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Hemolytic uremic syndrome following COVID-19; a case report

Elham Emami[1], **Samaneh Safari**[2*], **Pedram Javanmard**[3]

[1]Pediatric Nephrology Research Center (PNRC), Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Clinical Research Development Unit, Hajar Hospital, Shahrekord University of Medical Sciences, Shahrekord, Iran
[3]Division of Endocrinology, Diabetes, and Bone Disease, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, USA

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ABSTRACT

High incidence of thromboembolic diseases in patients with coronavirus disease 2019 (COVID-19) have been reported that can affect several organs ranging from cutaneous thrombosis to pulmonary embolism, stroke, coronary thrombosis or kidney infarction. There are two proposed mechanisms for these phenomena, disseminated intravascular coagulation (DIC) and endotheliopathy. We report a case of 11-year-old girl presented to the emergency department with generalized tonic colonic seizure with upward gaze which was repeated in emergency room. Respiratory distress and loss of consciousness happened which led to her intubation. Due to increased serum creatinine levels and impaired consciousness which was associated with thrombocytopenia and hemolysis, she underwent plasmapheresis three times by the diagnosis of hemolytic uremic syndrome. Additionally, antihypertensive therapy was conducted. The patient's condition improved and was discharged with good circumstances. Two weeks later the patient returned with thromboembolism that happened in the distal part of her left hand which underwent fasciotomy and thrombectomy.

Case report

Implication for health policy/practice/research/medical education:
In this case report, we showed hemolytic uremic syndrome and thromboembolism in the brain led to seizure following COVID-19 development.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic which is one of the most significant modern-day public health challenge, has different manifestations. The most common symptoms are respiratory, however gastrointestinal, neurological, renal and other atypical symptoms can be seen (1,2). Recent studies showed several coagulation abnormalities and thrombotic complications in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) called COVID-19-associated coagulopathy (CAC), raising questions about appropriate management to prevent or treat thrombosis (3). Endothelial damage is thought to initiate thrombotic microangiopathy by activating the coagulation system, which in turn leads to formation of thrombin and the deposition of fibrin (4). Abnormalities of the coagulation cascade and the complement system, inflammatory mediators, and tubular and endothelial damage lead to chronic kidney disease (5-7).

Case Presentation

We presented an 11-year-old girl without past-medical history of seizure accompanied by generalized tonic colonic seizure and upward gaze approximately half an hour before admission that repeated in emergency room. After stabilizing with intravenous diazepam, sodium valproate began due to renal impairment in the course of hospitalization. The day after respiratory distress and loss of consciousness happened and then the patient was intubated and transferred to the intensive care unit. The patient had thrombocytopenia and an elevated serum creatinine level and anemia with high serum ferritin level. The diagnosis of COVID-19 was strongly suggested for the patient. The patient was found to be positive for SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) conducted by nasopharyngeal swabs.

Due to unstable general conditions and high serum creatinine with thrombocytopenia and hemolytic anemia,

***Corresponding author**: Samaneh Safari, Email: samane.safari.med@gmail.com

she underwent plasmapheresis for three times, with the impression of hemolytic uremic syndrome (HUS). ADAMTS13, H, B and I factors and C3, C4, CH50 complements, and also anti-dsDNA antibody were checked. The patient underwent fresh frozen plasma transfusion according to the prolonged partial thromboplastin time in the course of treatment. During the hospitalization, the blood pressure raised over 95 percentile for her age and gender and height which controlled with labetalol and hydralazine. The patient's state improved and extubated. Then serum creatinine reduced from 4 mg/dL to 2 mg/dL and remained at this concentration. Additionally brain MRI and MRA, were conducted due to episodes seizure, which showed microthrombosis.

Kidney Doppler ultrasound was normal. Plural effusion with a diameter of 16 mm in right side and 10 mm in left side was evident in chest sonography. The patient underwent a diagnostic ultrasound-guided aspiration of plural effusion. Abdominal sonography showed 200-250 mL free fluid with mild splenomegaly with the span of approximately 135 mm. Brain computed tomography (CT) scan showed hypodensity in occipital horn of right lateral ventricle. Brain magnetic resonance imaging (MRI) showed no vascular lesion, with hyper-intensity in subcortical U-fibers in both hemispheres of brain. Spiral high resolution computed tomography scan of the lungs revealed cardiomegaly with little pericardial effusion. Reticulonodular and ground glass opacities spread in both pulmonary parenchyma with small bilateral pleural effusion. The echocardiogram showed normal ejection fraction with normal coronary arteries and no valvular disorders. Laboratory results were presented in Table 1.

Level of glucose-6phosphate dehydrogenase (G6pd) was sufficient. In pleural fluid analysis; pH = 7, albumin = 1.2 g/dL, sugar =90 mg/dL, Lactic acid dehydrogenase = 80 U/L, RBC= 12.800 ($\times 10^6$/μL), WBC = 250×10^3 cells/mm,^{3} polymorphonuclear cell = 70%. Blood sugar, phosphate, serum calcium all yielded results within the normal limits. PCR from the nasopharyngeal swab was positive.

The patient was discharged in good condition with medical recommendations. Two weeks after the patient returned with thromboembolism which happened in the distal part of her left hand that underwent fasciotomy and thrombectomy. After discharge, serum creatinine level remained at 2 mg/dL. Further, the patient's proteinuria without hypoalbuminemia was continued.

Table 1. Laboratory results of the patients

Laboratory factor	Baseline time	Discharge time
White blood count	2.200×10^3	6.200×10^3
Lymphocyte (%)	38	36.5
Hemoglobin (g/dL)	7.8	12.5
Platelet (per microliter)	35 000	185 000
C-reactive protein (mg/L)	1+	-
Ferritin (ng/mL)	5200	-
Lactate dehydrogenase (U/L)	29	-
Creatinine (mg/dL)	4	2
Uric acid (mg/dL)	7	4
Alb (g/dL)	2.5	4
Blood urea nitrogen (mg/dL)	81	23
SGOT (U/L)	24	-
SGPT (U/L)	32	-
Alkaline phosphatase (IU/L)	250	-
Creatine phosphokinase (U/L)	48	-
Na (mEq/L)	128	138
K (mmol/L)	5.1	4.2
Erythrocyte sedimentation rate (mm/h)	54	12
Anti- double-strand DNA antibody (IU/mL)	0.5	-
C3 (mg/dL)	109	-
C4 (mg/dL)	27.1	-
CH50 (U/mL)	170	-
Perinuclear anti-neutrophilic cytoplasmic antibody	6.4	-
Urine specific gravidity	1008	-
Urine pH	8	-
Urine Pro (count)	2+	-
Urine WBC (count)	1-2	-
Urine RBC (count)	4-5	-
Venous blood gas pH	7.43	7.34
Venous blood gas PCO2 (mm Hg)	34.9	38.8
Venous blood gas HCO3 (mEq/L)	23.1	20.4
Partial thromboplastin time (s)	120	34
Prothrombin time (s)	13	12

Discussion

The COVID-19 rapidly spread throughout the world (1), caused by SARS-COV-2, has brought several unique pathologies, such as coagulopathy, prompting a desperate need for effective management. CAC can cause various thromboembolic complications, especially in critically ill patients. The pathogenesis is likely due to endothelial injury, immobilization, and an increase in circulating prothrombotic factors (8,9). Due to endothelial injury, renal endothelial cells also can be affected. Examination of kidney by biopsy specimens obtained from patients with thrombotic microangiopathy shows mesangiolysis and loss of endothelial cells, with expansion of the subendothelium and occlusion of capillary lumens. The fact that C4d, a complement fragment, may be detected in glomerular and peritubular capillaries in biopsy and autopsy specimens suggests the presence of an antibody-mediated process and complement activation (5,6). Infiltration of inflammatory cells, including CD3+ and CD8+ T cells and cytotoxic T cells, has also been detected in the glomeruli, tubules and interstitium (5). A predominance of natural killer cells in the kidney (thought to be due to chronic inflammation) may also exacerbate endothelial injury (7). A final common pathway to injury probably links inflammatory mediators and tubular and endothelial damage, finally leading to chronic kidney disease. The initial evaluation of a patient who has an elevated serum creatinine level should focus on determining the cause of increase. It is important to obtain a complete urine analysis, urinary albumin to

creatinine ratio, complete blood count with evaluation of blood smear, and levels of serum lactate dehydrogenase, haptoglobin, and calcineurin inhibitors. The management of acute kidney injury is largely supportive; it includes the withdrawal of nephrotoxic drugs, a reduction in the dose of calcineurin inhibitors, fluid intake and fluid output measurement from the time of admission to the intensive care unit with further steps to improve the effective circulating volume. However, to achieve these goals in patients with severe acute kidney injury, dialysis may be required (10-12). In the presence of microangiopathic hemolytic anemia (red cell fragmentation), we usually observe and elevated lactate dehydrogenase levels, kidney dysfunction (>50% increase from the base line serum creatinine level or a 50% decrease in creatinine clearance from baseline), neurologic involvement without other identification cause, with negative direct and indirect Coombs tests. A revised grading system assesses the severity of thrombotic microangiopathy primarily on the basis of the serum creatinine level, need for dialysis, the presence of encephalopathy, or a combination of these factors (13). The presence of concurrent renal and neurologic dysfunction and a schistocyte count of 4% or greater on the peripheral blood smear does not however identify patients with probable thrombotic microangiopathy who are also at high risk for a poor outcome (13).

Conclusion

HUS and thromboembolism in the brain leading to seizure can happen following COVID-19 in which requires fasciotomy and thrombectomy.

Authors' contribution

MSS, EE and PJ wrote the manuscript. SS and EE were the physicians of the patient and completed data and helped in writing draft. SS treated and followed the patient and revisited the case. MSS, EE and PJ reviewed the reported laboratory results. All authors were involved in the writing, review and editing of the manuscript and read and signed the final paper.

Conflicts of interest

The authors declared no conflicts of interest.

Ethical issues

This case report was conducted based on the World Medical Association Declaration of Helsinki. The patient has given us a written informed consent for publication as a case report. Additionally, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors

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