Thrombotic Microangiopathy in a Severe Pediatric Case of COVID-19

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ABSTRACT: In this case report, we report a pediatric patient with COVID-19 and atypical hemolytic uremic syndrome (aHUS). A 3-year-old girl with fever and respiratory distress was admitted to the hospital. The patient tested positive for COVID-19 by a PCR test. As her respiratory distress increased and blood gas indicated deep respiratory acidosis on the third day of the pediatric intensive care unit follow-up, the patient was intubated and ventilated. Thorax computerized tomography (CT) showed bilateral effusion and atelectasis. During her follow-up, the pleural effusion resolved but there were marked consolidation areas and ground glass opacities compatible with COVID-19 on the follow-up CT. On the 10th day, she became anuric and developed progressive thrombocytopenia and persistent microangiopathic hemolytic anemia, which were suggestive of HUS given a high creatinine level (1.9 mg/dl), an undetectable haptoglobin level, reticulocytosis (8%), and an LDH level of 2540 U/l. Direct Coombs test returned negative. Examination of a peripheral blood smear revealed schistocytes. Disseminated intravascular coagulation was ruled out by normal INR and PTT. In the light of the available findings, we considered the patient to have thrombotic microangiopathy (TMA) triggered by COVID-19. It was not a TTP-form of TMA but rather an aHUS type, based on an ADAMTS13 activity level >5%. Hence, plasmapheresis was performed with fresh frozen plasma (FFP). After 4 weeks, she became completely asymptomatic, and her hemodynamic parameters normalized. COVID-19 induced uncontrolled complement activation leading to the development of aHUS. Early diagnosis and treatment may reduce morbidity and mortality since its treatment options.

KEYWORDS: COVID-19, pediatric patient, hemolytic uremic syndrome

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Introduction

Coronavirus disease 2019 (COVID-19) has become a public health threat to people all over the world during the last year. The lower airway is the primary target of the infection.[1] Acute respiratory distress syndrome (ARDS), septic shock, and coagulation dysfunction are severe complications of this infection, but such severity is rare in children.[2] COVID-19 is also associated with a thrombotic state with an increased risk of thrombosis and disseminated intravascular coagulation (DIC).[3] The complement system plays a central role in the pathology of thrombotic microangiopathy (TMA). Complement hyperactivation in COVID-19 was accompanied by histopathologic evidence particularly in the lungs consistent with TMA.[4,5] COVID-19 may also cause acute kidney injury due to thrombosis.[6,7] However, there has not yet been definitive evidence linking COVID-19 with thrombotic microangiopathies (TMA) such as hemolytic uremic syndrome (HUS). However, it has been previously reported that viruses such as the H1N1 virus can cause HUS.[8] In recent months, there is growing speculation that TMAs play a big role in COVID-19.[9] In this case report, we aimed to report a pediatric patient with COVID-19 and HUS. This is a rare COVID-19 presentation of its kind.

The ethics committee approval of the case report was obtained from the Kahramanmaraş Sütçü İmam University Clinical Research Ethics Committee. Written informed consent was obtained from the patient's parents for the details included in the report.

Case Description

A 3-year-old girl with fever and respiratory distress was admitted to the intensive care unit. There was no known disease in her past history but her family history was notable for secondary parental consanguinity. She had a sibling who had died from fever 1 day after her admission to the hospital at the age of 7 months; and a cousin of her had died due to an unknown cause at the age of 1.5 years. In the pediatrics clinic, she was started on ampicillin-sulbactam and azithromycin treatment against an upper respiratory tract infection, and the treatment was also continued in the intensive care unit. Her initial COVID-19 Polymerase Chain Reaction (PCR) was negative. Her general status was poor. Her consciousness level was low and she appeared confused. Her blood pressure was 170/78 mmHg, heart rate 110/min, body temperature 39°C, and SpO_2 88% on room air. Her weight was 13 kg (50th

Table 1. Laboratory results, clinical course and interventions.

VARIABLE	DAY 3-6	DAY 6-10	DAY 10-16	DAY 16	DAY 28
Clinical evaluation	Admission to hospital	Admission to ICU	Intubated		Recovered
Hg (g/dl) (11.5-15.5)	6.5	5.4	7.5	6.7	11.6
Thrombocyte/µl (150 000-400 000)	503 000	62 000	29 000	118 000	192 000
Leukocyte/mm^3 (6000-17 500)	16 160	28 580	8570	12 400	
Lymphocyte/mm^3 (1500-3000)	5980	10 520	2230	4300	
CRP (mg/l) (5 < N)	22	93	36	64	3
D-dimer (ng/ml) (250 < N)		5820	7840	3520	140
Fibrinogen (mg/dl) (200-400)	405	303		134	
Ferritin (µg/l) (7-140)	1688	1512	1950	1935	
LDH (U/l) (150-500)	1090	2540	784	519	230
Creatinine (mg/dl) (0.3-0.7)	0.8	1.9	0.9	0.9	0.6
Urea (mg/dl) (5-18)	44	56	52	36	
C3 (mg/dl) (70-150)	131		142		
C4 (mg/dl) (10-30)	10.9		34.7		
Peripheral O_2 saturation	92	80	Intubated	94	
Urine output (cc/kg/hour)	2.2	0.1	0.9	2.3	
Pharmacologic therapy	Ampicillin-Sulbactam, Azithromycin	Hydroxychloroquin and favipiravir			

percentile), height 104 cm (50th percentile). There were crackles in both lungs, which were more prominent in the left lung. Deep tendon reflexes were normoactive. Light reflex was normal in both eyes. The patient's second COVID PCR test resulted positive 7 days after the first PCR test; thus, hydroxychloroquine and favipiravir were added to the treatment. As her respiratory distress increased and blood gas indicated deep respiratory acidosis (pH: 6.96, pCO_2: 91 mmHg, and HCO_3: 22 mEq/l) on the third day of the pediatric intensive care unit follow-up, the patient was intubated and ventilated with the SIMV-PC mode. Her blood count revealed a hemoglobin level of 6.5 g/dl, a white blood cell count of 16 160/mm^3, and a platelet count of 503 000/mm^3. Blood chemistry results were as follows: blood urea nitrogen 44 mg/dl, creatinine 0.8 mg/dl, AST 65 U/l, ALT 57 U/l, total bilirubin 0.68 mg/dl, sedimentation rate 60 mm/hour, and D-dimer 5820 µg/l (80-500 µg/l; Table 1). Thorax computerized tomography (CT) showed bilateral effusion and atelectasis (Figure 1A). During her follow-up, the pleural effusion resolved but there were marked consolidation areas and ground glass opacities compatible with COVID-19 on the follow-up CT (Figure 1B). As she had persistent fever at the end of 72nd hour of antibiotic treatment, her therapy was changed to teicoplanin and cefotaxime. Urine output started to decrease from the fourth day on, and amlodipine was started for high blood pressure (120/85 mmHg). Hypertension was initially refractory to calcium channel blockers and enalapril; therefore, esmolol infusion was started. The patient needed furosemide infusion and albumin transfusion during this period. Peripheral blood smear showed 64% polymorphonuclear leukocytes, 16% lymphocytes, and 4% bands, as well as clustered platelets, anisocytosis, microcytosis, +1 hypochromia, and locally polychromatic young lymphocytes. Bone marrow aspiration was performed due to the suspicion of hemophagocytic lymphohistiocytosis since her LDH was 1162 (U/l) ferritin 1512 ml/ng, D-Dimer 7840 ng/ml, and triglyceride 247. The examination of bone marrow aspirate revealed a normocellular bone marrow with cells from each series and stage. Dyserythropoiesis, signs of dysplasia, storage cells, and hemophagocytosis were not observed. Renal Doppler ultrasound revealed kidneys with a normal size and echogenicity as well as a normal renal vasculature. An echocardiogram showed left ventricular hypertrophy and first to second degree mitral insufficiency, most probably due to systemic hypertension. Azithromycin was stopped on the fifth day and cefotaxime was tapered to meropenem due to ongoing fever. Intravenous immunoglobulin (IVIG) was administered at a dose of 1 g/kg to the patient whose fever persisted on the seventh day. Repeated erythrocyte transfusions were given due to persistent profound

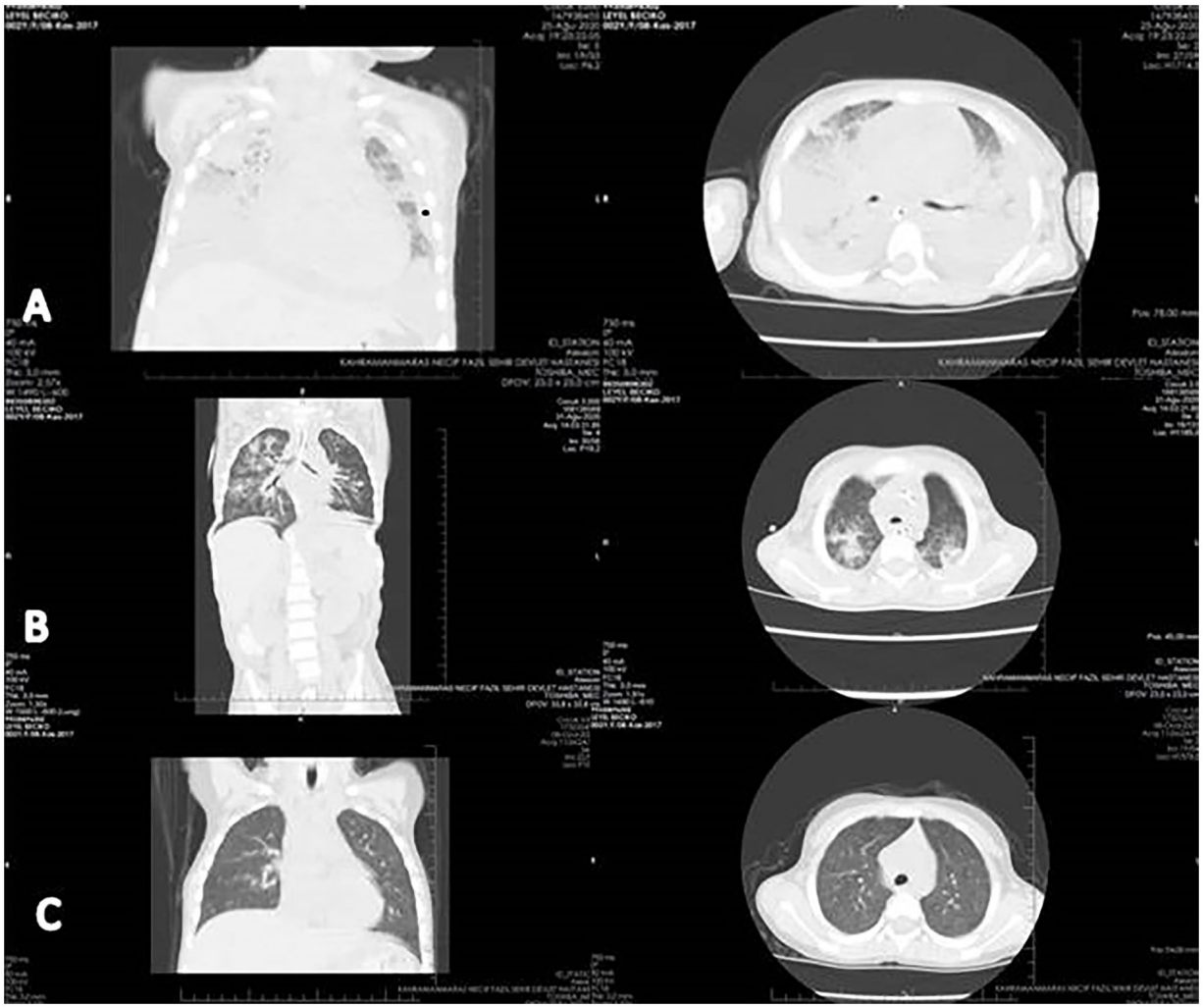

Figure 1. Chest CT scan images: (A) Bilateral pleural effusion, atelectasis, and consolidation on day 1. (B) Regression of bilateral pleural effusion hour predominant ground glass opacities and consolidations on day 16. (C) Control CT on day 45. Sequelae pleuroparenchymal shrinkage and faintly circumscribed, slightly ground glass densities are observed in the middle lobe of the right lung and at the level of the lower lobes of both lungs. There is a large regression in the findings compared to previous thoracic CT.

anemia detected in the serial examinations. On the 10th day, she became anuric and developed progressive thrombocytopenia and persistent microangiopathic hemolytic anemia, which were suggestive of HUS given a high creatinine level (1.9 mg/dl), an undetectable haptoglobin level, reticulocytosis (8%), and an LDH level of 2540 U/l. Direct Coombs test returned negative. Examination of a peripheral blood smear revealed schistocytes. All the above-stated findings confirmed the diagnosis of HUS. ADAMTS-13 activity level and activity were in the normal range, so we ruled out congenital thrombotic thrombocytopenic purpura. Disseminated intravascular coagulation was ruled out by normal INR and PTT. In the light of the available findings, we considered the patient to have thrombotic microangiopathy (TMA) triggered by COVID-19. It was not a TTP-form of TMA but rather an aHUS type, based on an ADAMTS13 activity >5%. Hence, effective performed with fresh frozen plasma (FFP). As she was also anuric, she was treated with 3 hemodialysis sessions. The patient was extubated after the fifth day of plasmapheresis. After the sixth session of plasmapheresis, urine output started to appear and gradually increased to 0.9 cc/kg/hour. LDH values started to fall and blood pressure was reduced. Her platelet count also started to rise. The patient's hypertension began to recover, and esmolol infusion was discontinued subsequently. However, oral antihypertensive medication was continued. After 4 weeks, she became completely asymptomatic, and her hemodynamic parameters normalized (Hg: 11.6 g/dl, platelet: 192 000/µl, CRP: 3 mg/l, creatinine: 0.6 mg/dl, LDH: 230 U/l, and D-Dimer: 140 ng/ml). Therefore, she was discharged with oral antihypertensive treatment that was discontinued at 6 weeks after discharge. No mutation was detected in the atypical HUS genetic panel sent for differential diagnosis of genetic HUS associated with alternative complement pathway; Complement Factor H, Complement Factor I, membrane cofactor protein mutations. A control CT showed sequel pleuroparenchymal shrinkages as well as faintly circumscribed, slightly ground glass densities in the middle lobe of the

right lung and at the level of the lower lobes of both lungs. There was a significant regression of the findings found in the previous thoracic CT (Figure 1C).

Discussion

Atypical hemolytic uremic syndrome is a common cause of acute renal failure in children. Its presentations include microangiopathic hemolytic anemia, thrombocytopenia, and progressive renal failure. There have been numerous reports of infectious triggers for HUS and TMA, including H1N1 Influenza virus, human immune-deficiency virus, Epstein-Barr virus, and parvovirus B19.[10-12] The coexistence of hemolytic anemia with COVID-19 has been reported during this pandemic.[13] Some cases of atypical HUS during the course of COVID-19 has also been previously reported.[14,15] This patient had thrombotic microangiopathy triggered by COVID-19 infection, Coombs-negative hemolytic anemia, thrombocytopenia, and renal failure, which were accompanied by normal ADAMTS-13 levels; thus, she was considered as having COVID-19-associated HUS. This is a rare case report of a child with COVID-19 developing HUS. Since HUS developed following a COVID-19 infection, it is likely that COVID-19 was an infectious trigger for this patient's condition. The possibility of the diagnosis as aHUS with TMA onset triggered by COVID-19 is higher than "COVID-19 related HUS," the reasons are: This is a 3 year kid, early onset of HUS, higher possibility of aHUS due to genetic background. Family history (premature death): a sibling died after a fever at 7 month and a cousin died at 1.5 years old with unknown cause.

This pandemic has shown us that COVID-19 patients have a typically high sepsis-induced coagulopathy score and elevated D-dimer level.[16] There is evidence that COVID-19 causes a complement-mediated inflammation and a thrombotic microangiopathic process.[3] COVID-19 may activate mannose-binding lectin binding and mannose-associated serine protease 2 by the viral S glycoprotein.[4] Thereafter, the lectin pathway is activated, leading to sustained alternative complement pathway amplification, inflammation, and endothelial injury.[4,17] The treatment is the same as standard HUS treatment; so, we began plasmapheresis. Because of its urgency in initiating plasmapheresis for our suspected case of thrombotic microangiopathy, we started plasmapheresis treatment before collection of patient specimen to test for ADAMTS13. This therapeutic potential can be of use as an adjunctive treatment for the management of cytokine storm and coagulopathy in COVID-19 respiratory viral pandemics.[18] Although the relationship between COVID-19 and HUS has not been fully clarified, preliminary results of a study on the effectiveness of C5 inhibitor eculizumab, an important agent that has been used in the treatment of atypical HUS in recent years, in suppressing inflammation in moderate-severe coronavirus-related cases have also been published.[19,20] Eculizumab treatment was among the next-line treatments considered after the initiation of plasmapheresis treatment. Eculizumab treatment was not used because this case responded quickly to plasma exchange and did not have a recurrent HUS attack during follow-up; also, no mutation was found in the genetic study.

Conclusion

COVID-19 constitutes a universal threat nowadays, necessitating strengthening the immune system. COVID-19 patients are at potential risk of aHUS. Virus induced uncontrolled complement activation leading to the development of aHUS. Early diagnosis and treatment may reduce morbidity and mortality since its treatment options.

Author Contributions

Dr Dalkıran conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Dagoglu, Dr Taner, Dr Kara, and Dr Oncu designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. Dr Kandur conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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