Adult post COVID-19 multisystem inflammatory syndrome and thrombotic microangiopathy

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Case Report

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Abstract

Background: The coronavirus disease 2019 pandemic has affected millions of people worldwide but medium and long-term consequences are unknown. Clinical series of Kawasaki-like multisystem inflammatory syndrome in children (MIS-C), occurring after SARS-Cov-2 spreading, have been recently described.

Case presentation: We describe a case of post COVID-19 MIS in a 46-year-old man, with biopsy-proven renal thrombotic microangiopathy (TMA). Specific complement inhibition with Eculizumab was initiated promptly and lead to a dramatic improvement of renal function.

Conclusion: Our case suggests that post COVID-19 MIS is not restricted to children and that TMA could play a central role in the pathophysiology of this syndrome

Background

The coronavirus disease 2019 (COVID-19) pandemic caused by *SARS-Cov2* has affected millions of people worldwide. In adults, COVID-19 is typically characterised by severe interstitial pneumonia and hyperactivation of the inflammatory cascade.¹ There is growing evidence that COVID-19 affects the endothelial system leading to endothelial dysfunction characterised by a pro-inflammatory and pro-coagulative state.^{2,3} However, medium and long-term consequences of COVID-19 are unknown. Clinical series of Kawasaki-like multisystem inflammatory syndrome (MIS), occurring after viral clearance, have been described in children, without histological data.⁴ Recently, a similar case report of MIS was described in an adult.⁵ We report a case of post-COVID-19 MIS in adulthood with biopsy-proven thrombotic microangiopathy (TMA) and improvement after Eculizumab therapy. This case suggests that post-COVID19 MIS is not restricted to children, and that TMA could play a central role in its pathophysiology. Complement blockers might represent promising therapeutic targets in these patients.

Case Presentation

A 46-year-old patient of African ancestry with history of arterial hypertension and obesity (BMI = 36 kg / m²) was admitted to our hospital for hypertensive emergency (189/123 mmHg) and fever. He did not take any medication. Physical examination was normal. SARS-Cov2 PCR on naso-pharyngeal swab was negative (repeated twice), but COVID-19 serology was positive for IgG (80 UA/mL, positive if >12 UA/mL, Immunoassay YHLO iFlash 1800) and negative for IgM. No previous COVID-19 symptoms were reported and no personal treatment, neither self-medication nor toxic intake were noticed to the anamnesis. Thoracoabdomino-pelvic CT scan was unremarkable. First investigations revealed an inflammatory state, anaemia, thrombocytopenia and an acute kidney injury (AKI). Serum creatinine (sCr) level was 169 µmol/L associated with 1g per day proteinuria, aseptic pyuria, no hematuria and low natriuresis (< 20 mmol/L). C-Reactive protein (CRP) level was 312 mg/L and neutrophil count was 18.7 G/L (**Table 1**). On day 4, the patient presented evanescent facial erythema and developed acute myocardial dysfunction

with reduced left ventricular ejection fraction to 40%, pericardial effusion and high sensitive Troponin (hsTroponin) elevation. Taking into account the frequency of vascular thromboses related to Covid-19 disease, a curative anticoagulant treatment with heparin was started. On day 5, neurological impairment appeared with coma leading to intubation and mechanical ventilation. Cerebrospinal fluid analysis was unremarkable. Abnormal supratentorial periventricular MRI signals responsible for a restriction of the diffusion testified to an acute vasculitis. No immunosuppressive treatment was introduced because of concomitant tracheal aspiration positive for *Enterobacter Aerogenes* treated with Trimethoprim-Sulfamethoxazole. On day 7, myocardial and renal function worsened (sCr 660 $\mu\text{mol/L}$), requiring initiation of Dobutamine and renal replacement therapy(RRT).

Renal biopsy light microscopy revealed typical lesions of TMA including fibrin thrombi within glomeruli and myxoid intimal alterations of arterioles and small-to-medium sized renal arteries. The remaining glomeruli were normal without hypercellularity. Significant interstitial infiltrate mainly composed of neutrophils responsible for severe tubulitis and moderate acute tubular necrosis were also present (**Figure 1A**). Immunofluorescence study showed isolated mesangial complement C3c positive deposits without evidence for IgG, IgA, IgM, C1q nor C4d deposits (**Figure 1B**). Immunocytochemistry study showed C5b-9 deposits at the same localization (**Figure 1C**). ADAMTS13 activity was normal (26 %), anticardiolipin, anti β 2GP1, lupus anticoagulant anti-DNA antibodies and Cryoglobulinemia were negative. Complement work-up evaluation found: serum C5b-9 469ng/mL (normal < 420ng/mL), C3 1030mg/L (normal ranges: 660-1250mg/L), C4 69 mg/l (93-380mg/L), CH50 64% (70-130%), no anti-factor H antibodies. Genetic complement studies are ongoing.

On day 8, specific complement inhibition with Eculizumab therapy (900mg) was initiated.

Three days later, cardiac function and neurological impairment improved, urine output increased and blood creatinine decreased, allowing to withdraw Dobutamine, RRT and mechanical ventilation (Table). On day 15, the patient received another course of Eculizumab (900mg). On day 30, patient was discharged from the hospital, sCr was 109 $\mu\text{mol/L}$ and cardiac MRI showed no pericardial effusion, no sequelae of segmental hypokinesia and ejection fraction of the left ventricle was evaluated at 50%.

Discussion And Conclusion

To date, we describe here the first case of adult post-COVID19 MIS associated with thrombotic microangiopathy.

In this case, IgG positive serology, negative PCR swab and the absence of pulmonary involvement demonstrate the post-infectious nature of this syndrome, occurring after viral clearance. Strikingly, our patient presented clinical characteristics of a systemic autoinflammatory disorder similar to post-COVID-19 MIS recently observed in children.^{4,6} A case of adult MIS has been recently described, with similar characteristics unless renal dysfunction. In this case, skin biopsy revealed intra-epithelial collections of

neutrophils with necrotic keratinocytes.⁵ Similarly, in our case, renal biopsy revealed an aggressive interstitial infiltrate, mainly composed of neutrophils, together with TMA.

Kidney involvement is frequent in COVID-19 as more than 40% of cases have abnormal proteinuria at hospital admission.⁷ Few histological data are available, showing in most cases ATN, collapsing glomerulopathy or TMA in patients with ongoing Covid-19.⁸⁻¹¹ TMA injury has been also reported in lungs and skin with sustained activation of the complement alternative and lectin pathways, during COVID-19.¹⁵ TMA pathophysiology involves multiple hits but complement activation plays a crucial role.^{12,13} Our case suggests for the first time that endothelial involvement and TMA, could have a major role in post-Covid 19 MIS, even in the absence of active SARS-CoV-2 infection. In our patient, histological findings consisting in glomerular C3c and C5b9 deposits, together with elevated sC5b9 levels, were suggestive of complement system activation, involving the formation of the membrane attack complex (MAC).

Eculizumab is a monoclonal anti-C5 antibody that blocks the formation of the MAC on endothelial cells surfaces and has revolutionized the prognosis of renal TMA known as atypical Haemolytic and Uremic syndrome.^{17,18} A previous report has suggested the safety and potential benefits of Eculizumab in COVID-19,¹⁹ and randomized trials are currently ongoing (SOLID-C19 trial, NCT04288713). Whether or not Eculizumab could have a role in post-COVID-19 MIS will need further studies.

This description suggests that post-COVID-19 MIS is not restricted to children.⁵ It also shows for the first time that complement-mediated thrombotic microangiopathy could play a central role in its pathophysiology. Similar cases are expected in countries affected by SARS-Cov2 pandemic.

Abbreviations

AKI: Acute Kidney Injury

BMI: Body Mass Index

CRP: C-Reactive protein

hsTroponin: High Sensitive Troponin

MAC: Membrane Attack Complex

MIS-C : multisystem inflammatory syndrome in children

PCR: Polymerase Chain Reaction

RRT: renal replacement therapy

sCr : Serum creatinine

Declarations

Competing interests: The authors declare that there is no conflict of interest regarding the publication of this article.

Ethics approval and consent to participate: The authors declare that the patients reported here provided consent for use of their medical records for publication. As description of case is not considered as research, no approval of the hospital ethics committee is needed.

Consent for publication: After information, a signed consent was obtained from the patient to publish the clinical presentation along with any identifying images to be published in the study.

Availability of data and materials: All data and materials are available on demand. This patient has never been reported in a previous publication.

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Authors' contributions: IB and FP have written the manuscript. MR is the pathologist who made the diagnosis and took photograph as figure 1. KEK, LMC, MM participated to the proofreading and the collection of data. AM and LTR performed the biochemical and genetic analysis of the alternate complement pathway. FP is the corresponding author.

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Table

Table. Clinical and laboratory findings

Finding	Days from hospital admission																				30
	1	2	3	4	5	6	7	8*	9	10	11	12	13	14	15*	16	17	18	19		
Clinical	Respiratory status	SB	SB	SB	O2	MV	MV	MV	MV	MV	MV	MV	SB	SB	SB	SB	SB	SB	SB	SB	
	Dobutamine (gamma/kg/min)	-	-	-	-	-	-	5.75	10	10	10	5	-	-	-	-	-	-	-	-	
	Urine output (L/day)	-	-	-	0.3	0.3	0.5	0.7	0.8	0.9	3	7.8	6.9	7.4	5.2	6.3	4.2	2.8	2.7	2.2	
	Temperature (°C)	40.7	40.6	40	40.2	39.1	38.7	38.4	37.3	38.1	36.3	36.8	36.2	36.1	36.2	36	35.7	34.7	35.7	36	
Laboratory	Creatinine (μmol/L)	169	225	348	536	627	666	RRT	691	RRT	441	395	324	256	208	167	147	130	151	129	
	CRP (mg/L)	312	469	528	621	551	462	319	292	213	153	87	58	45	32.9	25	19	12.9	11.4	8.8	
	Leukocyte count (G/L)	18.7	15.7	20	25	25.1	26.8	25.7	26.7	19.9	17	12.3	11.9	10.3	9.3	7.7	8	5.5	4.4	3.3	
	Lymphocyte count (G/L)	0.4	-	0.7	1.1	-	1.8	1.7	0.7	-	1.4	0.7	0.8	-	1.2	1.1	0.6	0.8	0.8	1	
	Hemoglobin level (g/dL)	12.3	9.8	8.3	7.5	7.1	6.6	7.3	7	6.2	6.7	7.6	7.8	8.7	8.7	9.2	9.7	8.8	9.7	9.3	
	Platelet count (G/L)	98	90	97	288	392	450	392	339	260	261	267	267	311	315	330	347	304	326	300	
	INR	1.1	-	1.1	1.2	-	1.2	1.3	-	-	-	-	-	-	-	-	-	-	-	-	
	LDH (UI/L)	461	432	473	-	-	-	491	636	435	449	413	386	-	372	358	333	280	288	243	
	CPK (UI/L)	-	-	1082	-	-	-	825	-	-	-	-	-	-	-	-	-	-	-	-	
	hsTroponine (ng/L)	25	74	-	1006	1700	2791	2464	1669	-	1048	628	481	294	214	130	98.7	-	120	140	
	Haptoglobin (g/L)	-	-	-	2.91	2.91	-	-	-	-	-	-	-	-	-	-	-	2.67	2.41	2.71	
	Ferritin (μg/L)	-	3206	-	-	3538	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Fibrinogen (g/L)	-	-	7.1	10.9	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	Triglycerides (mmol/L)	2.12	-	-	2.87	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	schistocytes (%)	-	-	<1	<1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<1	
	ProtU / creatU (mg/g)	996	-	-	-	-	686	-	-	-	-	-	-	-	-	-	-	-	-	90	
Others	HBV, HCV, HIV 1 serology : negative ; glycosylated ferritin 12% (N > 20%); Antinuclear antibodies 1/160; Anti-DNA antibodies: negative; Cryoglobulinemia : negative; anti-cardiolipoin antibodies: negative; antib2gp1 antibodies: negative; lupus anticoagulant: negative; Anti-neutrophil cytoplasmic antibody : negative																				

SB: spontaneous breathing; O2: oxygenotherapy; MV: mechanical ventilation; RRT: Renal Replacement Therapy.

*Eculizumab 900mg on day 8 and day 15.

Figures

Figure 1

Kidney biopsy findings. A) Light microscopy analysis: Fibrin thrombi within glomerular capillary loops (black triangle). Small inter-lobular artery with intimal mucoid alterations and endothelial cells swelling (black arrow). Arteriolar occlusion (*). Polymorphonuclear infiltration with tubulitis (red arrow head) and granular casts (yellow arrow head) (Jones methenamine silver staining, x200). B) Immunofluorescence study showing predominant mesangial and sub-endothelial C3 deposits in glomeruli and in glomerular arteriole. (Anti-C3 fluorescein isothiocyanate-conjugate x400). C) Immunohistochemistry study showing positive C5b-9 staining in arterioles, inter-lobular artery and glomeruli within the mesangium (Mouse IgG, B7 antineoepitope, 1 X40). 1 Kindly provided by Prof. P. Morgan (Cardiff Institute of Infection&Immunity, UK)