28	32	43
Hemoglobin (11.7-15.3 g/dl)	7.1	10.2	7.2	14.0
Platelet count (150-400X10^3/μL)	98	197	138	281
LDH (120-300 U/L)	495	216	498	177
Haptoglobin (0.3-2 g/L)	0.17	0.96	0.04	0.47

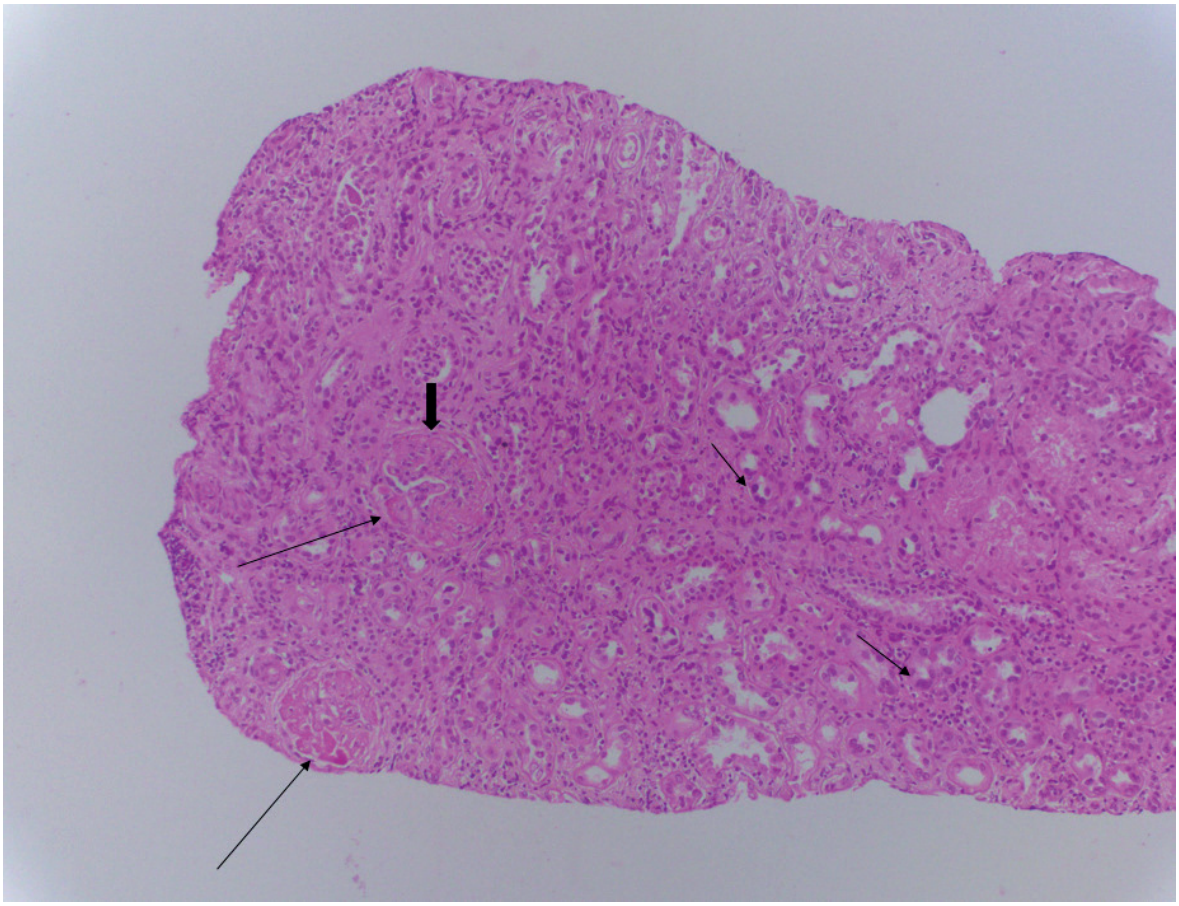

Fig. 1. Fibrin thrombus in the glomerulus (long thin arrows), capillary obliteration (short thick arrow), and nuclear atypia (short thin arrows) in tubulus epithelial cells (H&E).

within the normal range and the genetic panel for HUS (*CD46, CFH, CFHR5, CFI, C3, DGKE, THBD*) was negative. The steroid dose was tapered and the patient was discharged on the 28th day for treatment with hemodialysis three days a week.

One month after discharge, she was admitted to the pediatric nephrology clinic with no complaints. The periorbital and pretibial edema continued and she had hypertension. Laboratory results revealed hemolytic anemia with the presence of schistocytes, thrombocytopenia and renal failure consistent with HUS relapse (Table I). Eculizumab (anti-C5a monoclonal antibody therapy, 900 mg/4 weeks) was initiated. While there was no significant decrease in hemoglobin levels, the platelet counts decreased despite eculizumab therapy. In the search for other causes of thrombocytopenia, her COVID-19 PCR was positive again after four weeks, although she had no complaints. Therefore, eculizumab treatment was abandoned. Viral genome sequencing tests to distinguish between reactivation or reinfection with COVID-19 could not be performed due to the unavailability of this test. Plasma exchange was performed five times with one-day intervals, leading to an increase in the platelet count to 124×10^3/μL. Eculizumab treatment was recommenced two weeks later. Although the platelet counts remained within the normal range, the renal functions did not improve within three months of eculizumab therapy. The patient underwent renal transplantation from her mother due to end-stage kidney disease. Her renal functions and hematologic parameters were within the normal range at her last visit six months after

transplantation (Table I). An informed consent was obtained from the family for the publication of this case report.

Discussion

The case presented suffered two HUS relapses associated with the COVID-19 infection. Despite eculizumab and plasma therapy, her renal functions did not improve and she developed chronic kidney disease. This led us to consider the possibility that COVID-19 was a contributing factor to chronic kidney disease in addition to the HUS relapses.

At the time of admission to our center for further investigation, she had undergone hemodialysis in another center and was being treated with antibiotics (tazobactam and ceftriaxone). The initial clinical presentation was acute, her growth was within the normal range and renal ultrasonography revealed normal renal lengths. This led us to consider the development of acute kidney injury. We attributed hyperparathyroidism in this patient to vitamin D deficiency rather than chronic kidney disease. Our presumed diagnoses for the etiology of acute kidney injury included HUS, crescentic glomerulonephritis and acute tubulointerstitial nephritis (ATIN). There was a strong suspicion of HUS based on the clinical and laboratory findings, including direct Coombs-negative hemolytic anemia, thrombocytopenia and renal failure. Although the rapid deterioration in renal function was initially considered related to crescentic glomerulonephritis, acute tubulointerstitial nephritis was also a possible diagnosis. This consideration was based on her urine microscopy findings being inconsistent with glomerulonephritis, the absence of oliguria and the presence of COVID-19 infection. The renal biopsy findings were consistent with HUS and featured a tubular atypia appearance associated with COVID-19. We could not show the presence of COVID-19 due to the absence of specific staining. However, acute kidney injury was evidenced by the absence of interstitial fibrosis.

SARS-CoV-2 infection was reported to be a trigger for atypical HUS in children in a review.[7] Additional evidence has shown that COVID-19 may activate an alternative complement pathway, proven by the deposition of mannose-binding lectin (MBL), mannose-associated serine protease 2 (MASP2) and C3b, C4b and C5b-9 on the endothelial cells of patients with COVID-19-associated thrombosis.[8] Eculizumab treatment can thus be considered an effective treatment option in patients with HUS triggered by COVID-19. Numerous adult cases are extensively detailed in the literature[2,5,9,10] but only five pediatric HUS cases are associated with COVID-19 infection.[6,11-13] One of the pediatric cases was a 14-year-old female patient presenting with fever, abdominal pain, diarrhea and SARS CoV-2 PCR positivity.[6] She developed myocarditis, coronary artery ectasia, Coombs (-) hemolytic anemia, thrombocytopenia and acute kidney injury. The patient was initiated on continuous renal replacement therapy (CRRT) on the 10th day, and on eculizumab on the 14th day. Following the first dose of eculizumab, there was no need for CRRT and renal functions showed improvement at three weeks. Another case was a 16-month-old male with a history of intrauterine growth retardation, microcephalia, and corpus callosum agenesis.[13] He was admitted to the hospital presenting with fever, vomiting and respiratory distress, testing positive for SARS-CoV-2 PCR. He developed diabetic ketoacidosis, nephrotic range proteinuria and persistent hypertension. On the 11th day of hospitalization, he developed HUS. Following the first dose of eculizumab, anemia and thrombocytopenia showed improvement. His renal functions improved at 21 days. Dalkıran et al.[11] reported a 3-year-old pediatric case presenting with respiratory distress, fever and COVID-19 PCR positivity. On the 10th day, the patient developed HUS and was initiated on hemodialysis and plasmapheresis. Hemolysis and renal functions were improved on the 6th and 28th days of plasmapheresis, respectively. Nomura et al.[12] reported five pediatric patients with COVID-19 and kidney dysfunction, of whom two presented with HUS

and diarrhea (6- and 9-year-old males). One of them received multiple therapies, including steroids, plasmapheresis, and IVIG. However, he became dialysis dependent at seven months. The other patient received only supportive care and developed chronic kidney disease at three months.[12] Eculizumab (anti-C5 monoclonal antibody) therapy was a successful treatment option in the reported cases.[6,11,13] Therefore, we opted to initiate eculizumab therapy. After four weeks of eculizumab treatment, the platelet counts decreased, but the patient tested positive for COVID-19 again. Platelet count showed improvement under plasma exchange therapy. Platelet counts remained within the normal range and hemolytic anemia did not develop under eculizumab therapy. However, renal functions did not show improvement.

Vrečko et al.[10] reported 28 adult cases with HUS, 15 of whom received therapeutic plasma exchange (TPE) with or without steroids as initial therapy, resulting in improvement in six patients. Sixteen patients received eculizumab therapy (as monotherapy or after the failure of TPE ± steroids to improve the condition). The renal functions of 10 patients who received eculizumab therapy improved, while six did not, similar to those of our patient. She had nephrotic range proteinuria, which could lead to insufficient plasma levels of eculizumab. C5 polymorphism was associated with nonresponsiveness to eculizumab therapy in patients with atypical HUS in Asian and Japanese people.[14] However, we were unable to evaluate these genetic changes.

When the patient's genetic analysis for HUS was negative, as reported, eculizumab therapy was discontinued. After her kidney impairment remained for six months, she was diagnosed with chronic kidney disease.

The majority of patients reported in the literature with HUS triggered by COVID-19 have severe diseases[11-13] and multisystemic diseases such as respiratory distress or cardiac involvement requiring intensive care unit (ICU) admission. In contrast to previous studies, our patient had a mild disease without systemic involvement or ICU requirement. Other differences from the reported cases included the absence of oliguria and active urine sediment.

In conclusion, COVID-19 can be associated with HUS, leading to end-stage renal disease. However, further studies are needed to assess the mechanisms leading to HUS to support the treatment of patients with COVID-19.

Ethical approval

We obtained informed consent from the patient's family.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SSD, EDV, YYK, FD, AD, BÖÖ; data collection: EDV, BÖÖ, FD; analysis and interpretation of results: SSD, YYK, AD; draft manuscript preparation: SSD, EDV, BÖÖ, AD, FD, YYK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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