Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Atypical HUS relapse triggered by COVID-19

To the editor: Microvascular injury, including thrombotic microangiopathy, has been widely reported as a hallmark pathologic feature of organ injury in the setting of coronavirus disease 2019 (COVID-19).[1] Accumulating data suggest that complement activation is implicated in the pathogenesis of COVID-19, including endothelial cell damage.[2–5] Some of these features are characteristic of atypical hemolytic uremic syndrome (aHUS), a prototypic disease of complement-mediated endothelial cell injury. We report the first case of aHUS relapse triggered by COVID-19.

The patient, a 28-year-old white woman, was diagnosed with aHUS at the age of 3. Genetic analysis revealed the presence of a heterozygous pathogenic variant (R59Stop) in the membrane cofactor protein–encoding gene. Subsequently, she presented 3 aHUS relapses at the age of 5, 20, and 27 years. The second relapse required dialysis before hematologic and renal remission was obtained following 4 plasma exchanges and treatment with eculizumab for 12 months. The third relapse, triggered by an extrauterine pregnancy, was treated with 3 months of eculizumab. Kidney biopsy performed at that time revealed moderate interstitial (20%) and glomerular (20%) fibrosis. The patient had chronic kidney disease stage 3B (glomerular filtration rate = 42 ml/min per 1.73 m^2 estimated using the Modification of Diet in Renal Disease formula) and hypertension requiring a treatment combining a calcium channel blocker and an angiotensin-converting enzyme inhibitor.

In September 2020, she presented with fever, dysphagia, and headache. Clinical examination showed moderate fever, an erythematous throat, infracentimetric cervical adenopathies, and hypertension (150/105 mm Hg). She had no lung involvement with a normal chest X-ray. Laboratory tests showed mechanical hemolytic anemia (hemoglobin = 8.4 g/dl, lactate dehydrogenase level at 1.5× the upper limit of normal, and undetectable haptoglobin), mild thrombocytopenia (platelet count = 106 G/l), acute kidney injury (serum creatinine = 2.6 mg/dl vs. 1.7 mg/dl at baseline), and significant proteinuria (protein-to-creatinine ratio of 0.21 g/mmol vs. 0.05 at baseline). aHUS relapse was diagnosed, and the patient was admitted to our nephrology department. In the context of the re-emergence of the SARS-CoV-2 pandemic in our region, COVID-19 was suspected and confirmed by a positive polymerase chain reaction test in a nasopharyngeal swab. Additional workup showed a decreased C3 serum level (0.65 g/L; normal range, 0.9–1.8) and a normal C4 level. Inflammatory markers were normal or moderately increased (C-reactive protein < 0.4 mg/dl [<10], ferritin = 392 μg/l [13–150], D-dimer = 512 ng/mL [<500], and interleukin-6 = 1.8 pg/mL [< 7]). Serum creatinine peaked at 2.9 mg/dl, and the platelet count decreased to 88 G/l. Treatment with the C5 blocker eculizumab was immediately restarted combined with penicillin prophylaxis and anticoagulation due to the increased risk of thrombosis in the setting of COVID-19.[6] Seven days after the start of eculizumab, the hematologic parameters (platelet count = 191 G/l) and renal function (serum creatinine = 2.2 mg/dl) improved, and the patient was discharged from the hospital. One month after diagnosis, the D-dimer level was normal (261 ng/ml), haptoglobin remained undetectable, and a mild decrease in the C3 plasma level persisted (0.65 g/l). Renal function improved, but serum creatinine (2.0 mg/dl) had not returned to baseline values.

It is well established that aHUS relapse may be precipitated by infections, including viral pathogens such as influenza or H1N1 virus.[7,8] This case is an illustration that COVID-19 is to be added to the list of the potential triggers of aHUS relapse. In this setting, the deleterious effect of the coronavirus 19 may arise from (i) a direct toxic effect on endothelial cells, as suggested by autopsies studies,[1] and/or (ii) a complement activation with ultimately complement-mediated endothelial damage, most particularly in patients with a constitutional defect in complement regulation, as in the patient presented herein. Indeed, it has recently been shown that, *in vitro*, SARS-CoV-2 activates the complement alternative pathway via its spike surface protein.[9] Similarly, markers of complement activation, including soluble C5b-9, are increased in a significant proportion of COVID-19 patients and correlate to the severity and prognosis of the disease prognosis.[4,5] Furthermore, C3 deficiency protects against the development of SARS-CoV infection in mice.[10] Finally, complement activation may also contribute to the hypercoagulable state in COVID-19 patients.[3]

Our patient had a clinically mild form of COVID-19 and no marked systemic inflammation. Nevertheless, virus-driven complement activation did occur and was most probably overamplified in the absence of a tight control of the complement alternative pathway, leading to the development of thrombotic microangiopathy. However, this is to date the only reported case of aHUS relapse triggered by COVID-19 despite the worldwide spread of COVID-19 epidemics. Nevertheless, our observation underlines the need for close monitoring of aHUS patients who discontinued eculizumab in the setting of COVID-19. It is also a further indication that complement blockade should not be discontinued in aHUS during infectious episodes, COVID-19 not being an exception.

DISCLOSURE

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Discrepant post-filter ionized calcium concentrations by 2 common gas analyzers in continuous renal replacement therapy using regional citrate anticoagulation: another piece of the puzzle

To the editor: During continuous veno-venous hemodialysis with regional citrate anticoagulation, ionized calcium (iCa) measurements in pre- and post-filter samples are used to adjust calcium and citrate flows. Post-filter iCa target concentrations are within a low range (0.25–0.34 mmol/L), and blood gas analyzers (BGAs) are mainly calibrated for physiological values (1.12–1.20 mmol/L). Bias between BGAs in these low-value measurements leads to errors in adjusting the citrate dose,[1,2] yet current regional citrate anticoagulation protocol is used worldwide despite the lack of standardization.[3,4]

Table 1 | Concordance of citrate dose adaptation induced by ionized calcium measured by ABL 90 Flex Plus (Radiometer, Copenhagen, Denmark) and GEM Premier 4000 (Werfen, Barcelona, Spain) analyzers in 50 post-filter samples, taken from 5 critically ill patients treated with continuous veno-venous hemodialysis with regional citrate anticoagulation

ABL GEM	Citrate dose decreased (Ca < 0.25)	Citrate dose unchanged (Ca = 0.25–0.34)	Citrate dose increased (Ca > 0.34)	Total
Citrate dose decreased (Ca < 0.25)	0	**15**	0	15
Citrate dose unchanged (Ca = 0.25–0.34)	0	**9**	**26**	35
Citrate dose increased (Ca > 0.34)	0	0	0	0
Total	0	24	26	50

Continuous veno-venous hemodialysis with regional citrate anticoagulation was conducted with blood flow rate at 100 ml/min and dialysate flow rate at 2000 ml/h (Multifiltrate, Fresenius Medical Care, Bad Homburg, Germany).

We analyzed 50 post-filter samples taken from 5 critically ill patients treated with continuous veno-venous hemodialysis–regional citrate anticoagulation, on GEM Premier 4000 (Werfen, Barcelona, Spain) and ABL90 Flex Plus (Radiometer, Copenhagen, Denmark) for low iCa concentrations (0.18–0.43 mmol/L). The Institutional Review Board of Montpellier University Hospital approved the study and waived the need for written consent (IRB-MPT_2020_03_202000392). Consents for publication were obtained. Despite a significant linear correlation ($r = 0.928$), the ABL90 results were higher than the GEM results, with a mean difference at 0.09 mmol/L, 95% confidence interval (0.07–0.11; Supplementary Figures S1 and S2). These discrepancies impacted citrate dose adjustment in 82% of measurements (Table 1), inducing a poor concordance (*Kappa* = 0.24) between BGAs.

Differences were not explained by BGAs' analytical performances, as both devices appeared to be reliable and reproducible (Supplementary Table S1), but potential BGAs calibration differences could be hypothesized. Given that discrepancies were higher in post-filter samples than in $CaCl_2$ diluted in saline (Supplementary Figure S1), a matrix effect could be involved. Our results pointed out the need for standardization of iCa monitoring to control risks of metabolic disorders (e.g., alkalosis, acidosis, hypernatremia, dyscalcemia) or filter clotting, in patients treated with continuous veno-venous hemodialysis –regional citrate anticoagulation. We, therefore, suggest calibrating BGAs using a commutable reference material close to the plasma composition (i.e., containing albumin, globulins, sodium, and other such components) but with very low iCa concentrations.

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