Case Report
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Hemolytic Uremic Syndrome Following Influenza A (H1N1) pdm09 Virus in a 14-Month-Old Girl

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Abstract
Hemolytic Uremic Syndrome (HUS) is characterized by the clinical triad of microangiopathic non-immune hemolytic anemia, thrombocytopenia, and acute renal failure. There are infections, genetic causes, malignancies, autoimmune diseases, drugs, and many unexplained causes in the etiology of HUS. The most common cause of HUS in children is Shiga toxin-producing Escherichia coli (STEC). In the literature, few influenza A (H1N1) pdm09 virus-related HUS cases are reported. In this case report, a case with hemolytic uremic syndrome associated with influenza A (H1N1) pdm09 virus infection is presented.

Keywords: Influenza A (H1N1) pdm09; Hemolytic Uremic Syndrome; Nephrotic Syndrome.

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Introduction
Hemolytic uremic syndrome (HUS) is a disease characterized by microangiopathic non-immune hemolytic anemia, thrombocytopenia, and acute renal failure (1). Many factors can cause HUS. Shiga toxin-producing *E. coli* is the most common cause of HUS in children (2). Another infection, influenza, can also cause HUS (3). Although influenza infection is generally seen as a self-limiting infection, it can also progress with complications. Complications of the influenza virus have been reported as pneumonia, myocarditis, myositis, rhabdomyolysis, neurological complications, and renal involvement (4-7). HUS, one of the renal complications, has been reported in a few patients in the literature (8-14).
In this article, we describe a 14-month-old girl who presented with HUS triggered by an influenza A (H1N1) pdm09 virus infection.

Case report
A 14-month-old female was admitted to our hospital with non-bloody diarrhea, oliguria (0.8 cc/kg/hour), vomiting, and fever. On the first examination, the patient was febrile (38.0˚C) and tachycardic (160 beats/minute) with a respiratory rate of 44/min and blood pressure of 94/64 mmHg (50th centile). She was saturating at 100% on room air. Physical examination showed marked edema in the labia majora and periorbital/pretibial area. Laboratory tests were as follows: total leukocyte count: $5.2x10^3$/µL, hemoglobin: 6.5 g/dL, platelet count: $125x10^3$/µL, urea: 32 mg/dL, creatinine: 0.57 mg/dL, serum sodium: 139 mEq/L, serum potassium: 4.2 mEq/L, serum calcium: 8.8 mg/dL, serum phosphorus: 4.3 mg/dL, serum albumin level: 36 g/L, aspartate aminotransferase: 26 U/L, alanine aminotransferase: <5 U/L, lactate dehydrogenase (LDH): 571 U/L, C-reactive protein:

6.7 mg/L, erythrocyte sedimentation rate: 41 mm/hour, cystatin C: 2.3 mg/L, reticulocytosis: 8%. Venous blood gas analysis showed pH: 7.36, partial pressures of oxygen (pO_2): 74 mmHg, carbon dioxide (pCO_2): 27 mmHg, bicarbonate (HCO^{3-}): 15 mmol/L, and lactate: 1 mmoL/L. Serum complement levels and immunoglobulin M (IgM) were within normal limits, haptoglobin (<10 mg/dL), IgG (5.2 g/L), and IgA (<0.278 g/L) were low, and direct coombs was negative. Peripheral blood smear revealed anisocytosis, poikilocytosis, and red blood cell fragmentation. Urine analysis revealed 4+ proteinuria and 4+ blood. Microscopic examination of the urinary sediment showed red blood cells (38/RBCs). The urine protein/creatinine ratio (UPCR) was 18.8 mg/mg. Urine and blood cultures were negative. *E. coli* and *Shigella* were not detected in fecal culture. Viral markers showed past cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections. Her viral serology tests were negative for EBV anti-viral capsid antigen (VCA) IgG/EA, anti-VCA IgM, anti-EBNA-1 IgG, CMV IgM, anti-Hepatitis A virus (HAV) IgM, anti HAV IgG, anti-rubella IgM, herpes simplex virus 1-2 IgG, anti HCV, varicella-zoster virus IgG, Parvovirus B19 IgM, Parvovirus B19 IgG, and anti-human immunodeficiency virus and positive for CMV IgG and anti-rubella IgG. ADAMTS13 was normal (%77). Antinuclear antibodies (ANA), anti-double-stranded DNA, and antinuclear cytoplasmic antibody titers were negative. There was no evidence of a secondary atypic HUS due to autoimmune disease. Cobalamin deficiency was excluded due to normal homocysteine and the absence of methylmalonic acidemia.

Influenza A PCR (FTD Respiratory Pathogens 21, Luxemburg) was positive for H1N1. Chest X-ray was normal. The cause of hemolysis was thought to be related to infection according to the Department of Pediatric Hematology because there was no significant elevation of LDH and kidney function tests or a significant decrease in the platelet count. Oseltamivir treatment was started and continued for 5 days. Amlodipine was started for hypertension (blood pressure: 111/76 mm/Hg). Alpha methyldopa and ramipril were added as blood pressure was not controlled with amlodipine. Although oseltamivir treatment was completed, renal biopsy was performed on the 17th day due to persistent low haptoglobin levels (<10 mg/dL), nephrotic proteinuria (UPCR: 12 mg/mg), and hemolysis (reticulocytosis 5%, LDH: 602 U/L). On day 23 (UPCR: 6.6 mg/mg), steroid treatment was started. Renal biopsy was compatible with TMA (Figure 1).

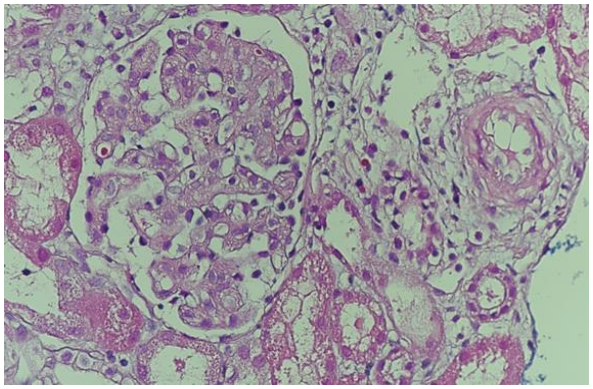

Figure 1. Basal membrane thickening, congestion and ischemic finding

The patient was diagnosed with HUS secondary to H1N1 infection. Laboratory results of the patient revealed LDH: 715 U/L, reticulocytosis 12%, urea: 67 mg/dL, albumin: 31 g/L, and UPCR: 6.6 mg/mg. Plasmapheresis was planned for the patient. However, fresh frozen plasma (FFP) was planned instead of plasmapheresis since the family did not accept the placement of a plasmapheresis catheter. On day 30, she was given FFP infusions (plasma dose was 15 mL/kg-2.5 ml/kg/hour and was given once daily), her laboratory tests were urea: 67 mg/dL, creatinine: 0.22 mg/dL, LDH: 354 U/L, haptoglobin: <10 mg/dL, UPCR: 5.8 mg/mg (Figure 2). Haptoglobin increased to 30 mg/dL on the 2nd day of initiation of FFP infusion.

Fresh frozen plasma was administered every day for 1 week. Then, a total of 13 doses of FFP were administered every other day. Hematological remission (LDH:279 U/L, hemoglobin:10.2 g/dL, haptoglobin:44 mg/dL, reticulocytosis:3%) occurred with FFP infusions but the urea level increased (urea: 97 mg/dl) and nephrotic proteinuria (UPCR: 10.2 mg/mg) and hypertension (116/79 mmHg) were not resolved. With these results, genetic tests were requested for the patient, considering that H1N1 infection might be a trigger for atypical HUS.

However, it was planned to start eculizumab since the results would have been ready with a delay. For this reason, eculizumab treatment was started after

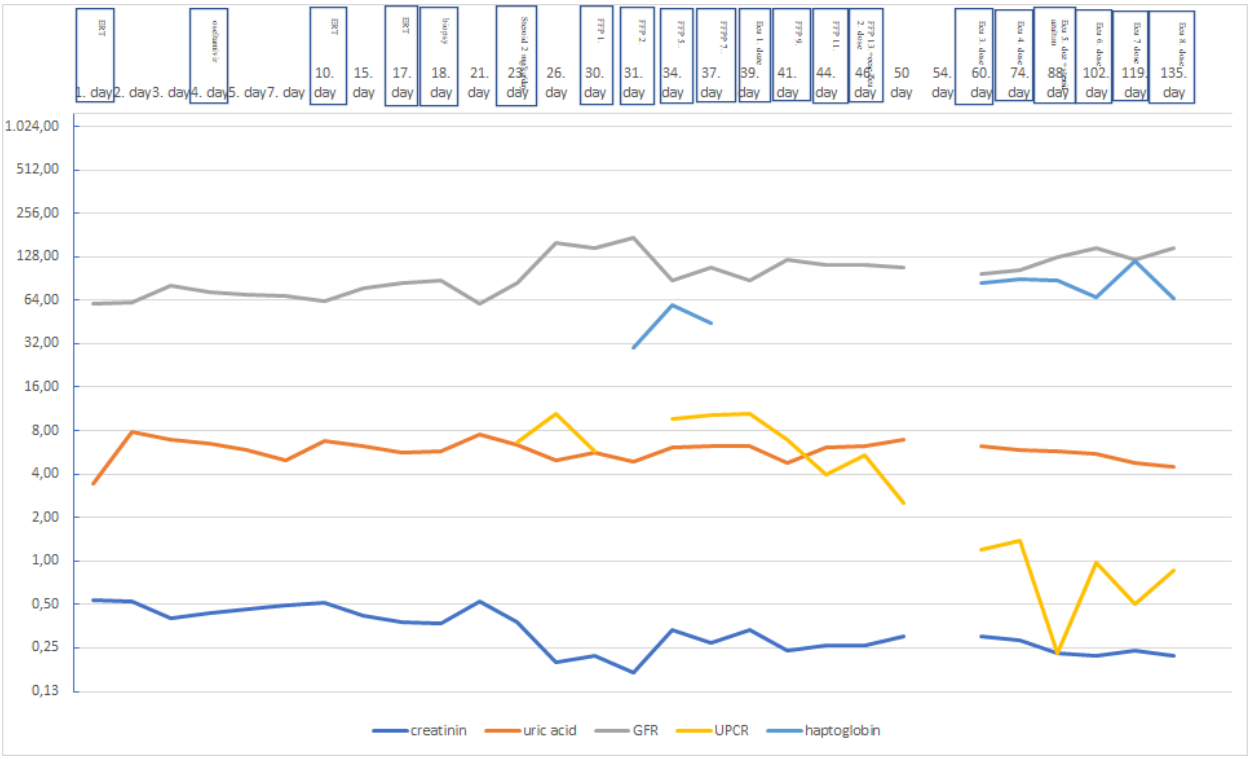

Figure 2. Serial laboratory tests of the patient

meningococcal vaccination against on the 39th day of hospitalization. The patient was discharged on the 50th day (laboratory tests were as follows: urea: 100 mg/dL, creatinine: 0.3 mg/dL, UPCR: 2.5 mg/mg). The results of lab tests on the last follow-up were as follows: urine pr/cr ratio: 0.5, urea: 36 mg/dL, hemoglobin: 10.7 g/dL, LDH: 217 U/L, and haptoglobin: 90 mg/dL. Eculizumab, steroid, antihypertensive treatments are still ongoing. No pathogenic genetic mutations were detected.

Discussion

Complications can be seen rarely in influenza infection. One of the renal complications is HUS. HUS associated with H1N1 has been presented in a few cases (8-14). In our case, ADAMTS13 was normal and therefore thrombotic thrombocytopenic purpura was excluded. E. coli and Shigella were not detected in fecal culture. Chest x-ray was normal, direct coombs was negative, pneumococci were not detected in culture, and pneumococcus was excluded. Serological tests for HIV, hepatitis B, and C, cytomegalovirus, and Epstein-Barr virus were negative and acute infection was ruled out. Malignancy, autoimmune disease, hereditary HUS and hereditary cobalamin metabolism disorders were also excluded. In our case, HUS was associated with H1N1 infection because no other etiology was found.

Hypertension is common in the acute phase of HUS. The cause of hypertension is activation of the renin-angiotensin system (RAS) due to renal ischemia or an excess of intravascular volume. If the intravenous volume is excessive, the first-line drug is diuretic therapy. If the intravenous volume is not excessive, the first-line drug is calcium channel blockers. RAS inhibitors can be used for renoprotection when hypertension or proteinuria persists after HUS begins to resolve (15). RAS inhibitors and calcium channel blockers are the most commonly used antihypertensive agents that are effective, safe, and well-tolerated in children (16). Antihypertensive treatment was initiated due to the detection of stage two hypertension. For this reason, calcium channel blocker was preferred first in our case and then ramipril and alpha methyldopa were added. Since the blood pressure could not be controlled, a different class of antihypertensive drugs was added to the treatment to take advantage of its different mechanism of action.

The mechanisms by which H1N1 triggers HUS are not yet clear. Some hypotheses have been proposed for the pathogenesis of HUS. One of these hypotheses is an altered immune response by activation of mononuclear cells that produce tumor necrosis factor-alpha. Another hypothesis is that viral neuraminidase plays a role in inducing HUS. Neuraminidase and hemagglutinin are major membrane glycoproteins found on the surface of the influenza virus. Viral neuraminidase cleaves sialic acid residues from various glycoproteins on the surface of red blood cells and unmasks Thomsen–Friedenreich cryptoantigen, which participates in hemolysis and renal failure (17-21).

HUS cases related to H1N1 infections have been reported to be treated with FFP infusions, oseltamivir, steroids, eculizumab, and dialysis when necessary (8, 13, 14). In our case, H1N1 was thought to be the causative agent of HUS. Therefore, oseltamivir treatment was started for H1N1. At the end of oseltamivir treatment, UPCR was still high in the patient, edema was ongoing on physical examination, and hemolysis findings were persistent (low haptoglobin- hemoglobin, high LDH). A renal biopsy was performed because edema and hemolysis findings persisted and UPCR was high despite steroid therapy. After detecting TMA in the renal biopsy, the patient received FFP treatment. Haptoglobin increased and hemolysis findings were resolved with FFP; however, hypertension and nephrotic proteinuria persisted and renal function tests continued to deteriorate. Since a sufficient renal function recovery was not obtained and genetic results would have arrived late, we decided to start eculizumab for the patient. Therefore, eculizumab was added to her treatment, which resulted in the improvement of blood pressure, nephrotic proteinuria and kidney function. Fresh frozen plasma infusions are a common treatment for HUS (15). While our approach in HUS is primarily plasma exchange, this treatment was not started because the patient's family did not accept catheter insertion. Fresh frozen plasma infusions were started at a dose of 15 mL/kg once daily. Five doses of FFP were given daily. Then, seven doses of FFP were given every other day. Thirteen doses of FFP were administered in total. Haptoglobin increased to 30 mg/dL on the 2nd day of initiation of FFP infusion in our case. Fresh frozen plasma infusions were continued until the platelet count, LDH, and hemoglobin levels returned to normal. Hematological remission occurred with FFP infusions despite persistent elevated hypertension, nephrotic proteinuria, and deteriorated renal function. Eculizumab is a monoclonal anti-C5 antibody that prevents the formation of C5. Eculizumab is suggested as an effective treatment to maintain hematological remission and preserve the kidney function (22,23). Since influenza virus infections and other infections can often trigger the onset of aHUS, eculizumab treatment can be administered (22,23).

In a case report by Rhee et al. (24), it was stated that eculizumab treatment could be an effective therapy for resistant HUS. H1N1 infection was thought to be a trigger for aHUS in this patient. Although hematological remission started with oseltamivir treatment, eculizumab treatment was given without waiting for genetic results because impaired kidney function tests, hypertension, and nephrotic proteinuria persisted. Then the patient's blood pressure improved and nephrotic proteinuria and kidney function tests regressed. No hemodialysis was required. Our patient also did not need an intensive care unit and mechanical ventilator

Conclusion

Although H1N1 infection is usually benign, it should be kept in mind that many complications may develop, including HUS. By presenting this case, we wish to remind that HUS may be difficult to treat with a high mortality and morbidity. Since kidney function recovery was only seen after adding eculizumab to her treatment, we believe that eculizumab may be a good choice to achieve sufficient renal function recovery in HUS cases probably triggered by H1N1 infections.

Conflict of Interest

The authors declare no conflicts of interest.

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References

1. Sens YA, Miorin LA, Silva HG et al. Acute renal failure due to hemolytic uremic syndrome in adult patients. Ren Fail 1997; 19:279–282.
2. Ardissino G, Salardi S, Colombo E, et al. Epidemiology of haemolytic uremic syndrome in children. Data from the North Italian HUS network. Eur J Pediatr 2016; 175:465.

3. Siegler R. The hemolytic uremic syndrome. Pediatr Clin North Am 1995; 42: 1505–1529.
4. Ayala E, Kagawa FT, Wehner JH, et al. Rhabdomyolysis associated with 2009 influenza A(H1N1). JAMA 2009; 302(17):1863-4.
5. Centers for Disease Control and Prevention (CDC). H1N1 flu. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009-2010 season. Available at:http://www.cdc.gov/h1n1flu/recommendations. htm/ Accessed September 24, 2009.
6. Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza. Crit Care Med 2009. [Epub ahead of print].
7. Centers for Disease Control and Prevention (CDC). Neurologic complications associated with novel influenza A (H1N1) virus infection in children - Dallas, Texas, May 2009. Morb Mortal Wkly Rep 2009;58(28):773-8.
8. Bento D, Mapril J, Rocha C, Marchbank KJ et al., Triggering of atypical hemolytic uremic syndrome by influenza A (H1N1). Renal Failure 2010; 32:6, 753-756.
9. Farinha A, Carrilho P, Felgueiras J, Natário A, Assunção J, Vinhas J. Haemolytic uraemic syndrome associated with H1N1 influenza. NDT Plus. 2010;3(5):447-448.
10. Çaltik A, Akyüz SG, Erdogan O, Demircin G. Hemolytic uremic syndrome triggered with a new pandemic virus: influenza A (H1N1). Pediatr Nephrol (2011) 26:147–148.
11. Watanabe T (2001) Hemolytic uremic syndrome associated with influenza A virus infection. Nephron 89:359–360.
12. Koh YR, Hwang SH, Chang CL, Lee EY, Son HC, Kim HH. Thrombotic thrombocytopenic purpura triggered by influenza A virus subtype H1N1 infection. Transfus Apher Sci. 2012;46(1):25-28.
13. Golubovic E, Miljkovic P, Zivic S, Jovancic D, Kostic G (2011) Hemolytic uremic syndrome associated with novel influenza A H1N1 infection. Pediatr Nephrol 26:149–150.
14. Tsujii N, Nogami K, Yoshizawa H, Hayakawa M, Isonishi A, Matsumoto M, Shima M (2016) Influenza-associated thrombotic microangiopathy with unbalanced von Willebrand factor and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 levels in a heterozygous protein S-deficient boy. Pediatr Int 58:926–929.
15. Igarashi T, Ito S, Sako M, Saitoh A, Hataya H, Mizuguchi M, et al. Study group for establishing guidelines for the diagnosis and therapy of hemolytic uremic syndrome. Guidelines for the management and investigation of hemolytic uremic syndrome. Clin Exp Nephrol. 2014 Aug;18(4):525-57.
16. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics 2017; 140.
17. Printza N, Roilides E, Kotsiou M, et al. Pandemic influenza A (H1N1) 2009-associated hemolytic uremic syndrome. Pediatr Nephrol. 2011; 26:143–144.
18. Bento D, Mapril J, Rocha C, et al. Triggering of atypical hemolytic uremic syndrome by influenza A (H1N1). Ren Fail. 2010; 32:753–756.
19. Trachtman H, Sethna C, Epstein R, et al. Atypical hemolytic uremic syndrome associated with H1N1 influenza A virüs infection. Pediatr Nephrol. 2011; 26:145–146.
20. Huang RT, Dietsch E, Rott R. Further studies on the role of neuraminidase and the mechanism of low pH dependence in influenza virus-induced membrane fusion. J Gen Virol. 1985;66 (pt 2):295–301.
21. Cochran JB, Panzarino VM, Maes LY, et al. Pneumococcusinduced T antigen activation in hemolytic uremic syndrome and anemia. Pediatr Nephrol. 2004;1 9:317–321.
22. Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. N Engl J Med. 2009; 360: 544-6.
23. Licht C, Greenbaum LA, Muus P, et al. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int. 2015; 87: 1061-73.
24. Rhee H, Song SH, Lee YJ, Choi HJ, Ahn JH, Seong EY, Lee SB, Kwak IS. Pandemic H1N1 influenza A viral infection complicated by atypical hemolytic uremic syndrome and diffuse alveolar hemorrhage. Clin Exp Nephrol. 2011 Dec;15(6):948-52.