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A 31-Year-Old Man with COVID-19-Associated Empyema and Lupus Anticoagulant

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Patient: Male, 31-year-old
Final Diagnosis: COVID provoked thromboembolism • COVID-19
Symptoms: Bleeding • thrombosis
Medication: —
Clinical Procedure: Thoracentesis • video-assisted thoracoscopic surgery (VATS)
Specialty: Hematology • Infectious Diseases

Objective: Unknown ethiology • Unusual clinical course

Background: COVID-19 was declared a pandemic in March 2020 in the United States. It has been associated with high mortality and morbidity all over the world. COVID-19 can cause a significant inflammatory response leading to coagulopathy and this hypercoagulable state has been associated with worse clinical outcomes in these patients. The published data regarding the presence of lupus anticoagulant in critically ill COVID-19-positive patients is limited and indicates varying conclusions so far.

Case Report: Here, we present a case of a 31-year-old man who was admitted to the hospital with COVID-19 pneumonia, complicated with superadded bacterial empyema and required video-assisted thoracoscopic surgery with decortication. This patient also had prolonged prothrombin time on preoperative labs, which was not corrected with mixing study. Further workup detected positive lupus anticoagulant and anti-cardiolipin IgM along with alteration in other coagulation factor levels. The patient was treated with fresh frozen plasma and vitamin K before surgical intervention. He had an uneventful surgical course. He received prophylactic-dose low molecular weight heparin for venous thromboembolism prophylaxis and did not experience any thrombotic events while hospitalized.

Conclusions: COVID-19 infection creates a prothrombotic state in affected patients. The formation of micro-thrombotic emboli results in significantly increased mortality and morbidity. Routine anticoagulation with low molecular weight heparin can prevent thrombotic events and thus can improve patient outcomes. In patients with elevated prothrombin time, lupus anticoagulant/anti-cardiolipin antibody-positivity should be suspected, and anticoagulation prophylaxis should be continued perioperatively for better outcomes.

MeSH Keywords: Anticoagulants • COVID-19 • Lupus Coagulation Inhibitor

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926623

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Background

Corona Virus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), is a global problem, with the number of cases increasing exponentially since the outbreak in December 2019 [1]. Although the initial cases were detected in the city of Wuhan, Hubei Province, Central China, COVID-19 was declared as a pandemic globally in March 2020. Uncertain pathogenesis along with a lack of vaccination and targeted medications have made the control of disease challenging and caused many deaths all over the world [2]. Treatment thus far as per the Chinese literature with minimal data has been supportive of oxygen therapy as needed, antiviral medications, steroids, empiric antibiotics, continuous renal replacement therapy (CRRT), and intravenous immunoglobulins (IVIG) [3]. Various drugs including Remdesivir have been studied and approved by the FDA in the USA for severe COVID-19. Favilavir has been approved in Japan, while chloroquine and hydroxychloroquine are being studied in clinical trials [4,5].

COVID-19 is believed to activate various complement pathways which lead to microvascular injury associated with procoagulant state and result in thrombotic events [6]. Coagulation dysfunction is thought to be one of the major causes of mortality in these patients [7], which varies ranging from COVID-19-associated coagulopathy to disseminated intravascular coagulation (DIC). Abnormal coagulation parameters, including elevated D-dimer and fibrin degradation products, are correlated with a poor prognosis [8]. However, there is not much published data regarding lupus anticoagulant (LA) in these critically ill patient populations, and the published data so far points to varying conclusions [8,9]. Here, we present a case of a 31-year-old man with positive lupus anticoagulant triggered by COVID-19 infection.

Case Report

A 31-year-old man with a past medical history of asthma and achalasia but no known personal or family history of coagulopathy or bleeding disorders presented to the Emergency Department (ED) with complaints of cough and chest pain for 3 days. His initial vital signs were significant for a heart rate of 145/minute and fever of 39.3°C but otherwise he had stable blood pressure (124/64 mmHg), respiratory rate (16/minute), and oxygen saturation of 92% on room air. A physical exam was significant for decreased breath sounds on the left hemithorax but was otherwise noncontributory. Initial bloodwork revealed elevated white blood cell (WBC) 19 900 m/mm^3 with

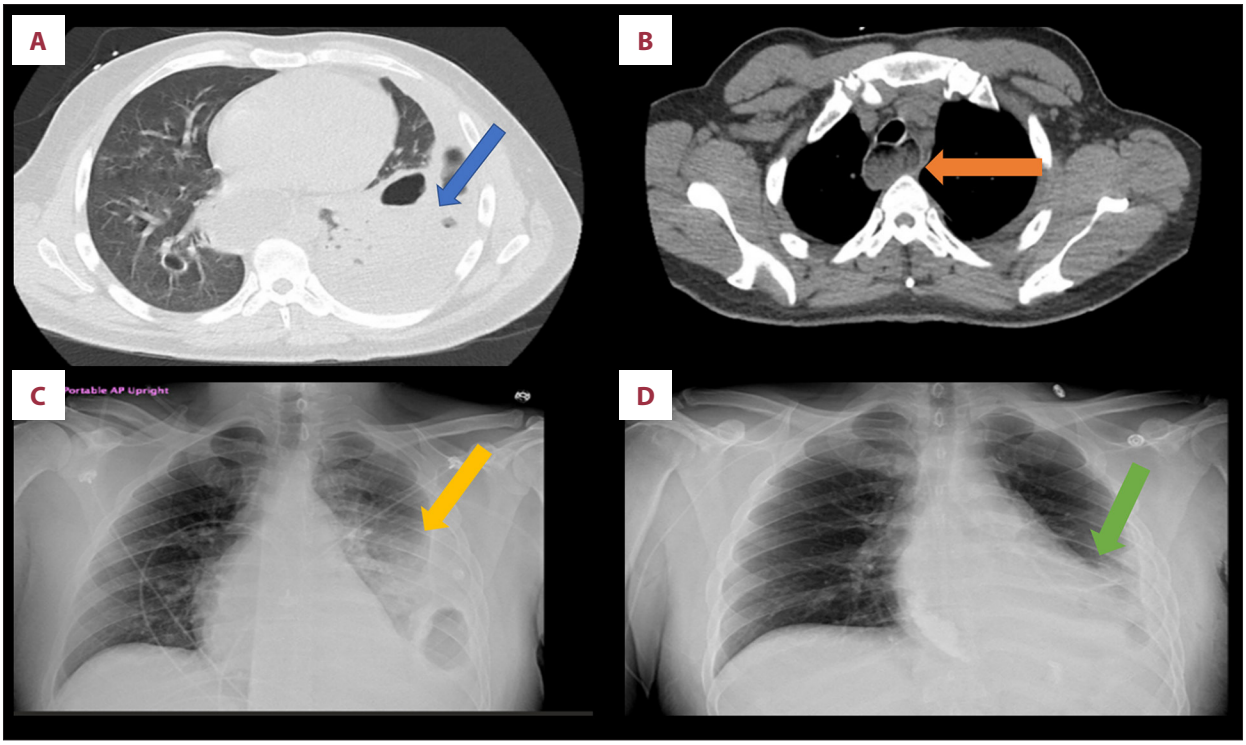

Figure 1. (**A**) CT of the chest shows empyema on the right lung; Blue arrow indicates empyema of the left lung. (**B**) CT of the chest showing dilation of distal esophagus; Orange arrow indicates dilated oesophagus. (**C**) CXR before chest tube insertion showing empyema; Yellow arrow indicated empyema air fluid level before insertion of chest tube. (**D**) CXR after chest tube insertion showing resolution of empyema; Green arrow indicates interval decrease in the air fluid level.

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Table 1. Results of hematology workup.

Parameter	Value	Reference range
Prothrombin time (PT)	27.7 seconds	9.4–12.5
International Normalized Ratio	2.4	0.8–1.1
Activated Partial Thromboplastin Time (APTT)	47.2 seconds	25.1–36.5
PTT LA (Partial Thromboplastin Time Lupus Anticoagulant) mixing	75 seconds	≤40
Immediate PTT-LA mix	Not corrected	
Immediate PT mix	10.8 seconds	≤11.5
Platelet count	420 K/uL	140–366
D-dimer	2590 FFEU/mL	0–499
Fibrinogen	590 MG/DL	200–393
Factor VII	45	60–150%
Factor VIII	302	50–180%
Factor XII	48	50–150%
B2- Glycoprotein I IgG Ab	<9	≤20 SGU
B2- Glycoprotein I IgM Ab	<9	≤20 SMU
B2-Glycoprotein I IgA Ab	<9	≤20 SAU
Lupus Anticoagulant	Detected	
Anti-Cardiolipin IgG	<14	≤14 GPL
Anti-Cardiolipin IgM	45	≤12 MPL
Anti-Nuclear Antibody	Negative	

left shift, while platelet count and hemoglobin were within normal limits. Liver function tests were mildly deranged, with an elevated ALT (alanine aminotransferase) of 84 U/L, total bilirubin of 1.3 mg/dL, and albumin of 2.6 gm/dl. Given his exposure to multiple COVID-19-positive contacts, he was subsequently tested by reverse transcription-polymerase chain reaction (RT-PCR) for SARS-COV-2 from a nasopharyngeal swab, which later came back positive. We used the Cepheid GenXpert system to detect SARS-COV-2. The initial chest X-ray (Figure 1C) was significant for prominent opacity with mixed density involving the left hemithorax and associated large left-sided effusion, concerning for left lower-lobe pneumonia with parapneumonic effusion. A subsequent computed tomography (CT) of the chest revealed left basilar airspace consolidation consistent with the necrotic or cavitating process and large left pleural effusion with extra-ventilatory air consistent with empyema (Figure 1A). A CT of the chest also showed ground-glass opacities in the right lung and a fluid-filled distal esophagus (Figure 1B). The patient deteriorated clinically over the following hours and was transferred to the Intensive Care Unit (ICU) for closer monitoring.

Cardiothoracic Surgery was consulted for potential intervention to treat the empyema. A pre-operative workup revealed that activated partial thromboplastin time (aPTT), prothrombin time (PT), and international normalized ratio (INR) were prolonged (Table 1). Mixing studies showed corrected PT, but not aPTT. His platelet count, D-dimer, and fibrinogen were elevated (Table 1). Hematology was consulted and recommended administration of low molecular weight heparin (LMWH) for venous thromboembolism (VTE) prophylaxis. Immediate aPTT was not corrected in mixing studies, suggesting the presence of immediate-acting inhibitors such as factor-specific inhibitors, LA, or anticoagulation therapies. Intrinsic coagulation factors (II, VIII, IX, X, XI), LA, anti-cardiolipin antibodies, and anti-glycoprotein antibodies were also obtained (Table1). Fresh frozen plasma (FFP) and vitamin K were given due to elevated PT prior surgery. The patient underwent the procedure but also was started on LMWH in the immediate post-operative period, without any bleeding complications. An updated hematology workup a week later showed normal levels of Factor II, V, IX, and IX, and no evidence of factor-specific inhibitors.

The patient underwent multiple interventions without any hematologic complications. Two chest tubes were placed at the bedside, followed by video-assisted thoracoscopic surgery (VATS) with full decortication. Bronchoscopy and left lower-lobe lavage were also performed. Empyema was suspected to be secondary as a result of aspiration due to the patient's history of achalasia. He also had esophagogastroduodenoscopy and PEG (percutaneous endoscopic gastrostomy) tube placement concomitantly. Discharge from the chest tube was sent

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for culture and came back positive for Streptococcus angiosus. He was successfully discharged on a 6-week course of intravenous ertapenem for empyema and recovered without further issues. A repeat chest X Ray was done post chest tube insertion showing resolution of empyema as seen in Figure 1D.

Discussion

Viral illnesses including Hepatitis-C, human immunodeficiency virus (HIV), Epstein–Barr virus (EBV), and Hepatitis-B as per meta-analyses have been associated with an increase in anti-phospholipid, anti-cardiolipin, and anti-β2-glycoprotein-1 antibodies and cause prothrombotic state resulting in thromboembolic events [10,11]. COVID-19 results in acute respiratory distress syndrome (ARDS) through a cytokine storm which thereby increases pulmonary vascular shunting through microvascular injury and thrombus formation [12]. COVID-19-associated coagulopathy (CAC) is characterized by elevated fibrinogen and D-dimer levels and is associated with thrombotic events [13]. There are cases with multiple infarcts in the different parts of the body reported in China with positivity for anti-cardiolipin IgA antibodies as well as anti-β_2-glycoprotein I IgA and IgG antibodies [14]. In a study of the Chinese population, treatment with LMWH based on sepsis-induced coagulopathy score and elevated D-dimer levels improved outcomes [15].

Tang et al. reported statistically significant increased mortality correlating with higher D-dimer and fibrin degradation product levels, and longer PT and aPTT. They found that 71.4% of non-survivors and 0.6% of survivors met the criteria of DIC during their hospital stay [8]. In a separate letter to the editor, Tang reported that very few of their patients had positive LA results and concluded that the antiphospholipid antibody does not exist universally in COVID-19 patients [9]. In a recent letter to the editor, Harzallah et al. reported their experience with 56 COVID-19 patients in Mulhouse, France [16]. They found that 45% (n=25) of cases were lupus anticoagulant-positive, whereas only 10% (n=5; 3 also with LA) of the patients were positive for anti-cardiolipin or anti-β_2-glycoprotein. The authors emphasized the importance of early anticoagulant therapy, although in acute infections, lupus anticoagulant elevation can be seen, often not requiring therapy. Another interesting report, by Bowles et al., reported LA results performed in 34 patients, and 31 (91%) were positive. When lupus anticoagulant-positive patients' plasma is mixed with an equal amount of normal plasma, prolongation of aPTT was seen in these specimens. Although heparin was detected in 28 of the 35 specimens that can cause false-positive detection of lupus anticoagulant, the authors concluded that the heparin effect was neutralized due to the assay containing heparinase. The authors also suggested that the use of anticoagulation for the prevention and treatment of VTE should not be limited in COVID-19 patients with prolonged aPTT [17].

As mentioned before, our patient had prolonged PT/INR and aPTT but had no clinically significant bleeding complications. The concern in our case was that the elevated fibrinogen and platelet counts may put the patient at risk of thrombosis. Therefore, hematology recommended LMWH for DVT prophylaxis despite the abnormal PT and aPTT noted with no personal/family history of bleeding disorder. His prolonged aPTT is due to positive lupus anticoagulant and anti-cardiolipin antibody, which will not cause bleeding but possibly increase the risk of thrombosis. Although observed in a small study, there has also been a potential beneficial effect of supplementing dipyridamole in severely ill COVID-19 patients [18]. This suggests that the pathophysiology of thrombosis associated with COVID-19 differs in comparison to non-COVID patients [19]. Further studies should determine the role of lupus anticoagulant in the pathogenesis of COVID-19-associated thrombosis.

Conclusions

In COVID-19 patients with prolonged aPTT but no history of coagulopathy or bleeding, it is reasonable to suspect positive LA, anti-cardiolipin antibody, or anti-β_2-glycoprotein-1 antibody. Prolonged aPTT should not be a barrier to surgery. Instead, immediate VTE prophylaxis is recommended perioperatively. Earlier detection of this prothrombotic state and appropriate anticoagulation with LMWH or direct oral anticoagulant, although not studied, may prevent adverse thrombotic events in critically ill COVID-19 patients.

Conflict of interest

None.

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