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Atypical Hemolytic and Uremic Syndrome Triggered by Infection With SARS-CoV2

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INTRODUCTION

Atypical hemolytic and uremic syndrome (aHUS), as a form of thrombotic microangiopathy, (TMA) is characterized by a genetic or acquired dysregulation of complement activation, leading to endothelial cell lesions and thrombosis of the small vessels, hemolysis, thrombocytopenia, and acute kidney injury.[S1] Here, we report 2 cases of complement mediated aHUS triggered by infection with SARS-CoV-2.

CASE PRESENTATION

Case 1

A 22-year-old woman was traveling abroad in early January 2021 to visit her boyfriend. Returning to Germany, a mandatory SARS-CoV2 antigen test was performed. The antigen test and a subsequent polymerase chain reaction test showed SARS-CoV-2 infection. Although no symptoms of a respiratory tract infection were present, she had to see her general practitioner (GP) due to diarrhea with persistent vomiting and loss of taste. As the condition did not improve, she presented to the emergency department of another hospital 4 days after she had returned from her trip. Physical examination revealed a normotensive, alert, oriented patient who was pale and in acute distress.

Initial Laboratory Findings

Laboratory findings at admission revealed thrombocytopenia with 28,000 platelets/μl. Hemolytic anemia was present, with a hemoglobin level of 5.5g/dl, elevation of lactate dehydrogenase (LDH) to 2066 U/l, and acute kidney injury (Kidney Disease: Improving Global Outcomes [KDIGO 3] with a serum creatinine of 560 μmol/l.

Clinical Course

During the first days of admission, the patient received 5 packed red blood cell transfusions due to ongoing hemolysis. The detection of schistocytes on a peripheral blood smear confirmed thrombotic microangiopathy, and daily plasma exchange using fresh frozen plasma as substitution solution was initiated. After exclusion of ADAMTS13 deficiency, the diagnosis of aHUS was made, plasma exchange treatment was stopped after the third session, and treatment with the C5-inhibitor eculizumab was initiated. A renal biopsy confirming TMA was performed at day 9 after admission, which was complicated by postinterventional bleeding that was treated by endovascular coiling (Figure 1). Platelet count normalized and hemolysis resolved during the first 10 days (Figure 2a). Hemodialysis treatment could be tapered and finally stopped. Notably, the cycle thresholds value of this patient had already increased to over 35 before plasma exchange was initiated, marking the serologic recovery from SARS-CoV-2 before treatment for aHUS was initiated. During follow-up, the likely pathogenic *CFH* (complement factor H) splice variant c.3493+5G>A (chr1:g.196715134G>A) was identified, which affects a

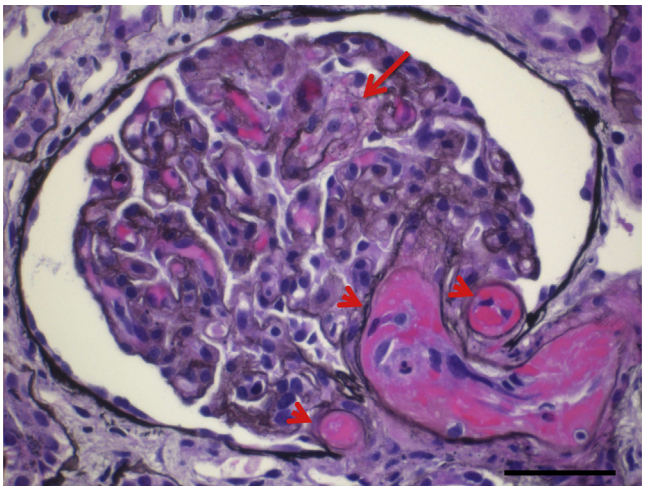

Figure 1. Renal biopsy specimen from case 1 patient. Representative micrograph of thrombotic microangiopathy revealing several glomerular thrombi (arrowheads), 1 of them extending from ectatic preglomerular arteriole into the glomerulum. Mesangiolysis with fibrillar appearance of mesangial tissue containing red blood cell fragments can also be seen (arrow). Ec, eculizumab; IHD, intermittent hemodialysis. Jones methenamine stain combined with hematoxylin and eosin. Bar = 50 μm.

highly conserved residue and is predicted to be pathogenic by all 8 bioinformatics prediction tools used. The change is not reported in any database (gnomAD minor allele frequency/MAF 0%) and has not been described in the literature so far. Internally, we have already detected this variant in our laboratory in 1 of our patients, who demonstrated a similar phenotype and did not bear another variant of (likely) pathogenic character. Conclusively, it is most likely that the above *CFH* variant was causative in our patient.

Case 2

A 52-year-old woman with a history of mild hypertension saw her general practitioner (GP) because of flu-like symptoms, loss of taste, and exhaustion. The GP initiated antibiotic treatment with amoxicillin. Ten days later, the patient returned to the GP with additional abdominal pain and cramps. Blood sampling revealed acute kidney injury (KDIGO 2) with a serum creatinine of 3 mg/dl (264 μmol/l). The patient was readmitted to the hospital. At presentation in the emergency unit, point-of-care testing (Abbott) was positive for SARS-CoV-2. Physical examination showed a hypertensive (162/82 mm Hg), alert, oriented patient in acute distress.

Initial Laboratory Findings

Laboratory findings at admission revealed a hemoglobin level of 9.4 g/dl, elevation of LDH to 885 U/l, and acute kidney injury (KDIGO 1), with a serum creatinine of 2.9 mg/dl (255 μmol/l). Interestingly, platelets were normal with 318,000/μl, but were reported to have been "unusually high" in the past (>400,000/μl).

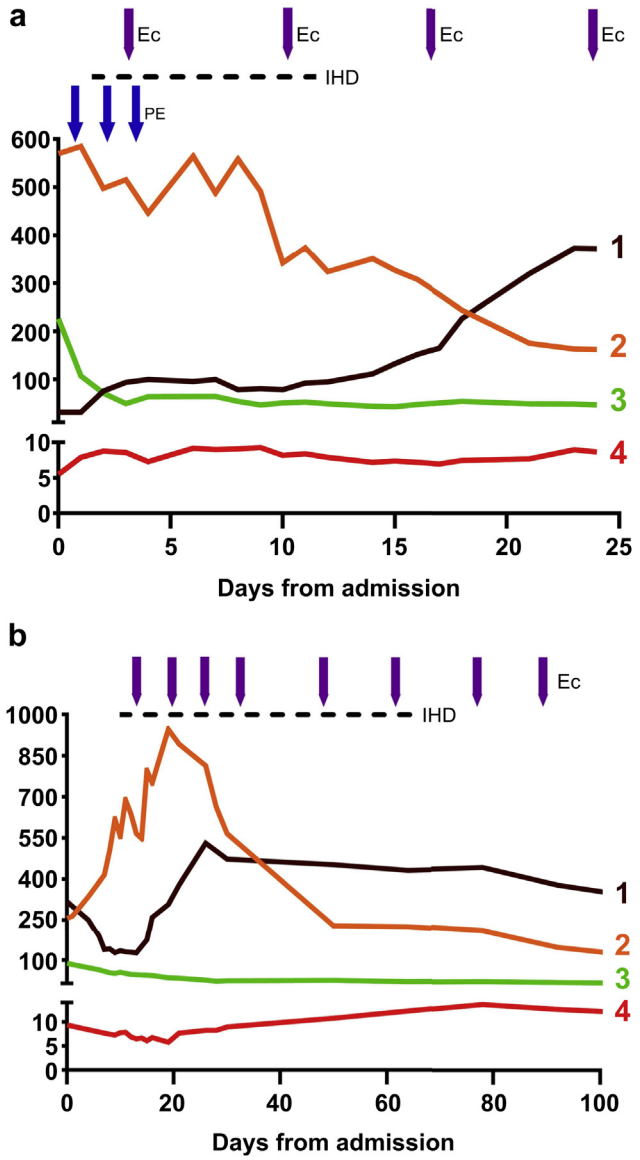

Figure 2. (a) Clinical course of case 1 patient. (b) Clinical course of case 2 patient. 1 = platelets (*10^3/μl); 2 = creatinine (μmol/l); 3 = lactic dehydrogenase (U/dl); 4 = hemoglobin (g/dl). Ec, eculizumab; IHD, intermittent hemodialysis; PE, plasma exchange.

Clinical Course

During the following days, the patient developed progressive hemolytic anemia with detection of schistocytes on a peripheral blood smear and platelets decreased to a minimum of 128,000/μl. Because of progressive renal injury, a renal biopsy was performed 4 days after admission, which was complicated by a postinterventional bleeding, with transfusion of 4 units of packed red blood cells concentrates. Hemodialysis treatment was started 10 days after admission because of volume overload. A renal biopsy specimen showed fibrin-rich glomerular and pre-glomerular thrombotic microangiopathy (Supplementary Figure S1). As ADAMTS13 deficiency had already been excluded (activity 36%), diagnosis of aHUS was made, and

treatment with the C5-inhibitor eculizumab was initiated. Platelets increased to a maximum of 531,000/μl, and hemolysis resolved within 13 days (Figure 2b). Renal recovery was slow, and the patient remained on dialysis treatment for almost 2 months. During follow-up, diagnostic genetic testing revealed the heterozygous variant c.2792G>A p.(Cys931Tyr) (chr1:g.196709758G>A) in *CFH*. Almost all bioinformatic tools (20 of 22 tools used) predict its pathogenicity. To our knowledge, this variant has not yet been reported in the literature (HGMD 2020.4), nor has it been annotated in any database (gnomAD/ MAF 0%). The change is located in the complement control protein 16 domain (CCP16) and affects 1 of 4 conserved cysteine residues of CCP16, which contribute to the tertiary structure of the protein via the formation of 2 disulfide bridges (Cys931-Cys973 and Cys959-Cys984, respectively). Pathogenic changes in these structurally important cysteines, for example, p.(Cys959Tyr) and p.(Cys973Tyr), have been described in patients with CFH deficiency.[S2–S4] They result in severely impaired secretion of the resulting proteins (quantitative deficiency) and reduced ability to regulate complement in the liquid phase and at cell surfaces. Overall, the variant detected can be classified as likely pathogenic according to the respective American College of Medical Genetics and Genomics (ACMG) guidelines. Both patients received vaccination against meningococci, as recommended, and complement inhibitor treatment is currently continued.

DISCUSSION

Endothelial cell activation and thrombotic as well as microangiopathic complications have been described in COVID-19 disease.[1] These features, possibly mediated by complement activation, have led to the assumption of aHUS as a contributing factor in the pathomechanism in COVID-19, and have triggered clinical studies using C5-blockade in the treatment of COVID-19 disease.[2] Commonly recognized triggering factors of aHUS include infections, malignancies, transplantation, pregnancy, or systemic diseases.[S1]

Here, we present 2 cases of female patients with first aHUS episodes after infection with SARS-CoV-2 and recovering from COVID-19 disease, who were successfully treated with eculizumab. In our patients, these episodes mark the first manifestations of aHUS. A pathogenic complement factor H mutation was found in both women presenting as young to middle-age adults.

Yu *et al*. have recently shown that the SARS-CoV-2 spike protein subunits may serve as potent activators of the alternative pathway of complement (APC) by possibly disturbing the binding capacity of factor H to heparin sulfate on cell surfaces and therefore significantly reducing the regulating capacities of factor H in inhibiting the activity of C3 convertase.[3] In patients with inherent CFH mutations, this mechanism may become clinically relevant. In addition, a relapse case of triggering aHUS in a patient with a pathogenic MCP mutation after a mild case of COVID-19 disease has been recently reported by Ville *et al*.[4] Therefore, also other genetic alterations in complement, with a focus on membrane-bound factors, may cause an aHUS episode in patients after infection with SARS-CoV-2, even if the patient may have clinically recovered from the infection. Genetic abnormalities are thought to be present in 50% to 70% of patients with aHUS.[5]

In conclusion, our case reports underline that an infection with SARS-CoV-2 should be recognized as a potent trigger in patients with inherent complement defects, even when the symptoms of infection are mild or the patient has recovered from COVID-19 disease (Table 1). Clinical and laboratory findings suspicious for hemolytic anemia, with/or thrombopenia, should prompt further diagnostic workup regarding thrombotic microangiopathies (Table 2). Cases of unexplained thrombocytopenia as well as aHUS-like syndromes have been reported after vaccination against SARS-CoV-2.[6,7] Vaccination against and infection with SARS-CoV-2 have been associated with new cases or relapses of certain nephropathies such as IgA nephropathy or minimal change disease, hinting toward a link with immune dysregulations.[8,9] Our cases suggest that patients with inherent complement defects may be at risk for relapsing or presenting with a first episode of aHUS

Table 1. When to suspect *atypical hemolytic uremic syndrome* (aHUS) in a patient with confirmed infection with SARS-CoV-2

Platelet count	<150,000/μl *or* ≥25% decrease from baseline
Microangiopathic hemolysis	Schistocytes, elevated lactate dehydrogenase (LDH), decreased heptaglobin, decreased hemoglobin and hematocrit
Organ involvement	Renal impairment including high blood pressure *and/or* neurological symptoms (e.g., confusion, seizures) *and/or* gastrointestinal symptoms (diarrhea, abdominal pain, gastroenteritis)
Rule out TTP	ADAMTS13-activity >10%

Table 2. Key teaching points

1. Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by microangiopathic hemolytic anemia, thrombocytopenia and organ involvement (mainly acute renal injury).
2. aHUS results from excessive complement activation causing endothelial damage, which can be treated by therapeutic complement inhibition.
3. Several "triggers" have been identified to induce complement activation such as infections, arterial hypertension, malignancies, transplantation, pregnancy, or systemic diseases.
4. Genetic alterations (when classified as pathologic) in complement regulating genes make patients more susceptible to aHUS episodes, especially when being exposed to a "trigger."
5. An infection with SARS-CoV2 should be recognized as a potential "trigger" for aHUS.

when infected with SARS-CoV-2. The endothelial damage and activation of the alternative complement system possibly mediated by the spike-protein or other virus components may therefore be independent of clearance of the virus and seroconversion.

DISCLOSURE

The study was supported by the DEFEAT Pandemics platform of the Federal Ministry of Education and Research (BMBF) to TW. All the other authors declared no competing interest.

PATIENT CONSENT

The authors declare that they have obtained consent from the patients discussed in this report.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References

Figure S1. Renal biopsy specimen of second case.

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