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LETTER TO THE EDITOR

Possible microangiopathic overlap between COVID-19 and Shiga toxin-associated hemolytic uremic syndrome

To the Editor:

We have recently encountered a case of Shiga toxin-associated hemolytic uremic syndrome (Stx-HUS) and concomitant coronavirus disease 2019 (COVID-19) in a 3-year-old male, with some features suggesting potential microangiopathy overlap between the two conditions.

The child presented to our hospital with fever, coryza, cough, decreased urine output lasting for 3 days, and a history of non-bloody diarrhea 1 week prior to admission. Polymerase chain reaction (PCR) screening indicated infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At presentation, the patient showed signs of dehydration and was normotensive. Initial laboratory workup showed microangiopathic hemolytic anemia (MAHA), thrombocytopenia, hematuria, nephrotic range proteinuria, and acute kidney injury (AKI), consistent with the diagnosis of HUS. Stool PCR was positive for Stx1/Stx2 and eaeA genes, complement component 3 (C3) levels were mildly decreased, both soluble terminal complement complex (sC5b-9) levels and D-dimer levels were increased, and ADAM metallopeptidase with thrombospondin type 1 motif, 13 (ADAMTS-13) activity was normal. See Table S1 for details.

The patient was initially treated with intravenous fluids; however, at the second day of admission, he developed anuria, and automated peritoneal dialysis (APD) was initiated. As the patient remained febrile and significantly increased levels of procalcitonin were found (29 μg/L, normal: 0–0.05 μg/L), empirical therapy with meropenem was started.

The patient was continued on APD with persistent thrombocytopenia, MAHA, and AKI. D-dimer levels were repeated at day 10 since admission and were significantly elevated up to 13,265 μg/L (normal: 45–265 μg/L). Considering concomitant COVID-19, a decision to add corticosteroids (intravenous dexamethasone 0.15 mg/kg once daily) and low-molecular weight heparin (LMWH; subcutaneous nadroparin 60 IU/kg once daily) was made. Following the introduction of this therapy, patient's D-dimer and markers of TMA (thrombotic microangiopathy) decreased significantly, eventually leading to discontinuation of APD 16 days after its initiation. The time course of the disease is summarized in Figure 1. The patient was discharged *with* stable condition at day 22, with estimated glomerular filtration rate (eGFR) of 54.9 ml/min/1.73 m^2, mild anemia, and normal platelet count, persistent proteinuria and hematuria. Further follow-up data were unavailable because the patient continued care in another country (homeland).

Stx-HUS is the most common form of TMA in the pediatric population caused by Stx-producing *Escherichia coli*. Following its release in the gut, Stx reaches systemic circulation and binds to endothelial receptors that are abundant in kidney. Apart from direct cytotoxic effects, Stx activates local inflammatory response, prothrombotic pathways, and alternative complement pathway, eventually leading to microvascular thrombosis, MAHA, and end-organ dysfunction.[1,2]

Thrombotic sequelae, such as macro- and microvascular thrombosis, have also been implicated as an important feature of COVID-19, and LMWH prophylaxis is recognized as a part of its management in selected patients.[3–5] Apart from the flares of pre-existing or development of de novo complement-mediated HUS or thrombotic thrombocytopenic purpura, COVID-19 has also been linked to development of distinct TMA-like states. The mechanisms of COVID-19-induced TMAs, although remain elusive, may resemble those of Stx-mediated injury, including severe endothelial injury, alternative complement pathway activation, and shift toward prothrombotic milieu.[6] In addition, evidence of complement system activation has been reported in children with severe COVID-19, with 89% demonstrating signs of TMA.[7] Recent data also suggested that predilection to microthrombosis may be partly mediated by imbalance in von Willebrand factor (vWF)-ADAMTS13[8]; therefore, may respond to steroids and anticoagulants without requiring plasma exchange.[6]

Thus far, only one case of Stx-HUS with COVID-19 has been reported in a 24-year-old female who developed alternating hemiparesis, and received eculizumab with complete resolution of neurological symptoms but limited details on the course of TMA were provided.[9] Considering that both Stx-HUS and COVID-19-associated TMA develop at least in part due to severe endothelial injury, it is likely that COVID-19 could have aggravated the course of HUS in our patient. This is supported by the finding of extreme elevation of D-dimer levels (>40 times the upper normal limit), which is uncharacteristic for isolated HUS and rapid response to COVID-19-specific therapy.[10] There might be a complex pathophysiologic interplay between Stx-HUS and COVID-19, but our patient had normal ADAMTS-13 activity and only mild signs of complement system activation, consistent with findings in isolated Stx-HUS.[11]

According to the available guidelines, children hospitalized for COVID-19-related illness with significantly elevated D-dimer levels should receive LMWH prophylaxis for venous thromboembolism.[12] Thromboprophylaxis was initially withheld in our patient due to profound thrombocytopenia and necessity for surgical interventions for peritoneal dialysis. However, the initiation of LMWH and steroids due to the lack of expected clinical improvement and signs of progressive TMA with remarkable increase in D-dimer levels, clearly resulted

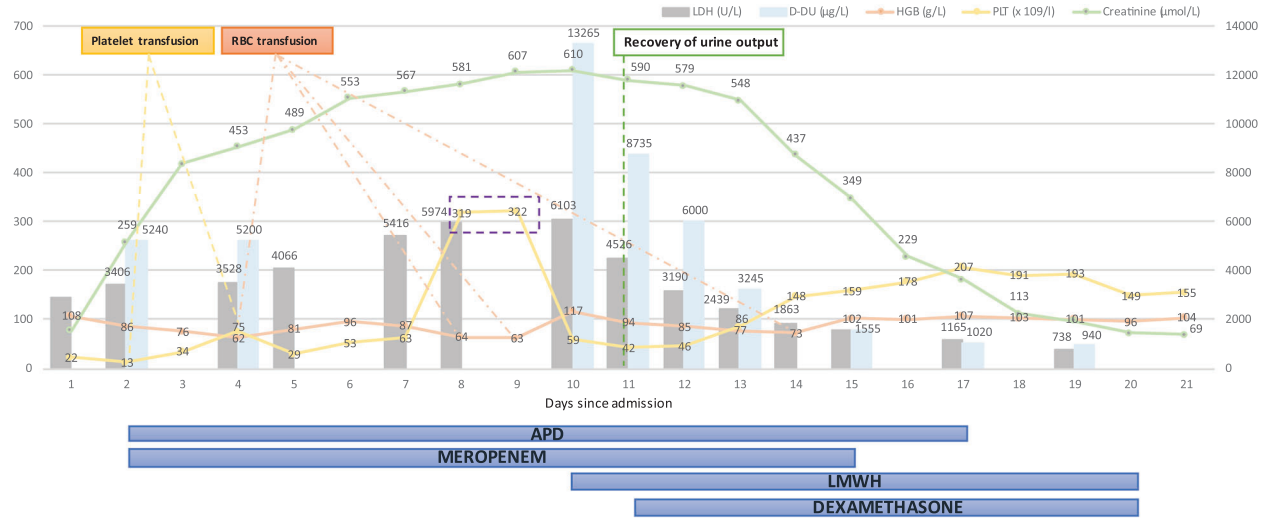

FIGURE 1 Time course of the disease, including the dynamics of principal laboratory results and treatment summary. The violet rectangle represents a false elevation of platelet count as measured by automated hematology analyzer (secondary to schistocytosis), which was confirmed by morphologic identification of platelets. APD: automated peritoneal dialysis; D-DU: D-dimer; HGB: hemoglobin; LDH: lactate dehydrogenase; LMWH: low-molecular weight heparin; PLT: platelet count; RBC: red blood cells

in reduction of TMA activity. Neither steroids nor LMWH have been shown to be effective in the treatment of isolated Stx-HUS,[1] thus the observed response could be explained by attenuation of COVID-19-induced coagulopathy, although causality cannot be inferred.

Our observation suggests the need for vigilance of the coagulation state in patients with COVID-19 and concomitant TMA predisposing conditions. Further studies on COVID-19-mediated TMA with a focus on their optimal treatment strategies are needed.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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