SARS-CoV-2 and Anti-Cardiolipin Antibodies

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ABSTRACT: The current COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to distinct diagnostic and management challenges for front-line healthcare workers. The risk of excessive coagulation activation leading to a cascade of thrombotic events in critically ill patients with SARS-CoV-2 is now well reported. We discuss a recent case of COVID-19 with concurrent acute pulmonary embolism and a positive cardiolipin antibody (IgM). The presence of antiphospholipid antibodies is key to diagnosing antiphospholipid syndrome (APS). However, their presence can be transient or persistent after viral infections. Serial inflammatory markers in conjunction with anti-phospholipid antibody testing is critical for the diagnosis of APS in this emerging patient population. Our case report reviews details suggestive of APS in the setting of SARS-CoV-2 and aims to provide clinical diagnostic clues that could help warrant further workup and assist with management strategies.

KEYWORDS: SARS-CoV-2, covid-19, antiphospholipid syndrome, anticardiolipin, coagulopathy, critical care, coronavirus, pulmonary embolism, thrombosis, hematology

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Introduction

Patients hospitalized for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are at risk for excessive coagulation activation leading to thrombotic events and poor prognosis.[1-3] Recently, Harzallah et al[4] reported on antiphospholipid antibody testing in 56 patients with confirmed or suspected SARS-CoV-2. Of these, 25 patients were found to be positive for lupus anticoagulants, while 5 patients had either anticardiolipin or anti–β2-glycoprotein 1 antibodies. Similarly, Zhang et al[5] described 3 SARS-CoV-2 patients with coagulopathy, thrombocytopenia, and the presence of anticardiolipin IgA who developed multiple cerebral infarcts. A Dutch observational study found a remarkably high incidence (49%) of thrombotic events in patients with SARS-Cov-2 after adjusting for the competing risk of death.[6] Based on a review of literature, it appears that SARS-CoV-2 induces a hypercoagulable state; theorized to be associated with hypoxia, immobilization, or disseminated coagulopathy.[4-11] Further, elevated levels of antiphospholipid antibodies may contribute to between SARS-Cov-2 and an acquired coagulopathy.[8] However, the exact mechanisms remain unclear.

Case Presentation

We report a case of COVID-19 with concurrent acute pulmonary embolism and a positive cardiolipin antibody (IgM). Our patient is a 64-year-old male with chronic obstructive pulmonary disease (not on home oxygen), asthma, obstructive sleep apnea, hypertension, obesity, and a previous history of hepatitis C who originally presented on with complaints of shortness of breath, loss of appetite, fatigue, and diarrhea for 1 week. His oxygen saturation was 86% on room air. Nasopharyngeal swab testing by RT-PCR for SARS-CoV-2 was positive and the patient was then admitted to the intensive care unit. Despite worsening respiratory status, he refused intubation; he was started on hydroxychloroquine, azithromycin, ceftriaxone, and prednisone, as at that time the existing data supported their use in this patient population. Two days later, he was transferred to floor on a non-rebreather. The patient continued to improve and required only 2 liters of oxygen and was discharged home.

The following week, the patient returned to the hospital complaining of severe right-sided pleuritic chest pain. His vital signs included a heart rate of 120's and a respiratory rate of 30's while on 2 liters/minute of oxygen with good saturations. The patient was re-admitted for COVID-19 pneumonia. The next day, he remained tachycardic requiring 4 liters of oxygen. D-dimer was 3404 and a subsequent computed tomography angiogram of chest revealed multifocal pneumonia and multiple bilateral pulmonary emboli with right heart strain (Figure 1). Intravenous (IV) heparin treatment was planned but delayed for 36 hours because of persistently elevated partial thromboplastin time (PTT) while off any anticoagulation medication. IV heparin was eventually started without referencing PTT, and the dosing of heparin was rather adjusted based on anti-factor Xa. Three days later, the patient was discharged home on rivaroxaban. His labs revealed positive titers for cardiolipin antibody IgM while IgG was not detected. Additionally, a hereditary hypercoagulable workup was negative, ruling out other potential of coagulation (Table 1).

Discussion

The presence of antiphospholipid antibodies is key to diagnosing antiphospholipid syndrome (APS). However, their presence

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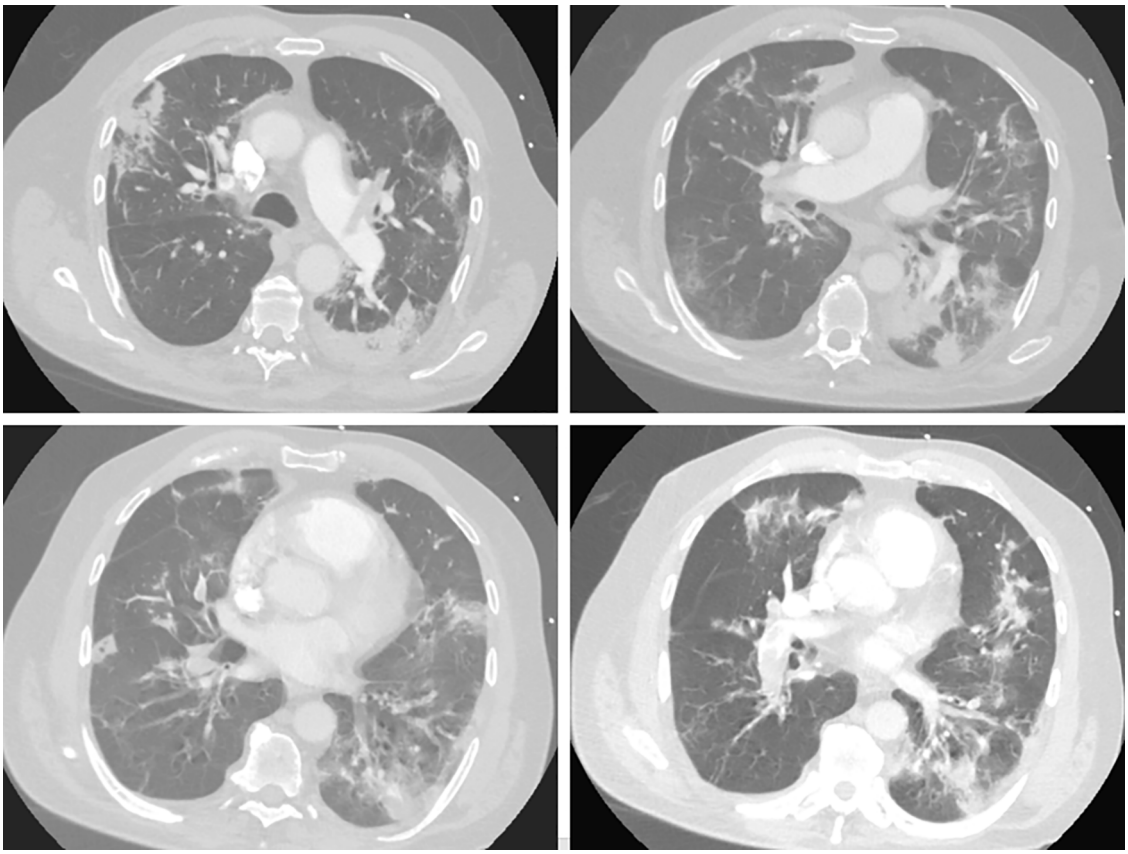

Figure 1. Computed tomography angiogram of chest revealed multifocal pneumonia and multiple bilateral pulmonary emboli.

Table 1. The table demonstrates the diagnostic findings on each of the labeled dates during the patients' hospitalization.

	ONSET OF SYMPTOMS	4 DAYS AFTER ONSET OF SYMPTOMS	13 DAYS AFTER ONSET OF SYMPTOMS	17 DAYS AFTER ONSET OF SYMPTOMS	NORMAL RANGE
White cell count (per mm^3)	11,300	12,200	11,200	6500	4400-10,700
Neutrophils (%)	82	83.1	78.6	69.4	45-72
Lymphocytes (%)	13	11.4	11.5	20.3	16-40
Monocytes (%)	2	4.3	8.6	8.1	5.5-13.5
Platelet count (per mm^3)	231	405	271	276	140-375
Hemoglobin (g/liter)	17.5	14.7	13.6	13.5	13.5-17
Alanine aminotransferase (units/liter)	108	ND	67	ND	10-55
Aspartate aminotransferase (units/liter)	234	ND	40	ND	6-32
Creatinine (mg/deciliter)	1.33	0.86	0.91	0.86	0.7-1.4
Lactate dehydrogenase (units/liter)	863	ND	247	ND	105-235
C-reactive protein (mg/deciliter)	8.9	ND	9.9	ND	0-0.8
Interleukin 6 (pg/ml)	90.52	ND	ND	ND	0-5.0
Troponin I (ng/ml)	0.03	ND	0.02	ND	<0.05
Procalcitonin (ng/ml)	0.39	ND	ND	ND	<0.10

(Continued)

Table 1. (Continued)

	ONSET OF SYMPTOMS	4 DAYS AFTER ONSET OF SYMPTOMS	13 DAYS AFTER ONSET OF SYMPTOMS	17 DAYS AFTER ONSET OF SYMPTOMS	NORMAL RANGE
Serum ferritin (ng/ml)	1877	ND	616.1	ND	11-435
Prothrombin time (s)	11.5	ND	14.5	ND	9-12
Activated partial-thromboplastin time (s)	37.1	ND	41.4	76.2	24-35
Fibrinogen (mg/deciliter)	ND	ND	689	ND	200-500
d-dimer (ng/ml)	720	ND	3404	ND	-
RT-PCR COVID-19	detected	ND	detected	ND	PCR detection
Imaging features	Interval development of mild patchy bilateral airspace disease on Chest X-Ray on April 4th		Multifocal pneumonia and multiple bilateral pulmonary emboli as below with prominence of the right side of the heart and the main pulmonary artery per CT chest angiogram on April 17th		
Additional hypercoagulability studies performed on April 19	Protein C activity 145% (ref. range 70%-180%); protein S activity 60% (ref. range 70%-150%); DRVVT 41 s (ref. range <=45 s), DRVVT mix not indicated; factor V Leiden not detected; prothrombin gene G20210 not detected; anti-neutrophil cytoplasmic antibody negative; anti–β2-glycoprotein I ND; cardiolipin antibody IgG <14 GPL (ref. range <= 14 GPL) and IgM titer positive 50 (ref. range <= 12 MPL)				

Abbreviations: DRVVT, dilute Russell's viper venom time; GPL, IgG phospholipid units; MPL, IgM phospholipid units.
*ND denotes not determined.

can be transient or persistent after viral infections.[12] According to the International Society of Thrombosis and Hemostasis criteria for APS it is necessary to determine anti–ß2-glycoprotein 1antibodies and 2 positive antibody tests separated by 12 weeks are required for diagnosis (because the phenomenon is often transient). This proves increasingly difficult during the current pandemic as many patients are lost to follow up. Furthermore, we don't have enough long term follow up data to know if these patients truly have antiphospholipid syndrome, or if the antiphospholipid antibodies are transient and in response to the septic phase of SARS-CoV-2. Currently, the risk factors, prevalence, and timing of the development of antiphospholipid antibodies in SARS-CoV-2 is not yet understood. Additional prospective clinical epidemiologic studies are warranted to explore the coagulopathy patterns in these patients.

In our opinion and in the current pandemic, these suspected patients should be further worked up for APS and clinicians should not withhold the use of anticoagulation therapies due to an increase in PTT alone nor should they withhold thrombolytic therapy in the event of a high-risk pulmonary embolism solely on the basis of a prolonged PTT.[13] We believe doing so may ultimately delay treatment and possibly lead to worse outcomes. Finally, once APS is confirmed, we suggest switching to subcutaneous low molecular weight heparin as opposed to a direct oral anticoagulant based on its increased risk of thrombotic events in the setting of APS.[14] This basis for such a modification of therapy must be based on repeated measurements of positive antibodies.

In summary, the risk of developing thromboembolism in patients with SARS-Cov-2 is a growing concern. This coupled with the paradoxical prolongation of PTT in APS makes management challenging. We suggest patients who are hypercoaguable who are found to have features suggestive of APS (ie, prolonged PTT, IgM cardiolipin antibodies) should be closely monitored with a full APS workup and followed-up after hospital discharge as the optimal treatment plan may differ.

Author Note

MJ, MS and KZ wrote and edited the paper.

Consent

The patient gave consent for publication of this manuscript.

Disclosure

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