CASE REPORT

A severe case of systemic lupus erythematosus-associated diffuse alveolar haemorrhage post-COVID-19 infection

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SUMMARY

Coronavirus disease 2019 (COVID-19) is a life-threatening respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There have been numerous cases of COVID-19 with autoimmune and rheumatic manifestations, including systemic lupus erythematosus (SLE). However, the association between SLE and COVID-19 infection remains unclear. Here, we report a young female who was diagnosed with severe SLE with lupus nephritis and diffuse alveolar hemorrhage 1 month after COVID-19 infection. She was admitted to the intensive care unit and required mechanical ventilation. Despite being given high doses of corticosteroids, cyclophosphamide, intravenous immunoglobulin and initiated on plasmapheresis, she continued to deteriorate and eventually died. Previous case studies have reported newly diagnosed SLEs post-COVID-19 with varied clinical manifestations, ranging from benign and self-limiting features to life-threatening systemic syndromes. More studies are required to understand the mechanisms triggering these immune-related manifestations so that early diagnosis can be achieved and the appropriate therapy administered.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease which can affect many organs. Its pathogenesis is not fully understood, but evidence suggests a multifactorial aetiology, including genetic, environmental and hormonal factors.1

COVID-19 has caused a global pandemic since late 2019. Its clinical spectrum is broad, ranging from asymptomatic infection to life-threatening cytokine storm and multiorgan dysfunction. Previous articles have reported the detection of autoantibodies in COVID-19 patients and development of autoimmune diseases associated with COVID-19 infection.2 However, the role of COVID-19 in autoimmunity remains unclear.

To date, there are only a few reported cases of SLE triggered by or developed after COVID 19 infection. Most of these patients developed mucocutaneous manifestations, vasculitis, serositis, cytopenias and nephritis which mostly improved with immunosuppressive treatments. Here, we describe a case of severe SLE with diffuse alveolar hemorrhage (DAH) post-COVID-19 infection who did not improve despite administration of immunosuppressive agents and plasmapheresis.

CASE PRESENTATION

An 18-year-old girl presented with polyathralgia for three months associated with fever, constitutional symptoms, dyspnoea, facial swelling and frothy urine for 1 week. She had background history of well-controlled bronchial asthma diagnosed at the age of 8 years old. She had just recovered from COVID-19 category 2, 1 month prior without need for admission. She did not have any family history of autoimmune disorder or malignancy.

Her vital signs on admission were stable. On physical examination, she had facial puffiness and minimal pedal edoema bilaterally. Her cardiovascular, respiratory and abdominal examination were unremarkable. Otherwise, she did not have alopecia, malar or discoid rash and oral ulcers. Laboratory investigations revealed pancytopenia, mild acute kidney injury, hypoalbuminemia and raised inflammatory markers (Table I). Her direct Coomb's test was positive, while her full blood picture did not show any features of hematological malignancies or haemolysis. Urinalysis revealed proteinuria and haematuria with the presence of pathological casts. Her quantified 24-hour urine protein was 2.8 g over 24 hours. Tests for human immunodeficiency virus, hepatitis B and C were negative. Her electrocardiogram showed normal electrical activity, while her chest radiograph showed presence of fluid in fissures with mild cardiomegaly. Her complement levels were low and serologies were positive for antinuclear antibodies (1:640, homogenous) and anti-dsDNA. The clinical and laboratory findings led to the diagnosis of SLE (2019 ACR/EULAR score of 26) with hematological and renal involvement. A renal biopsy was performed, which revealed Class IV Lupus nephritis (Activity index 16/24, chronicity index 2/12). She was treated with 500 mg of intravenous methylprednisolone for 3 days and 500 mg of intravenous cyclophosphamide subsequently for active SLE. Her symptoms improved, and she was discharged with tapering oral prednisolone.

She was readmitted 5 days later with fever, dyspnoea, lethargy and worsening bilateral leg swelling. Vital signs on

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Table I: Blood investigations during first admission

	Admission Day 1	Admission Day 8	Admission Day 15	References
White blood cells	3.6	6.0	9.9	4–10 × 10^9/L
Hemoglobin	8.6	8.5	7.8	13–17 g/dL
Platelet	89	146	197	150–410 × 10 9/L
Absolute neutrophil	1.9	3.8	3.2	2–7 × 10 9/L
Absolute lymphocyte	1.4	2.0	1.8	1–3 × 10 9/L
Urea	9	10.3	19.61	2.76–8.07 mmol/L
Sodium	137	137	139	136–145 mmol/L
Potassium	4	3.1	4.0	3.4–4.5 mmol/L
Creatinine	157	137	139	44–80 umol/L
Albumin	12		24	32–54 g/L
Bilirubin	8		5.3	< 21 u/L
Alanine transaminase	6		10	<23 u/L
Alkaline phosphatase	44		34	45–87 u/L
Lactate dehydrogenase	306			<279 u/L
Creatinine kinase				<123 u/L
Erythrocyte sedimentation rate	140			0–12 mm/H
C-Reactive protein	1.6			<5 ng/LC
3/C4	0.07/0.02			C3 : 0.90–1.80 g/L C4 : 0.10–0.40 g/L
ANA	1:640 (homogenous)			
dsDNA	Positive			
ENA	Anti-DSF 70: positive Anti-SSa/Ro : positive Anti-Ro52: positive Anti-nucleosome: positive Anti-histone: positive			
Antiphopholipid antibodies	LA: negative aCL: negative B2GP1: negative			

ANA, antinuclear antibody; dsDNA, double-stranded DNA; ENA, extractable nuclear antigen; LA, lupus anticoagulant; aCL. anti-cardiolipin antibody; B2GP1, anti-beta 2 glycoprotein 1 antibody; C3, complement 3; C4, complement 4.

Table II: Blood investigations during second admission

	Day 1	Day 3	Day 6	Day 15	Day 25	References
White blood cells	7.4	1.6	2.3	3.9	11.2	4–10 × 10^9/L
Hemoglobin	5.9	4.5	5.5	7.6	7.0	13–17 g/dL
Platelet	120	52	42	50	29	150–410 × 10^9/L
Absolute neutrophil	6.2	1.3	1.7	2.3	10.5	2–7 × 10^9/L
Absolute lymphocyte	0.5	0.3	0.7	0.4	0.6	1–3 × 10^9/L
Urea	15.2	14.1	21.2	25.5	32.8	2.76–8.07 mmol/L
Sodium	139	141	145	142	141	136–145 mmol/L
Potassium	3.9	3.9	3.6	4.3	4.6	3.4–4.5 mmol/L
Creatinine	124	115	116	116	224	44–80 umol/L
Albumin	21	18	29	24	24	32–54 g/L
Bilirubin	13	14	25	28	32	< 21 u/L
Alanine transaminase	15	11	10	22	11	<23 u/L
Alkaline phosphatase	40	28	33	44	47	45–87 u/L
Aspartate transaminase	21	17	20	57	51	<27 u/L
Lactate dehydrogenase	261	331	290	300	290	<279 u/L
Creatinine kinase	22			58	85	<123 u/L
Erythrocyte sedimentation rate						0–12 mm/H
C-Reactive protein	3.2	40		36	216.8	<5 ng/L
PT		10.7	11.0	11.1		9.4–11.0s
INR		1.03	1.06	1.07		0.90–1.10
APTT		21.4	21.9	25.1		22.2–31.0s
C3	0.26					C3: 0.90–1.80 g/L
C4	0.4					C4 : 0.10–0.40 g/L

PT, prothrombin time; INR, international normalised ratio; APTT, activated partial thromboplastin time

admission revealed blood pressure of 131/75 mmHg, pulse rate of 119 beats per minute, temperature of 38.5oc and oxygen saturation of 91% under room air. On physical examination, she appeared tachypnoeic with a respiratory rate of 28 breaths per minute. There were coarse crepitations heard over bilateral lower and middle zones of the lungs, while her cardiovascular and abdominal examinations were unremarkable. Laboratory investigations showed severe anaemia, thrombocytopenia, mild acute kidney injury and hypoalbuminemia (Table II). Polymerase chain reaction for COVID-19 was negative. Her chest radiograph revealed bilateral lower zone to midzone consolidations. She did not have any signs of overt bleeding. She was promptly started on intravenous piperacillin-tazobactam, hydrocortisone, face mask oxygen supplementation and transfused with one unit of packed cell.

Unfortunately, she continued to deteriorate 3 days later as she developed persistent fever, worsening anaemia and desaturation. Repeated chest radiographs revealed worsening infiltrates over bilateral lung fields and she was intubated for respiratory distress. On day 6 of admission, she developed multiple bouts of fresh blood and blood-stained aspirate from her endotracheal tube accompanied by frequent desaturations with progressive increment in ventilatory settings.

She was treated with multiple courses of antibiotics and antifungals, including carbapenems, polymyxin B and fluconazole. There was no evidence of ongoing haemolysis. She was transfused with 11 units of packed cell in total. The presence of positive hemosiderin laden macrophage on tracheal aspirate cytology confirmed the diagnosis of diffuse alveolar hemorrhage and she was initiated on plasmapheresis. She completed six sessions of plasmapheresis. She developed carbapenem-resistant Enterobacteriaceae (CRE) *Klebsiella pneumoniae* bacteraemia after the 6th session of plasmapheresis and shortly oliguric acute kidney injury, requiring continuous renal replacement therapy. She continued to receive IVIG as salvage therapy and methylprednisolone, but her condition did not improve. She eventually passed away after 25 days of admission.

DISCUSSION

Viral infections are one of the triggers for SLE. Many mechanisms have been implicated in virus-induced autoimmunity, including molecular mimicry, innate immunity activation, direct cytotoxicity and others.[3] COVID-19 has been implicated as one of the possible triggers for autoimmune disease, including SLE. Fernandez-Ruiz et al.[4] postulate that a baseline increase in interferon activity in SLE protects against contracting or developing adverse outcomes from COVID-19.[4] Sawalha et al believe that COVID-19 infection in SLE patients leads to a delayed and dysregulated IFN response, causing a hyperinflammatory response and a worse outcome.[5]

DAH is a life-threatening condition caused by bleeding from the pulmonary microcirculation and is characterised by anaemia, haemoptysis, diffuse pulmonary infiltrates on radiograph and hypoxaemia. DAH in SLE is caused by alveolar capillaritis due to deposition of immune complexes in the lungs. Although the incidence of DAH in SLE is only 0.6–5.4%, it carries a mortality rate as high as 85.7%.[6] Older age, longer SLE disease duration, plasmapheresis or mechanical ventilation, concurrent infection, active lupus nephritis, hypoalbuminemia, hypocomplementemia and thrombocytopenia are poor prognostic factors for SLE-associated DAH.[7] There is lack of randomised controlled trials for treatment of SLE-associated DAH. Besides implementing supportive therapy, use of methylprednisolone, cyclophosphamide, intravenous immunoglobulins (IVIGs), plasmapheresis and rituximab have been described in various case reports. Plasmapheresis is an effective therapy for autoimmune DAH as it removes pathogenic immune complexes. A recent large study showed 55% improvement in patients with autoimmune disease associated DAH treated with plasmapheresis.[8] Rituximab has also been described in several case reports to successfully treat DAH. Due to its delayed action, rituximab is often used in combination with other therapies, such as glucocorticoids or cyclophosphamide. Other experimental strategies such as administration of intrapulmonary recombinant Factor VIIa, use of extracorporeal membrane oxygenation support and mesenchymal stem cell transplantation have been described in the literature with varying success.[9]

In our case, we postulate that her previous COVID-19 infection triggered a dysregulated immune response leading to severe manifestations of SLE, including lupus nephritis and DAH in which she responded inadequately to glucocorticoids, cyclophosphamide, plasmapheresis and IVIG therapy. Although infectious complications of plasmapheresis therapy have not been emphasised previously, there is a possibility that our patient was severely immunodeficient after plasmapheresis and cyclophosphamide therapy, rendering her more susceptible to nosocomial infections and a rapid deterioration in her condition.

We identified eight published case reports describing the diagnosis of SLE after COVID-19.[10] Including our case, patients who developed SLE after COVID-19 infection had a mean age of 39 years old and 6 patients were females. The mean duration to diagnosis of SLE post-COVID-19 infection was 22 days. Interestingly, six out of the nine patients had renal failure, five out of nine patients had serositis and four out of nine patients had athritis. None of the patients had DAH except our case. Six out of the nine patients survived while the remaining three patients, including our patient died.

CONCLUSION

In conclusion, we present a patient diagnosed with severe SLE following COVID-19 infection. She developed Class IV lupus nephritis and DAH one month after COVID-19 infection and responded poorly to glucocorticoids, cyclophosphamide, IVIG and plasmapheresis. Our case highlights the need to be aware of the development of severe lupus disease post-COVID-19 infection as prompt diagnosis and appropriate therapy could potentially improve patient outcomes.

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CONFLICT OF INTEREST

None.

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