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Case Report

Fatal thrombotic microangiopathy in an infant with COVID-19: a case report

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ABSTRACT

Background. While macrovascular thrombosis is common in adult COVID-19 patients, thrombotic microangiopathy as a part of endothelitis might play an important role in severe organ dysfunction. Thrombocytopenia-associated multiple organ failure (TAMOF) is a thrombotic microangiopathy syndrome that is associated with endothelial damage. Herein, we aim to report a pediatric TAMOF case related to SARS-CoV-2 infection which has been scarcely reported to date.

Case. A 7-month-old boy who became severely ill after being infected with SARS-CoV-2 required advanced critical care treatments such as continuous renal replacement therapy, therapeutic plasma exchange, and extracorporeal membrane oxygenation. A heart and lung biopsy obtained during sternotomy showed thrombotic microangiopathy. Despite early plasma exchange, mortality was inevitable because of severe liver failure.

Conclusions. This case report implies that SARS-CoV-2 infection could cause TAMOF in children. To the best of our knowledge, this is the second SARS-CoV-2-induced pediatric TAMOF case. More studies are needed to determine alternative treatments for patients with TAMOF who are resistant to conventional therapies.

Key words: COVID-19, TAMOF, thrombotic microangiopathy, therapeutic plasma exchange.

Thrombocytopenia-associated multiple organ failure (TAMOF) is a thrombotic microangiopathy syndrome that is associated with endothelial damage caused mostly by infections. TAMOF results from immune dysregulation and impaired A Disintegrin And Metalloproteinase with ThromboSpondin type 1 motif member 13 (ADAMTS13) activity. TAMOF is characterized by new onset thrombocytopenia and progression to at least two organ system failures. Von Willebrand factor (vWF) and ADAMTS-13 (or vWF-cleaving protease) play a central role in TAMOF. Herein, we aimed to report a TAMOF case related to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19).

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Case

A 7-month-old boy was brought to the emergency department with vomiting, diarrhea, decreased urine output, and respiratory distress. He was born to nonconsanguineous parents in the 35th week of pregnancy with a history of polyhydramnios and was diagnosed with anal and esophageal atresia, and an H-type tracheoesophageal fistula. Shortly after birth, he had repair surgery (resection of the fistula and end-to-end anastomosis of the esophageal blind sides) and a colostomy for anal atresia. He was intubated for 4 days, suffered from sepsis due to *Klebsiella pneumoniae*, pleural effusion requiring drainage, and was discharged after 2 months. He had thrived well since then; however, he visited the hospital for vomiting and decreased

weight gain due to gastroesophageal reflux one week before. On physical examination, fever, tachycardia, tachypnea, severe dehydration, weak pulses, prolonged capillary refill time, generalized hypotonia, impaired consciousness, and intercostal retractions were profound. After three fluid boluses, he needed adrenaline infusions and was intubated for severe respiratory distress and hypoxia. Both nasopharyngeal swabs and deep tracheal aspirates were positive for SARS-CoV-2, (England variant). Chest X-ray showed bilateral patchy infiltration. Primary laboratory data showed mild metabolic acidosis, increased lactate level (10 mmol/L), leukopenia (2,900 cells/mm^3), and neutropenia (270 cells/mm^3) (Table I).

Table I. Laboratory findings of the patient.

Laboratory parameter	Baseline (1 week before)	At presentation	Before TPE	Day 3	Day 6	Day 8	Day 12
pH		7.27	7.36	7.38	7.19	7.22	7.34
pCO_2 (mmHg)		53.3	45.6	50.7	48.6	40.7	44.9
HCO_3 (mmol/L)		21.5	23.6	27.8	16.5	16.0	22.8
Base excess (mmol/L)		-2.7	0.7	5.2	-9.8	-10.8	-1.2
Lactate (mmol/L)		1.6	1.5	1.3	7.4	17	7.1
White blood cell (/mm^3)	13,100	2,900	3,900	11,400	4,700	6,100	6,100
Lymphocyte (/mm^3)	7,950	2,100	1,700	790	570	100	420
Neutrophil (/mm^3)	2,460	270	2,000	10,360	4,000	3,650	5,420
Platelet (/mm^3)	419,000	295,000	62,000	147,000	28,000	23,000	66,000
Hemoglobin (g/dL)	12.5	12.3	11.3	11.2	11.4	14.3	12.2
ALT (U/L)	16	35	80	105	866	4,134	66
AST (U/L)	36	190	245	341	1,456	3,479	887
CK (U/L)	27	150	367	350	250		365
GGT (U/L)	20	25	27	17	134	270	165
ALP (U/L)	223	161	117	92	69	176	157
Albumin (gr/dL)	3.4	2.8	2.27	2.68	2.89	2.77	2.86
Total bilirubin (mg/dL)	0.25	0.21	0.35	0.17	1.11	4.26	12.3
Direct bilirubin (mg/dL)	0.04	0.128	0.07	0.05	0.71	1.89	6.9
INR	1.01	1.75	1.75	1.35	4.0	2.94	2.9
Sodium (mEq/L)	135	142	142	143	138	138	138
Potassium (mEq/L)	3.68	2.99	3.26	3.39	4.15	3.15	3.63
Calcium (mg/dL), corrected	10.6	8.4	8.2	8.9	8.6	10.3	10.6
Phosphorus (mg/dL)	4.97	6.59	5.74	2.41	3.37	3.3	1.83
Creatinine (mg/dL)	0.23	0.89	0.70	0.55	0.95	0.64	0.29
Blood urea nitrogen (mg/dL)	14.7	53.3	46.5	25.3	28.4	11.0	2.8
Uric acid (mg/dL)	4.58	17.8	11.97	7.93	5.98	6.89	0.43
Troponin-I (ng/L)	-	236	190				
Ferritin (μg/L)	-	1,001	1,237	110	1,850	35,910	660
Interleukin-6 (pg/mL)	-	6,525	7,291	1,156	2,816	2,814	75.6
C-reactive protein (mg/dL)	-	2.41				2.89	2.19
Procalcitonin (ng/mL)	-	246	352	12.4	90		

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CK: creatine kinase, GGT: gama-glutamyltransferase, INR: international normalized ratio, TPE: therapeutic plasma exchange.

Although platelet count was in the normal range (295,000 cells/mm^3), it decreased from 419,000 cells/mm^3 during his last routine visit six days ago. The pediatric risk of mortality (PRISM-III) score was 22, probability of death rate was 26%. Multiorgan dysfunction syndrome score was 9 and the pediatric logistic organ dysfunction (PELOD) score was 32 on admission day. Echocardiography was normal (75% of the ejection fraction). Because thrombocytopenia was accompanied by dysfunction of two major organ systems, the diagnosis was TAMOF. He was treated with therapeutic plasma exchange (TPE) three times. TPE was suspended because the PELOD score decreased to 2 and platelet count increased to 147,000 cells/mm^3. On the 6th day, he was extubated with non-invasive ventilation. However, within 24 hours' acute respiratory distress syndrome (ARDS) occurred accompanied by severe cardiovascular failure so he underwent central venoarterial (right atrium-aorta) extracorporeal membrane oxygenation (ECMO) with a centrifugal pump and pediatric oxygenator (Liliput 2, Sorin group™). Central cannulation was chosen according to the experiences of the surgical team and available equipment. During sternotomy for ECMO cannulation, with the family's permission, heart, and lung biopsies were obtained to better understand the pathophysiological processes of SARS-CoV-2 infection in children. It revealed increased alveolar inflammatory cells and thrombotic microangiopathic changes in the small vessels of the alveoli. Myocardial edema and differences in the volumes and shapes of myofibers but no inflammatory cells were detected on myocardial biopsy. He received broad-spectrum antibiotics which were tapered later because no bacterial or fungal organisms were detected on sequential blood and other body fluid cultures. Daily TPE with 1.5 times of plasma volume was performed for TAMOF with significant liver failure (maximum ALT level was 3,450 U/L). Intravenous immunoglobulin (IVIG) (0.4 gr/kg, 5 days) was given between TPE sessions as in the Zipper method of Hacettepe.[1] Levosimendan infusion was started right after ECMO initiation because of significantly impaired left ventricular dysfunction requiring full cardiac support (120 ml/kg of blood flow rate). Continuous venovenous hemodiafiltration was started through the ECMO circuit for hypervolemia and renal failure. Because the ferritin, interleukin-6 and procalcitonin levels peaked for the second time anakinra (1 mg/kg, 2 doses) was added. The maximum ferritin level was recorded as 35,910 μg/L (Fig. 1) just before initiating anakinra and levosimendan. He showed a good response to the combination of TPE, IVIG, and anakinra treatment around the 12th day. However, he lost his brainstem reflexes on the 14th day and died the next day (Fig.1). Written informed consent was obtained from the parents for this case report.

Discussion

Approximately 80% of children infected with SARS-CoV-2 develop mild to moderate disease and the incidence of critical illness is high in children under 1 year old.[2] Herein, we report a fatal TAMOF case associated with SARS-CoV-2. TAMOF is characterized by severe organ dysfunction and often new onset thrombocytopenia. The common pathophysiology of thrombotic microangiopathies is systemic endothelial injury. Abnormally large vWF multimers induce platelet aggregation resulting micro-thrombi in vessels that cause organ damage.[3] Endothelial dysfunction is also an important feature of SARS-CoV-2 infection.[4] Extensive micro-thrombosis promoted and aggravated by endothelial dysfunction which might be the result of direct viral effects and/or systemic inflammation could explain the profound elevation of D-dimers and thrombocytopenia in severe COVID-19.[5] Although ACE2 expression and other endothelial biomarkers are the hallmark of both pulmonary and non-pulmonary pathology of COVID-19, Mancini et al.[6] showed a quantitative imbalance between the vWF and ADAMTS13, with a seven-fold increased vWF antigen to ADAMTS13 activity ratio associated with severe COVID-19 that required intensive care and mechanical ventilation.

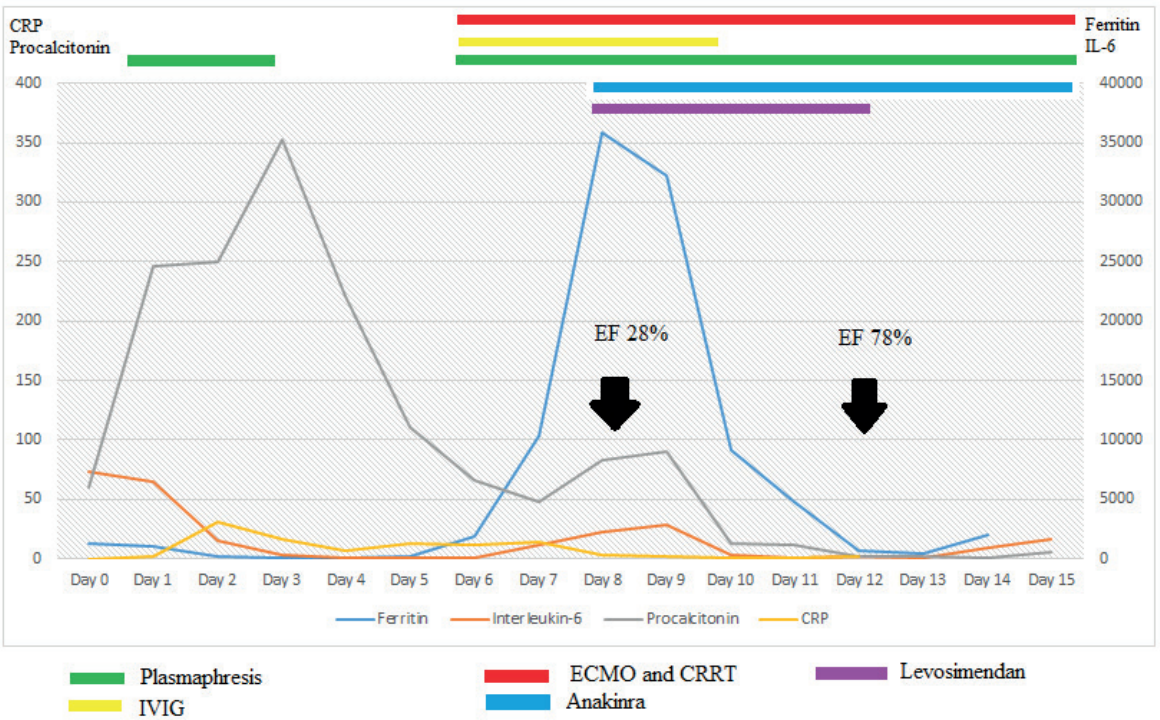

Fig. 1. The chronological interventions to the patient. Levels of ferritin are shown in μg/L, Interleukin-6 in pg/mL, CRP in mg/dL and procalcitonin in ng/mL.

We did not have the chance to study ADAMTS13 activity or vWF antigen levels in our patient. However, severe organ dysfunctions and new onset thrombocytopenia with evidence of acute SARS-CoV-2 infection led us to treat the patient as COVID-19-related TAMOF. The diagnosis of TAMOF was later supported by microangiopathy findings in the pathological specimen. Thrombotic microangiopathy and its relation to COVID-19 is well-defined in adults, however, few pediatric cases have been reported to date.[7,8] Latimer et al.[7] reported a patient who survived intensive treatment. Our patient improved after three days though a severe cytokine storm was the main reason for his worsening. After penetrating respiratory epithelial cells, SARS-CoV-2 triggers an immune response with proinflammatory cytokine production due to the rapid activation of Th1 cells. By the infiltration of macrophages and neutrophils into the lung tissue, which results in a cytokine storm.[9] Although multiple TPE, anakinra, IVIG, and steroid treatments alleviated the cytokine storm and levosimendan infusion corrected the left ventricular function (Fig.1), the liver failure had become the main determinative factor for death. Severe liver failure resulting from cytokine storm might have contributed to brain damage although ongoing treatment of plasmapheresis. Direct myocardial invasion of the virus can cause myocarditis and death.[10] That our patient's myocardial biopsy showed no viral particle, but myocardial edema and elevated serum inflammatory markers suggested multisystemic involvement.

Daily plasma exchange until thrombocytopenia reverses can restore the ADAMTS13 and other coagulation factors and improve the organ failures in TAMOF.[11] It also has the advantage of removing proinflammatory cytokines. The fresh frozen plasma acquired from the patients who recovered from COVID-19, called convalescent plasma, used to treat COVID-19 patients in active phase of infection. The specific antibodies in convalescent plasma help the patient fight against the virus.[12] Latimer et al.[7] have reported a similar pediatric case that resolved after two

sessions of plasma exchange and aggressive supportive care. They explained that the reason for the avoidance of multiple plasmapheresis was the concern of the clearance of antibodies against SARS-CoV-2. Unlike them, we carried out multiple plasmapheresis because of severe hepatic failure.

To the best of our knowledge, this is the second SARS-CoV-2 induced pediatric TAMOF case. Although COVID-19 causes a mild clinical phenotype in children, TAMOF should be considered in patients with severe organ dysfunction and new onset thrombocytopenia.

Ethical approval

Written informed consent was obtained from the parents for this case report.

Author contribution

The authors confirm their contribution to the paper as follows: study conception and design: BB, SK; data collection: ÖSN; analysis and interpretation of results: ÖSN, KT; draft manuscript preparation: ÖSN, SK. 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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