



# Concomitant new diagnosis of systemic lupus erythematosus and COVID-19 with possible antiphospholipid syndrome. Just a coincidence? A case report and review of intertwining pathophysiology

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Received: 14 June 2020 / Revised: 20 July 2020 / Accepted: 23 July 2020 / Published online: 28 July 2020  
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## Abstract

In the midst of the COVID-19 pandemic, further understanding of its complications points towards dysregulated immune response as a major component. Systemic lupus erythematosus (SLE) is also a disease of immune dysregulation leading to multisystem compromise. We present a case of new-onset SLE concomitantly with COVID-19 and development of antiphospholipid antibodies. An 18-year-old female that presented with hemodynamic collapse and respiratory failure, progressed to cardiac arrest, and had a pericardial tamponade drained. She then progressed to severe acute respiratory distress syndrome, severe ventricular dysfunction, and worsening renal function with proteinuria and hematuria. Further studies showed bilateral pleural effusions, positive antinuclear and antidouble-stranded DNA antibodies, lupus anticoagulant, and anticardiolipin B. C3 and C4 levels were low. SARS-Cov-2 PCR was positive after 2 negative tests. She also developed multiple deep venous thrombosis, in the setting of positive antiphospholipid antibodies and lupus anticoagulant. In terms of pathophysiology, COVID-19 is believed to cause a dysregulated cytokine response which could potentially be exacerbated by the shift in Th1 to Th2 response seen in SLE. Also, it is well documented that viral infections are an environmental factor that contributes to the development of autoimmunity; however, COVID-19 is a new entity, and it is not known if it could trigger autoimmune conditions. Additionally, it is possible that SARS-CoV-2, as it happens with other viruses, might lead to the formation of antiphospholipid antibodies, potentially contributing to the increased rates of thrombosis seen in COVID-19.

**Keywords** Antiphospholipid syndrome · Autoimmunity · COVID-19 · Cytokine release syndrome · Systemic lupus erythematosus

## Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease caused by a complex interplay of genetics and environmental exposure with various possible triggers [1]. Coronavirus disease 19 (COVID-19) is an infection caused by a novel coronavirus SARS-CoV-2, which became a pandemic in 2020 after an initial outbreak in Wuhan, China [2].

Early reports from COVID-19 pathophysiology suggest that an overt inflammatory response, akin to cytokine release syndrome, could be a major contributing factor in the morbidity and mortality [3]. It is known that both SLE and APLS can be triggered by viral illnesses [4–6]; however, there is very little literature to suggest that COVID-19 could be potentially associated with SLE presentation, although that was already theorized in the literature [7].

Patients with SARS-CoV-2 infection show a severe inflammatory cytokine release storm which leads to high expression of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-alpha, that leads to clinical presentations similar to autoimmune diseases [7]. It is well documented that environmental triggers, such as viral infection, lead to the activation of innate and acquired immune response in genetically predisposed patients. Therefore, one can suspect that genetically predisposed

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patients show viral susceptibility, and this can lead to the development of rapid autoimmune dysregulation causing hyper-inflammatory autoimmune diseases [7].

We present a catastrophic case of new-onset SLE with possible antiphospholipid syndrome and concomitant COVID-19 in an 18-year-old female. We also discuss the pathophysiological basis for a possible association between those entities and implications for therapy.

## Case description

An 18-year-old Hispanic female with a past medical history of autism spectrum disorder and panic disorder presented to an outside hospital (OSH) due to a 2-day history of productive cough, shortness of breath, and fevers superimposed on a month's history of upper respiratory symptoms and overall malaise. In the OSH, she was noted to be tachypneic, tachycardic, and hypotensive, with subsequent deterioration into cardiac arrest. ROSC was achieved after 5 min. Point-of-care ultrasound in the emergency department showed pericardial effusion with tamponade physiology. Emergent pericardiocentesis was performed with drainage of 400 cc of amber colored fluid (exudate—3.6 g/dL protein, LDH 275 U/L) with subsequent improvement in hemodynamics. Initial labs were significant for serum creatinine (SCr) of 2.0 mg/dL, blood urea nitrogen (BUN) of 49 mg/dL, white blood cell (WBC) count of 10.500/ $\mu$ L (80% neutrophils), hemoglobin 9.5 g/dL, and platelets 242.000/ $\mu$ L. Arterial blood gas initially showed a pH of 7.2, PaCO<sub>2</sub> of 35 mmHg, and PaO<sub>2</sub> of 63 mmHg on 100% of fraction of inspired oxygen (FiO<sub>2</sub>). Chest X-ray showed multifocal airspace consolidation, predominantly in the middle and lower lung fields and bilateral pleural effusions. Follow-up transthoracic echocardiography showed left ventricular ejection fraction (LVEF) of 20–25% with left ventricle dilatation and no regional wall motion abnormalities.

She remained on mechanical ventilation and later developed severe acute respiratory distress syndrome (ARDS) with a PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 78, requiring very high positive end expiratory pressure (PEEP), up to 20, on high FiO<sub>2</sub> (80–100%). She tested negative for SARS-CoV-2 with PCR-RT, 4 days apart. Viral panel was otherwise negative. Of note, she developed lymphopenia with lowest absolute lymphocyte count of 0.3 thousand/ $\mu$ L.

Over the course of a week, her renal function deteriorated, and she developed anuria requiring hemodialysis (HD). As this progressed, further studies were performed. Urinalysis showed proteinuria (urine protein/creatinine ratio 2.84) and hematuria, and serologies were positive for antinuclear antibodies (1:2560), antidouble-stranded DNA, and low complement levels. Additionally, the patient was found to have

anticardiolipin antibodies as well as positive lupus anticoagulant. All those findings led to a diagnosis of SLE (ACR/EULAR 2019 score of 22) (Table 1).

During her stay at the OSH, she received pulse steroids for 3 days, 4 days of ceftazidime, vancomycin, azithromycin, and hydroxychloroquine. She was then transferred to our service for ECMO evaluation and higher level of care.

Upon admission, she was continued on steroids and underwent one session of plasmapheresis as a second line therapy for severe manifestations of SLE. Furthermore, there was still high clinical suspicion for COVID-19, and the patient was retested for a third time with PCR-NAAT, which came back positive. Then, plasmapheresis was discontinued due to a concern of possible removal of antibodies needed for the adaptive response to SARS-CoV-2. She was managed supportively for severe ARDS, including pronation for 3 days. She received 1 dose of tocilizumab as part of our hospital protocol for severe COVID-19 with elevated inflammatory markers. She also developed severe anemia and thrombocytopenia (respective nadirs 5.4 g/dL and 32.000), thought to be multifactorial, which resolved with supportive care and transfusions. She then developed multiple DVTs, raising concerns for antiphospholipid syndrome, and was started on anticoagulation.

She went into pulseless electrical activity arrest on combined day 17 of hospitalization and unfortunately passed away.

## Discussion

Systemic lupus erythematosus is a multisystem, autoimmune disease characterized by systemic inflammation and tissue damage. The disease is an interplay between the immune system, hormones, and the environment, as well as genetic susceptibility [1, 4, 8]. Our patient presented with a new diagnosis of SLE, possible APLS, and concomitant COVID-19. There are no reported cases, thus far, that we are aware of, of a patient diagnosed with both COVID-19 and new-onset SLE, although there were reports of an association between antiphospholipid syndrome and COVID-19 [9].

In this patient's case, there was overlap between findings consistent with SLE and COVID-19, such as myopericarditis and pulmonary compromise. Prior data showed that pericardial effusion is common in SLE, found in 10–54% of patients [10], while it is rare in COVID-19, subject of case reports [11]. Cardiac tamponade is uncommon but reported in both conditions [12–15]. Additionally, she had left ventricle dilation, reduced EF, global hypokinesis, and troponin elevation (peak 0.8 ng/dL), which, in the setting of pericardial effusion, likely suggests myopericarditis that could be seen in both SLE and in COVID-19 [10, 16].

Pulmonary manifestations are common in SLE, with pleural effusion being the most common one, affecting almost 50% of patients during their lifetime [17]. On the other hand, in COVID-19, pleural effusions are uncommon, roughly seen in about 2% of patients [18]. The patient also had multifocal

airspace consolidation on chest X-ray, which could be seen in 34% of SLE patients with pulmonary manifestations [17]. In comparison, in COVID-19, this imaging modality shows bilateral pneumonia appearance in about 70% of patients [19]. Our patient was not submitted to a high-resolution

**Table 1** Laboratory values

General	Labs at admission	Peak/nadir values	Other relevant labs
Hemoglobin (g/dL)	9.5	5.4 (day 2)	
Platelets (units/ $\mu$ l)	242.000	32.000	
White blood cell count (thousand/ $\mu$ l)	10.2	38.6	
Absolute lymphocyte count (thousand/ $\mu$ l)	1.5	0.3 (day 4)	
Creatinine (mg/dL)	2.0	4.6 (day 8)	
BUN (mg/dL)	49	82 (day 17)	
ABG - p.H/PaO <sub>2</sub> /PaCO <sub>2</sub> (mmHg)	7.2/35/63 on 100% FiO <sub>2</sub>		
Creatinine kinase (U/L)	564		
<b>Inflammatory</b>			
Ferritin ( $\mu$ g/L)	Not performed	2112 (day 16)	
LDH (U/L)	751	805 (day 8)	
CRP (mg/dL)	0.94	3.73 (day 8) (< 0.49 reference value)	
ESR (mm/h)	Not performed	38 (day 7)	
<b>Coagulation</b>			
D-dimer (ng/mL DDU)	1784 (<230)	2443 (day 11)	
Fibrinogen (mg/dL)	169 (148–435)		
INR	1.1	1.7	
PTT (s)	32	54	
Dilute Russell viper venom (s)		85	
Drvv <sub>t</sub> 1:1 mix (seconds)		59	
Drvv <sub>t</sub> confirmation		Positive, day 6	Negative, day 8
Anticardiolipin IgA (U/mL)		12.1 (< 12 reference value) day 6	Negative days 8, 13
Anticardiolipin IgM/IgG (U/mL)		Not performed day 6	Negative days 8.13
Antibeta-2-glycoprotein I IgM/ IgG		Not performed day 6	Negative day 8
<b>Immunology</b>			
Antinuclear antibody (HEp-2)		>= 1:2560, homogeneous pattern	
Antidouble-stranded DNA (IU/mL)		943 (< 4 reference value)	
Antihistone			Positive
Anti-SSA		Negative	
Anti-SSB		Negative	
Antismith		Negative	
Rheumatoid factor		Negative	
Anti-RNP antibody		Negative	
c-Anca		Negative	
p-Anca		Negative	
Antimitochondrial M2		Negative	
C3 (mg/dL)		29 (83–193)	
C4 (mg/dL)		9 (15–57)	
Urine protein/creatinine ratio			2.84
Urine hemoglobin			Positive
Urine RBCs			Too many to count
Beta-2-microglobulin			16.9 (1.21–2.70 reference value)

computerized tomography of the chest, whose findings would have been useful in differentiating those entities.

Regarding demographics in COVID-19, less than 1% of patients requiring ICU level of care were younger than 20 years old, and about 5% had less than 40 years of age with unreported prevalence of autoimmune diseases [2, 20]. Of note, our patient had 2 negative SARS-CoV-2 PCR tests and was positive on the third test, which could be explained by the reported sensitivity for nasopharyngeal swab being around 70% and operator dependent for an adequate specimen collection [21, 22]. Although we cannot exclude that she could also have acquired COVID-19 while hospitalized, literature is scarce on hospital-acquired COVID-19.

Generally, SLE patients are at an increased risk of infections due to the dysfunction in the innate and adaptive immune systems because of the development of autoantibodies, immune complexes, and impaired clearance of apoptotic and necrotic material [4]. In this context, COVID-19 generates a robust immune response. The S protein of coronavirus binds to the host cells via the angiotensin-converting enzyme 2, ACE2, fuses with the membrane, and releases the viral RNA [23]. The ACE2 receptor is found in the lower respiratory system, which leads to an inflammatory response in the lower lung airways. This causes a downstream initiation of pathways which can activate cytokines and chemokines such as IL-1, IL-2, IL-4, IL-7, IL-10, IFN-gamma, and TNF- $\alpha$  [3, 23]. This cytokine storm is thought to be central in this disease process that leads to acute respiratory distress syndrome and multi-organ failure [3, 23].

The adaptive immune system in patients with SLE is typically impaired and could be possibly further compromised in the infection with the novel coronavirus. Various studies have shown increased autoreactivity of helper T cells, cytotoxic T cells, B cell differentiation, and autoantibody production in SLE [8]. This leads to impairment in the production of interferon gamma, IL-1, IL-2, and TNF  $\alpha$ , compromising a Th1 type of response, which is, generally, more effective than a Th2 response against viral infections [8, 24]. The change in the cytokine production with the shift from the Th1 to Th2 cells has been described with HIV infection, and this could be a potential explanation in COVID-19 leading to the occurrence of autoimmune phenomenon and potentially disease. Prior reports also found an association between Epstein-Barr virus, parvovirus B19, retrovirus, and cytomegalovirus and the pathogenesis of autoimmune diseases [4, 5, 8]. Those factors might explain why the patient had severe COVID-19 and an unfavorable outcome. As a side note, both the patient's mother and grandmother had only mild COVID-19.

Additionally, the patient was found to have anticardiolipin A antibodies, lupus anticoagulant, and thrombocytopenia. While in the ICU, she developed multiple DVTs and was started on anticoagulation. This clinical presentation raised concern for APLS. Although it was not possible to fulfill the

modified Sapporo criteria as the patient unfortunately passed away before 12 weeks for repeat testing, two explanations are possible. First, she might have developed APLS in the setting of SLE [25]. Second, transient lupus anticoagulant and antiphospholipid antibodies are known to develop in the setting of viral infections, and a growing body of literature suggests that COVID-19 could also be associated with these findings [6, 9].

Although recent data has shown that COVID-19 predisposes to both venous and arterial thromboembolisms, the exact pathophysiology involved in this hypercoagulable state is not clear. However, there seems to be a severe inflammatory state that causes not only the life-threatening pneumonia but also a severe derangement of hemostasis [26]. While it was initially hypothesized that patients were hypercoagulable from acute disseminated intravascular coagulation (DIC), others believe that a profound derangement of hemostasis and endothelial dysfunction might be the etiology [26]. In addition to that, a case series reported that COVID-19 was associated with antiphospholipid antibodies and thrombosis in multiple vascular territories [9]. This could explain partially why as many as 31% of critically ill patients in the ICU with COVID-19 were found to have thrombotic complications [27].

Infectious agents have been shown, *in vivo*, to trigger the formation of antiphospholipid antibodies through molecular mimicry between bacteria or viruses and the beta2-glycoprotein-I (such as its lipid-binding site), especially in genetically susceptible patients, potentially leading to a prothrombotic state and fetal wastage [28, 29]. These patients can have both venous and arterial thrombi, most commonly lower extremity DVTs and ischemic strokes [28]. This could be through either the direct formation of thrombi or activation of endothelial cells, platelets, and other cells activating the coagulation cascade [28]. Viruses have been associated with formation of anti-beta-2-glycoprotein antibodies, which could be more strongly related to the characteristic manifestations of APLS [6, 29, 30]. Nonetheless, this could explain in part our patient's multiple DVTs, as well as the increased incidence of thrombotic complications in patients with COVID-19, and could guide clinicians who are diagnosing and managing future cases with similar thromboembolic complications. Furthermore, additional research is needed to determine if there is a relationship between antiphospholipid antibodies and hypercoagulability in COVID-19, including better understanding of how SARS-CoV-2 might induce the generation of these antibodies in predisposed individuals.

Different therapeutic approaches targeting the cytokine storm, such as IL-6 and IL-1 inhibitors, corticosteroids, and JAK2 inhibitors, are postulated as possible treatments for COVID-19 patients by blunting the dysregulated immune response [31–33]. The patient received high dose steroids as she had an indication for that from the SLE standpoint. She also

received Plaquenil and tocilizumab which were being used as compassionate drugs at that point. Further research on various medications for COVID-19 acting in the cytokine release syndrome is ongoing to answer if that might lead to better outcomes for patients.

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