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TO THE EDITOR:

COVID-19 as a potential trigger of complement-mediated atypical HUS

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Endothelial cell (EC) injury has emerged as a hallmark of infection resulting from severe respiratory coronavirus 2.[1–3] Complement activation or dysregulation is another notable feature of COVID-19,[4,5] and elevated plasma levels of sC5b-9, a marker of activation of the complement terminal pathway, have been reported in up to 2/3 of COVID-19 patients,[6] and correlate with disease severity.[4,6]

Complement dysregulation is also a well-established pathogenic mechanism of a rare form of renal thrombotic microangiopathy (TMA), the atypical hemolytic uremic syndrome (aHUS), triggered by complement-induced EC damage.[7]

To date, renal TMA has been very rarely documented in the COVID-19 setting.[8,9] We report on 5 patients with COVID-19-associated renal TMA, among whom 4 tested patients carried complement genetic susceptibility factors for aHUS.

Patients with COVID-19-associated renal TMA were identified using the databases of the French HUS Registry and the

Table 1. Characteristics of 5 patients with COVID-19-associated renal TMA

Pt	Sex, age	NK//RT (nephropathy/ time from RT)	Time from COVID-19 diagnosis to TMA	At TMA diagnosis						Kidney biopsy	COVID-19 treatment	TMA treatment	Follow-up	Outcome
				SCr (mg/dL)	Plt (g/L)	Hb (g/dL)	Hapto. (g/L)	LDH (×ULN)	Puria (g/L)					
1	M, 66 y	NK	0 d	10 (HD)	50	9.2	<0.3	>ULN	NA	Glomerular and arteriolar thrombi and EC detachment. Mild ATN.	—	—	3 mo	HD
2	M, 71 y	RT (NAS/18 mo)	12 d	2.3	16	6.9	<0.3	1.7	1	Kidney biopsy performed 3 wk after TMA resolution Glomerulosclerosis. GBM duplication.	Oxygen (3 L/min)	PE (n = 4) Eculizumab (day 4; n = 3) Temporary discontinuation of tacrolimus/ everolimus.	1 mo	SCr 1.7 mg/dL (baseline values)
3	M, 35y	NK	30 d	1.9/7.9 (HD)	11	9.7	<0.3	9	Oliguria	Glomerular and arteriolar thrombi. Mild ATN.	—	PE (n = 11) Eculizumab (day 13; n = 1)	3 mo	HD
4	F, 26 y	RT (FSGS/3.5 mo)	0 d	7.2 (HD)	22	7.2	<0.3	>ULN	NA	—	—	PE (n = 3) Eculizumab (day 21; ongoing) Temporary tacrolimus discontinuation. Rituximab (n = 2)	4 mo	SCr 4.2 mg/dL Eculizumab continued.
5	F, 38 y	RT (IgAN/24 mo)	10d	3.2	103	10.4	<0.3	1.6	0.8	Extensive EC detachment from GBM. Mesangiolysis.	—	Decrease in tacrolimus dosage.	6 mo	SCr 1.8 mg/dL (baseline values)

ATN, acute tubular necrosis; F, female; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; Hapto, haptoglobin; Hb, hemoglobin; HD, hemodialysis; IgAN, immunoglobulin A nephropathy; LDH, lactate dehydrogenase; M, male; NA, not available; NAS, nephroangiosclerosis; NK, native kidneys; PE, plasma exchange; Plt, platelet count; Pt, patient; Puria, proteinuria; RT, renal transplantation; SCr, serum creatinine; ULN, upper limit of normal.

Table 2. Complement work-up performed in 5 patients with COVID 19-associated renal TMA

Pt	Time from COVID-19 diagnosis (d)	Time from TMA diagnosis (d)	C3 (mg/L)	C4 (mg/L)	sC5b-9 (ng/mL)	FH (%)	FI (%)	CD46 (MFI)	Anti-FH Ab (AU)	CFHR1-CFHR3 copy number	Complement genetics	Complement gene variant classification
1	13	3	840	301	761	70	100	12.3	Negative	1	*CFH* c.2266T>A p.Ser756Thr	Pathogenic (reduced FH plasma level)
2	13	1	1750	332	248	144	147	ND	Negative	1	*C3* c.463A>C p.Lys155Gln	Pathogenic (confers resistance to cofactor activity)[12]
	54	42	1040	187	322	109	130	17	Negative			
3	34	3	1320	415	303	91	66	10.3	Negative (sample collected after PE)	0	*CFI* c.1246A>C p.Ile416Leu	Pathogenic (reduced FI plasma level ; Not detected in supernatants and around 25% expression of WT in lysates)[11]
	108	77	1160	461	1094*	94	86	13.8	Positive (4130)			
	167	136	1050	357	570	112	66	ND	Positive (686)			
4	19	19	1220	454	ND	ND	ND	ND	Positive (1554)	2	*CFH* homozygous tgtgt haplotype	aHUS at-risk haplotype
	42	42	1470	507	345	130	161	ND	Positive (1171)			
	122	122	1210	430	ND	ND	ND	ND	Positive (516)			
5	0	0	1270	550	136	120	120	ND	Negative	ND	ND	ND

Normal range: C3: 615-1250 mg/L; C4: 93-380 mg/L; FH 70%-130%; FI 70%-130%; CD46: 13-19 MFI; sC5b9: <300 ng/mL.

CFH, complement factor H gene; CFHR, complement factor H-related protein; *CFI*, complement factor I; MFI, mean fluorescence intensity; ND, not determined; PE, plasma exchange.

*The patient had several complications related to a perirenal hematoma that occurred after kidney biopsy.

Complement reference Centre in Lausanne. COVID-19 infection was diagnosed in all cases, based on a positive polymerase chain reaction test for severe respiratory coronavirus 2 in oropharyngeal swab samples. Renal TMA was defined by at least 3 of the following criteria: (1) thrombocytopenia (platelet count <150 g/L), (2) mechanical hemolytical anemia (hemoglobin <10 g/dL, lactate dehydrogenase serum level >upper limit of normal [ULN], undetectable haptoglobin, presence of schistocytes on blood smear), (3) acute kidney injury (serum creatinine and/or proteinuria/creatininuria >ULN for age or an increase >15% compared with baseline), and (4) features of TMA in kidney biopsy.

Measurement of plasma C3, C4, CH50, factors H (FH) and I (FI), sC5b-9, and CD46 expression on granulocytes and tests for anti-FH antibodies were performed as previously described.[10] Screening for variants and complex rearrangements in complement factor H (*CFH*), complement factor I, membrane-cofactor protein, *C3*, and *factor B* genes was performed using next-generation sequencing and multiplex ligation-dependent probe amplification, as previously described.[10] All patients gave informed consent for genetic testing.

Five adult patients with COVID-19-associated renal TMA were identified in 5 French and Swiss nephrology, renal transplantation, and internal medicine units (Table 1; supplemental Figure 1, available on the *Blood* Web site). None had a personal or familial history of aHUS. Three patients were renal transplant recipients and the cause of their end-stage kidney failure was focal segmental glomerulosclerosis, immunoglobulin A nephropathy (n = 1), and nephroangiosclerosis (n = 1). They presented with a COVID-19-associated renal TMA, 3.5 to 24 months after renal transplantation. At TMA onset, they were receiving tacrolimus (n = 3) and everolimus (n = 1) and none had donor-specific antibodies. All patients had mild respiratory symptoms of COVID-19 and only 1 required low-grade oxygen therapy. The interval between COVID-19 diagnosis and TMA diagnosis ranged from 0 to 30 days. Patients 1, 3, and 4 presented with severe hypertension (systolic 163-212 mm Hg; diastolic 92-130 mm Hg). In all cases, renal dysfunction was severe (serum creatinine, 2.3-10 mg/dL) and 3 patients required hemodialysis. Thrombocytopenia was profound with a platelet count ≤50 g/L in 4 patients. Three patients had extrarenal TMA manifestations: neurological symptoms (confusion, central facial palsy) in patient 2 and intestinal involvement (pain, diarrhea) in patients 3 and 4 (documented by intestinal biopsy disclosing capillary thrombi in patient 3). Renal biopsy performed in 3 patients during the acute phase disclosed typical features of TMA (supplemental Figure 2). In patient 3, a biopsy of the kidney transplant performed 3 weeks after TMA resolution showed duplication/wrinkling of the glomerular basement membrane. In all biopsies, no significant immune deposits were detected. All patients had detectable (>20%) ADAMTS13 activity, and polymerase chain reaction for Shiga toxin in stool was negative in tested patients 2 through 4. No patients had evidence of disseminated intravascular coagulation, with normal fibrinogen, prothrombin, and partial thromboplastin time. Tacrolimus trough levels were 20, 9.2, and 5.7 μg/L in patients 2, 4, and 5, respectively.

Complement work-up performed at the time of TMA (Table 2) showed increased plasma C3 and C4 levels in all patients (probably as part of the inflammatory response) and mildly increased sC5b-9 plasma level in 1 patient. FH and FI plasma levels were decreased in 1 patient. Anti-FH antibodies were detected in 2 patients. In 3 of the 4 patients for whom DNA samples were available, a pathogenic rare variant was detected: 1 *CFH* variant known to be associated to decreased plasma FH levels in vivo, 1 complement FI variant associated to a decreased FI synthesis documented in vitro,[11] and 1 *C3* variant associated to an impaired C3 regulation.[12] An additional patient carried, in homozygosity, the haplotype H3 in the *CFH* gene (tgtgt), an established risk factor for aHUS.[7]

Two patients underwent plasma exchanges with fresh frozen plasma, whereas 3 were treated with eculizumab. Patient 4 received 2 infusions of rituximab for anti-FH antibodies. At the last known follow-up (1-6 months), 2 patients remained dialysis-dependent, 2 renal transplant recipients regained their baseline renal function, and a third had a decreased function of the renal transplant.

Data on COVID-19-associated TMA are scarce[9,13,14] (supplemental Table 1). We report here the first series of renal TMA in COVID-19 patients, which includes extensive complement work-up. The first remarkable finding is the sharp contrast between mild respiratory symptoms but severe renal (and in 3 patients extrarenal) TMA. Therefore, COVID-19–related morbidity was mainly due to TMA rather than to the pulmonary involvement. Three of the patients in the present series and 2 from previously published cases are renal transplant recipients. Underlying kidney graft (vascular) damage and tacrolimus/everolimus use and very high trough levels (particularly in patient 2), may have contributed to trigger TMA in the renal graft.

The second remarkable finding is the detection in 3 tested patients of complement gene variants associated to an altered regulation of the complement alternative pathway, and thus to an increased risk of complement-mediated EC injury. An additional tested patient had the at-risk haplotype (H3) in the *CFH* gene, which predisposes to aHUS. Interestingly, the only previously reported patient with COVID-19–associated renal TMA who was tested for complement gene variants, was found to carry a pathogenic rare variant in the *C3* gene and an at-risk haplotype in the membrane-cofactor protein gene.[9] Thus, to date, all 5 reported patients with COVID-19–associated renal TMA, who underwent genetic testing, carry a constitutional complement dysregulation. These findings require confirmation in larger series. Noteworthy, 2 patients were positive for anti-FH antibodies, but the pathogenic relevance of these autoantibodies is unclear, and their presence may reflect the stimulation of the immune system because of COVID-19, rather than a causal role in the TMA.

The discussion of the role of systemic complement activation has been one of the central issues in the management of COVID-19 patients.[6,15–19] Limited preliminary reports suggested a potential benefit of C5 blockade in severe forms of COVID-19,[6,15] but 2 prospective studies did not show any clear benefit of C5 or C5a

blockade in this setting.[20,21] However, the patients presented here had mild pulmonary COVID-19 manifestations and absent or moderate markers of systemic complement activation. These findings suggest that TMA in our patients resulted predominantly from intrarenal complement activation and ensuing EC damage, associated to a genetic dysregulation of the complement alternative pathway in at least 4 patients (ie, a clinical and genetic pattern of renal TMA similar to the one reported in complement-mediated aHUS). These similarities suggest that HUS is not a unique manifestation of COVID-19, but rather that COVID-19 is a newly identified potential infectious trigger for aHUS, in accordance with previous data on complement-mediated aHUS precipitated by viral infections, mostly influenza strains.[22] The awareness of a potential association of COVID-19 with complement-mediated aHUS may help improve patients' management. The use of anti-complement therapies should be considered in this form of HUS associated with COVID-19, to potentially limit kidney damage. However, the limited number of patients in the present series preclude any firm conclusions, and additional data are required.

In summary, COVID-19 is a potential newly identified trigger for complement-mediated aHUS. The identification of such association has important clinical implications and additional data are required.

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Authorship

Contribution: C.E.S., V.F.-B., and F.F. reviewed the data and drafted the manuscript; C.E.S., P.V.M., A.S., S.S., and V.F.-B. performed the complement workup; S.R. and L.D. analyzed the kidney biopsies; all the authors were involved in the management of the patients; and all authors read, commented on, and revised the manuscript before approval.

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Footnotes

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