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Life-threatening COVID-19 presenting as stroke with antiphospholipid antibodies and low ADAMTS-13 activity, and the role of therapeutic plasma exchange: A case series

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Abstract

We present a case series of three patients with COVID-19 who were admitted to our intensive care unit due to acute respiratory distress syndrome, brain infarction, pulmonary embolism, and antiphospholipid antibodies. We applied therapeutic plasma exchange on all cases. On intensive care unit admission, all patients had low (<10) Glasgow Coma Scale, and central nervous imaging showed multiple brain infarctions. COVID-19 was confirmed by reverse transcriptase polymerase chain reaction assays. Patients underwent rescue therapeutic plasma exchange using the Spectra Optia™ Apheresis System (Terumo BCT Inc., USA), which operates with acid-citrate dextrose anticoagulant as per Kidney Disease Improving Global Outcomes 2019 guidelines. A dose of 1.5 plasma volume was used for the first dose and then 1 plasma volume daily for a total of five doses. Plasma was replaced with Octaplas LG® (Octapharma AG, USA), which is an artificial fresh frozen plasma product that has undergone viral inactivation by prion reduction technology. We administered ARDS-net/prone positioning ventilation, empiric antiviral treatment, therapeutic anticoagulation, and intensive care unit supportive care. Laboratory tests showed lymphocytopenia; elevated levels of D-dimer, fibrinogen, total bilirubin, C-reactive protein, lactate dehydrogenase, and ferritin; as well as low levels of ADAMTS-13 activity and antibody. Serology tests depicted positive IgM and IgG antiphospholipid antibodies (anti-cardiolipin and anti-β2-glycoprotein 1 antibodies). No side effects of therapeutic plasma exchange were recorded. After the completion of therapeutic plasma exchange, patients improved clinically and gradually recovered neurologically (after 27–32 days). To conclude, in life-threatening COVID-19, especially when immune dysregulation features such as antiphospholipid antibodies exist, therapeutic plasma exchange could be an effective rescue therapy.

Keywords

COVID-19, antiphospholipid antibodies, brain infarction, ADAMTS-13 activity, therapeutic plasma exchange, artificial plasma

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Introduction

The novel SARS-CoV-2 (COVID-19) pandemic emerged from Wuhan, China, and spread worldwide.[1] Most patients with COVID-19 are asymptomatic; however, a minority of cases can present with life-threatening diseases, which are characterized by acute respiratory distress syndrome (ARDS), sepsis, multi-system organ failure (MSOF), cytokine release syndrome (CRS), neurological manifestations, and thrombo-embolic disease.[2–4] Recently, severe COVID-19 was associated with devastating central nervous system (CNS) pathology, including stroke, and acute disseminated encephalomyelitis.[5] Moreover, severe thromboembolic phenomena were observed in mechanically ventilated critically ill patients

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Table 1. Criteria for defining CRS in COVID-19.

One or more of the following criteria should be present[a]
C-reactive protein >100 or >50 mg/L but doubled in the past 48 h
Lymphocyte count $<0.6 \times 10^9$/L
Serum interleukin-6 (IL-6) $\geq 3\times$ upper normal limit
Ferritin >300 µg/L (or surrogate) with doubling within 24 h
Ferritin >600 µg/L at presentation and LDH >250 U/L
Elevated D-dimer (>1 µg/mL)

CRS: cytokine release syndrome; LDH: lactate dehydrogenase.
[a]We define the presence of one criterion for developing CRS as low risk, the presence of two to three criteria as moderate risk, and the presence of more than three criteria as high risk.

with COVID-19.[6–10] The clinically observed thrombotic microangiopathy in COVID-19 was further confirmed by the pathology results of post-mortem studies.[11,12]Also, this vasculopathy in COVID-19 has a comparable thrombotic phenotype and inflammatory profile (i.e. elevated C-reactive protein, D-dimers, ferritin, lactate dehydrogenase, and interleukin-6) with thrombotic microangiopathies such as thrombotic thrombocytopenic purpura.

The rationale for using therapeutic plasma exchange (TPE) as an adjunctive rescue therapy in life-threatening COVID-19 is that TPE can reduce the hyperinflammation associated with COVID-19, thus ameliorating the microangiopathy and preventing the evolution of MSOF. TPE, without protective antibodies, has been previously used with variable success in patients with severe sepsis, MSOF, and fulminant SARS-CoV, although its benefit remains undetermined in severe ARDS.[13,14] In a recent pilot study, our group showed that the application of TPE early in the course of life-threatening COVID-19 resulted in a reduction in inflammatory biomarkers and a favorable clinical outome.[15] Herein, we briefly discuss three COVID-19 patients who presented with ARDS, thromboembolic disease, brain infarction, and antiphospholipid antibodies.

Case

We present three patients who were admitted to our COVID-19 designated intensive care unit (ICU) due to ARDS, thromboembolic disease, and low Glasgow Coma Scale (GCS). The inclusion criteria for the application of TPE as rescue therapy in life-threatening COVID-19 are detailed elsewhere.[16] Briefly, adult (<18 years old) mechanically ventilated patients with confirmed SARS-CoV-2 infection and life-threatening features such as ARDS (according to the Berlin criteria), Acute Physiology and Chronic Health Evaluation II score ⩾20, severe sepsis/septic shock, MSOF, and associated CRS were eligible for TPE.[16] CRS was defined based on the criteria outlined in Table 1.

SARS-CoV-2 infection was confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) assays performed on nasopharyngeal swabs using QuantiNova Probe RT-PCR kit (Qiagen) in a Light-Cycler 480 real-time PCR system (Roche, Basel, Switzerland).[17,18] Upon ICU admission, CNS computed tomography (CT) scan and CT angiography revealed multiple diffuse brain infarctions, which were consistent with a microangiopathic pattern in all patients. Following written informed consent obtained by their legal representatives, the patients underwent rescue TPE, without protective antibodies. TPE was initiated 24–48 h after ICU admission, using the Spectra Optia™ Apheresis System (Terumo BCT Inc., USA), which operates with acid-citrate dextrose anticoagulant as per Kidney Disease Improving Global Outcomes 2019 guidelines.[19,20]A dose of 1.5 plasma volume was used for the first dose and then 1 plasma volume daily for a total of five doses (4 h/day). Intravenous calcium replacement, hydrocortisone 100 mg, and chlorpheniramine 10 mg were administered during TPE to reduce any potential side effects. Plasma was replaced with artificial Octaplas LG® (Octapharma AG, USA), which is a fresh frozen pooled plasma product that has undergone viral inactivation by prion reduction technology.[21]

The main characteristics and laboratory findings of our patients are summarized in Table 2. On ICU admission, they presented with ARDS, pulmonary embolism, and GCS <10. We administered ARDS-net/prone positioning ventilation, empiric treatment with ribavirin, interferon beta-1b, therapeutic anticoagulation (enoxaparin adjusted per body weight and renal function), and ICU supportive care.[22] No other putative immunomodulatory therapies such as tocilizumab were administered. Echocardiography and cardiac enzymes were normal. Baseline laboratory findings were lymphocytopenia, increased D-dimers, fibrinogen, and low levels of ADAMTS-13 activity/antibody (TECHNOZYM® ELISA).[23] Also, patients had increased levels of total bilirubin, C-reactive protein, lactate dehydrogenase, and ferritin (Table 2). Notably, follow-up serology tests, which were performed once, depicted IgM and IgG antiphospholipid antibodies (anti-cardiolipin and anti-β2-glycoprotein I antibodies). Lupus anticoagulant was not detected although the tests were carried out in the acute phase of the disease.

After five TPE sessions, no side effects of treatment such as coagulopathy, infection, and allergies were recorded. Sequential Organ Function Assessment (SOFA) scores from 8 to 9 (baseline) were reduced to <4 post-TPE. Partial arterial pressure of oxygen to fractional inspired concentration of oxygen (SPO_2 to FiO_2) ratios from 120 to 140 (baseline) increased to >300 post-TPE; hence, all patients were gradually weaned off the mechanical ventilation. All inflammatory biomarkers and lymphocyte counts were equally normalized post-TPE. ADAMTS-13 activity from 8% to 15% (baseline) increased to 22% to 28% post-TPE. All patients gradually recovered and neurologically improved (GCS >10); hence, they were all discharged to step-down units for rehabilitation. The ICU length of stay was 27–32 days (Table 2). RT-PCR for COVID-19 and microbiology were negative 30 days post-ICU admission.

Table 2. Characteristics, laboratory findings, and outcome measures of patients with COVID-19.

Characteristic	Patient 1	Patient 2	Patient 3
Demographic characteristics			
Age (years)	65	49	62
Sex	Male	Male	Female
Nationality	Asian	Asian	Middle Eastern
Baseline features			
Medical history	Hypertension, Diabetes	Previously healthy	Hypertension, diabetes
Symptoms prior to hospital admission	Fever, persistent cough, myalgias, dyspnea	Fever, persistent cough, headache, anosmia	Fever, persistent cough, diarrhea, headache
Duration of symptoms (days)	7	5	8
Cluster infection (Yes/No)	No	Yes	No
Baseline chest imaging findings	Bilateral opacities/infiltrates and subsegmental pulmonary embolism	Bilateral opacities/infiltrates and subsegmental pulmonary embolism	Bilateral opacities/infiltrates and subsegmental pulmonary embolism
Deep vein thrombosis (Doppler sonography)	Yes	No	No
Days from disease onset to thrombotic event	8	6	10
Findings on intensive care unit admission			
Days since disease onset	10	9	12
Sequential Organ Function Assessment score	9	9	8
Acute Physiology and Chronic Health Evaluation II score	21	22	21
Partial arterial pressure of oxygen to fractional inspired concentration of oxygen	120	120	140
Mechanical ventilation (Yes/No)	Yes	Yes	Yes
Laboratory findings			
White cell count (per mm^3)	12,270	9980	10,320
Total neutrophils	11,200	9,102	9,450
Total lymphocytes	210	190	230
Platelet count (per mm^3)	102,000	101,900	150,240
Hemoglobin (g/L)	112	116	109
Albumin (g/L)	25.7	24.8	23.2
Alanine aminotransferase (U/L)	45	62	34
Aspartate aminotransferase (U/L)	51	78	44
Total bilirubin (μmol/L)	24	28	27
Creatine kinase (U/L)	84	121	97
Creatinine (μmol/L)	74	71	59
High-sensitivity cardiac troponin I (pg/mL)	6.3	4.1	5.9

(Continued)

Table 2. (Continued)

Characteristic	Patient 1	Patient 2	Patient 3
Prothrombin time (s)	15.2	15.9	15.5
Activated partial-thromboplastin time (s)	45.1	44.8	47.1
Fibrinogen (g/L)	4.23	4.78	4.09
Fibrin degradation products (mg/L)	29.7	20.1	30.8
D-dimer (mg/L)	13.2	12.1	11.9
ADAMTS 13 activity (%)	10%	8%	15%
ADAMTS 13 IgG (U/L)	10	7	11
Serum ferritin (μg/L)	778	1006	1289
High-sensitivity C-reactive protein (mg/L)	142	201	169
Antiphospholipid antibodies[a]	Anticardiolipin, anti-β2-glycoprotein I IgM, and IgG	Anticardiolipin, anti-β2-glycoprotein I IgM, and IgG	Anticardiolipin, anti-β2-glycoprotein I IgM, and IgG
Central nervous system imaging features	Multiple cerebral infarctions in bilateral frontal/parietal lobes and bilateral cerebellar hemispheres	Multiple cerebral infarctions in bilateral frontal/parietal lobes	Right middle cerebral artery infarction and bilateral occipital lobe infarctions
Intensive care unit therapy	Ribavirin, antibiotics, therapeutic anticoagulation	Ribavirin, antibiotics, therapeutic anticoagulation	Ribavirin, antibiotics, therapeutic anticoagulation
Plasma exchange without therapeutic antibodies (sessions)	5	5	5
Outcome measures			
Days on mechanical ventilation	18	20	22
Intensive care unit length of stay (days)	27	30	32
Secondary bacterial infection (Yes/No)	No	No	No
Glasgow Coma Scale upon intensive care unit discharge	14	14	13
Hospital length of stay (days)	40	42	48

[a]Antiphospholipid antibodies (IgM and IgG): Patient 1: 42 MPL/44 GPL; Patient 2: 44 MPL/46GPL; Patient 3: 41 MPL/42 GPL. MPL refers to IgM phospholipid units: one MPL unit is 1 μg of IgM antibody; GPL refers to IgG phospholipid units: one GPL unit is 1 μg of IgG antibody. Laboratory reference values: $<$15.0 MPL or GPL (negative), 15.0–39.9 MPL or GPL (weakly positive), 40.0–79.9 MPL or GPL (positive), and $\geqslant$80.0 MPL or GPL (strongly positive).

Discussion

Life-threatening COVID-19 was linked to the development of CRS, vasculopathy, and CNS pathology.[2–5,24]The underlying mechanisms of brain infarction in COVID-19 could be indeed versatile as both microangiopathy and large artery disease were reported.[5] In this case series, follow-up serology tests depicted IgM and IgG antiphospholipid antibodies. These antibodies are characteristic in the diagnosis of antiphospholipid syndrome when at least two elevated measures are depicted 5–6 weeks apart. We were able to measure these antibodies only once; hence, their presence could have been attributed to other putative cofounders such as sepsis, critical illness, and strong immunological responses linked to COVID-19.[15,25] However, the strict biological diagnosis of CRS in COVID-19 remains debatable.[26,27] Notwithstanding, the main rationale for applying TPE on COVID-19 is the suppression of thromboinflammation and the amelioration of the ensuing microangiopathy. The latter was partially attributed to the ability of the virus in binding with the angiotensin-converting enzyme 2 (ACE2) receptor, thus causing direct endothelial injury and thromboinflammation, and promoting the dysregulation of the immune and the renin–angiotensin–aldosterone systems.[28]

Recently, we applied TPE on patients with life-threatening COVID-19 and associated CRS.[15] We showed that TPE can significantly reduce the levels of inflammatory biomarkers and improve the clinical outcome of critically ill patients with COVID-19 without causing any side effects. Herein, we present three distinct COVID-19 patients who had multiple brain infarctions, coagulopathy with associated antiphospholipid antibodies, and pulmonary embolism. The patients clinically improved after the administration of TPE. Various authors suggested that there is minimal immunosuppression associated with TPE compared to other immunomodulatory therapies, although this issue remains debatable.[13–16,21,28–31] TPE can discreetly remove significant proportions of interferon-gamma, interleukin-3, -10, -1B, -6, -8, and tumor necrosis factor-alpha.[13–16,20,28] In this series, no severe coagulopathy or disseminated intravascular coagulation (DIC) was recorded. We showed for the first time, to our knowledge, decreased levels of ADAMTS-13 activity in COVID-19, which were also correlated with progression to MSOF and poor prognosis in sepsis.[30,32] However, COVID-19-associated coagulopathy has distinct features compared to DIC as the former is mainly associated with increased D-dimer and fibrinogen levels. Thromboembolic disease is more common in COVID-19 compared to sepsis-induced coagulopathy. The present results further supported the notion that COVID-19-associated coagulopathy may exhibit overlapping features of hemophagocytic syndrome, antiphospholipid antibodies, and thrombotic microangiopathy.[33,34] Also, we used an artificial plasma product as replacement in the TPE regime. The rationale for using this product was its safety profile and reduced high-molecular-weight forms of von Willebrand factor.[21] TPE with artificial plasma replenishment resulted in a gradual increase in ADAMTS-13 activity and lymphocyte counts, and a subtle decrease in inflammation biomarkers such as lactate dehydrogenase, C-reactive protein, ferritin, and D-dimers in COVID-19 patients. No side effects of TPE such as allergies, coagulopathy, thrombotic events, infections, or deterioration of cardiac or renal function were recorded.

This report, albeit its several limitations that prevents its generalizability, illustrated the beneficial effect of TPE on patients with life-threatening COVID-19 with associated thromboinflammation and CNS pathology. In this case series, brain magnetic resonance imaging could not be performed on admission, thus rendering challenging the differential diagnosis between cerebral microangiopathy and a potentially reversible cerebral vasculitis. The lack of control brain imaging following clinical remission prevented a detailed analysis of the therapeutic results. Also, our patients might have improved due to other empiric treatments, including anticoagulation therapy, which were promptly administered; however, given the severity of their clinical picture, TPE might have helped.[2–10,35] TPE could be an alternative rescue therapy in severe COVID-19 compared to the more expensive and time-consuming convalescent plasma transfusions that did not show any additional survival benefit in recent trials.[36] However, the cost and resources of TPE are not negligible. This is why we advocated its use only as rescue therapy. Moreover, the natural course of SARS-CoV-2 viremia is obscure, with conflicting reports suggesting reinfections and/or persistently positive RT-PCR results; hence, the optimal TPE regime and the timing of therapy need to be further elucidated.[37,38] Nevertheless, we applied TPE early in the course of fulminant COVID-19 to mitigate full-blown CRS and ameliorate the ensuing thromboinflammation, which was characterized by decreased levels of ADAMTS-13 activity. Presumably, at an early stage of COVID-19, dysregulated immune system pathology and associated thromboinflammation may be equally important as viral replication per se.[39] This might at least partially explain why the administration of low-dose dexamethasone showed a beneficial effect on survival in critically ill patients with COVID-19.[40]

Conclusion

In life-threatening COVID-19, the underlying mechanisms of brain infarction, low levels of ADAMTS-13 activity, and ensuing thromboinflammation with microangiopathy may be attributed to versatile pathophysiology. TPE may discreetly improve the exaggerated inflammatory immune response and prevent the progression of microangiopathy and organ-related microthrombosis. In life-threatening COVID-19, especially when immune dysregulation features such as antiphospholipid antibodies exist, TPE could be an effective and safe rescue therapy.

Authors' contributions

All authors equally contributed to data acquisition/analysis and drafting this manuscript. All authors reviewed the final version of this manuscript and agree with its submission to the journal.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this case series was obtained by the Institutional Review Board of King Saud Medical City, Riyadh, Saudi Arabia (H-01-R-053, IORG0010374#, serial number: H1RI-29-20-01).

Informed consent

Written informed consent was obtained from a legally authorized representative for anonymized patient information to be published in this article.

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Data availability

All datasets used in this study are available by the corresponding author upon a reasonable request.

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