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Thrombolysis in severe COVID-19 pneumonia with massive pulmonary embolism

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ABSTRACT

Objective: No guidelines exist for the management of massive pulmonary embolism (PE) in COVID-19. We present a COVID-19 patient with refractory acute respiratory syndrome (ARDS), and life-threatening PE who underwent successful thrombolysis.
Case Presentation: A previously healthy 47 year old male was admitted to our hospital due to severe COVID-19 pneumonia [confirmed by Real-Time-Polymerase-Chain-Reaction (RT-PCR)]. He had rapidly evolving ARDS [partial arterial pressure of oxygen to fractional inspired concentration of oxygen ratio: 175], and sepsis. Laboratory results showed lymphocytopenia, and increased D-dimer levels (7.7 μg/ml; normal: 0–0.5 μg/ml). The patient was treated in the intensive care unit. On day-1, ARDS-net/prone positioning ventilation, and empiric anti-COVID treatment integrating prophylactic anticoagulation was administered. On hospital day-2, the patient developed shock with worsening oxygenation. Point-of-care-ultrasound depicted a large thrombus migrating from the right atrium to the pulmonary circulation. Intravenous alteplase (100 mg over 2 h) was administered as rescue therapy. The patient made an uneventful recovery, and was discharged to home isolation (day-20) on oral rivaroxaban.
Conclusion: Thrombolysis may have a critical therapeutic role for massive PE in COVID-19; however the risk of potential bleeding should not be underestimated. Point-of-care ultrasound has a pivotal role in the management of refractory ARDS in COVID-19.

1. Introduction

Recently, a preliminary analysis of a large US cohort of critically ill patients with severe novel SARS-CoV-2 disease (COVID-19) has suggested the benefit of systemic anticoagulation on their mortality [1]. Life-threatening COVID-19 is characterized by acute respiratory distress syndrome (ARDS), sepsis, multi-system organ failure, and thromboembolic disease [2]. The latter integrates both venous and arterial thromboembolic phenomena; while, the underlying pathophysiology remains poorly understood. The administration of enhanced systemic anticoagulation in patients with severe COVID-19, and Padua prediction score ≥ 4 or D-dimer>3.0 μg/ml has been previously suggested due to the increased occurrence of pulmonary embolism (PE) [3,4]. Scarce data exist though about the use and safety of thrombolysis for massive PE in patients with COVID-19. Herein, we are briefly discussing the case of a critically ill COVID-19 patient who underwent thrombolysis for life-threatening PE.

2. Case presentation

A previously healthy 47 year old male was admitted to our emergency department due to severe COVID-19 pneumonia, which was confirmed by Real-Time-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) [5,6]. The patient presented with rapidly evolving ARDS [partial arterial pressure of oxygen to fractional inspired concentration of oxygen (PaO_2/FiO_2) ratio: 175] and sepsis. Laboratory results showed normal coagulation profile, leukocytosis with lymphocytopenia (0.41×10^9/l; normal: $1.1–3.2 \times 10^9$/l), increased C-reactive protein (432.5 mg/l; normal: 0–7 mg/l), D-dimer (7.7 μg/ml; normal: 0–0.5 μg/ml), lactate dehydrogenase (1.107 units/l, normal: 100–190 units/l), and ferritin (1.283 ng/ml, normal: 23–336 ng/ml) [2]. The electrocardiogram depicted sinus

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tachycardia 119 b/min without any other abnormalities. A full work-up for other systemic disorders including thrombophilia and antiphospholipid antibodies screening was sent [7]. The patient was intubated and transferred to the intensive care unit (ICU). At that time, it was deemed unnecessary to perform a chest computed tomography (CT) scan due to the patient's critical state and COVID-19 status.

In the ICU (day-1), ARDS-net/prone positioning ventilation, and empiric treatment with ribavirin/ interferon beta-1b, ceftriaxone/ azithromycin, dexamethasone, and prophylactic anticoagulation has been administered as per hospital protocol [8]. On hospital day-2, the patient developed shock with worsening oxygenation (PaO_2/FiO_2: 95), and increasing norepinephrine requirements. Follow-up laboratory examinations revealed a slight increase of troponin-I levels (2.1 ng/ml; normal: <0.04 ng/ml). Point-of-care-ultrasound (POCUS) revealed a large thrombus migrating from the right atrium to the pulmonary circulation, and acute right ventricular (RV) dilatation and dysfunction (Fig. 1A, B, C; and Suppl. Video 1). However, lower-limb compression duplex sonography was normal. The dose of norepinephrine was increased, enoxaparin was weight-adjusted to a therapeutic dose (80 mg twice daily), and positive end-expiratory pressure was reduced (from 11 cm H_20 to 8 cm H_20) to compensate for venous return and RV function. Unfortunately, the patient's hemodynamic status and oxygenation did not improve. Therefore, intravenous alteplase (100 mg over 2 h) was administered as rescue therapy. The patient made an uneventful recovery without bleeding complications. On day four post-thrombolysis, he was weaned off vasopressors, and his PaO_2/FiO_2 increased to 290. Follow-up POCUS showed no right heart thrombi, and restored right ventricular function five days post-thrombolysis (Fig. 1D; Suppl. Video 2). He was extubated on day-10. RT-PCR for COVID-19, and microbiology were negative on day-17. The work-up for other systemic disorders including thrombophilia was negative. The patient was discharged to home isolation on hospital day 20 in good clinical condition. Oral Rivaroxaban was prescribed for three months [9].

3. Discussion

COVID-19 refractory ARDS may be due to the interplay of inflammatory pathologies targeting both the lung ventilation and perfusion ("dual-hit" pathology). Our patient had increased levels of D-dimer and inflammation biomarkers, and life-threatening thromboembolic disease [1-4]. An increased incidence of thromboembolic phenomena has been previously documented in critically ill COVID-19 patients [10-12]. Also, thromboembolic disease is a well-established feature of life-threatening COVID-19 [13-15]. Notably, cardiac involvement in COVID-19 includes arrhythmia (atrial fibrillation, ventricular tachyarrhythmia and fibrillation), cardiac injury [elevated troponin I and creatine kinase levels], fulminant myocarditis, heart failure, and PE [16-22]. SARS-CoV-2 could directly bind to the ACE-2 receptors causing diffuse endothelial injury [23], which in turn along with the ensuing inflammation may promote hypercoagulable states [1-4].

This case-report, albeit its limitations, illustrates that the administration of enhanced anticoagulation in patients with severe COVID-19, and Padua prediction score ≥ 4 or D-dimer>3.0 μg/ml may be a necessary critical care practice [3,4]. Surely, the risk of bleeding should be not underestimated; hence these patients require diligent ICU monitoring [1]. Catheter-directed thrombolysis for massive PE in COVID-19 has been previously described in a single case-report [24]. This is the first case, to our knowledge, that systemic thrombolysis is administered for life-threatening PE in a COVID-19 patient. No specific guidelines exist for the management of massive PE in COVID-19. Thrombolysis could be an effective and safe therapy for massive PE in mechanically ventilated COVID-19 patients. Also, we underline that POCUS, despite its inherent limitations, could be a flexible diagnostic and management tool in refractory ARDS due to COVID-19 [25]. Notably, post-thrombolysis, we have administered a new oral anticoagulant that may be useful in preventing future thromboembolic phenomena as SARS-CoV-2 reinfection and natural immunity remain obscure. However, the putative interaction of anticoagulation therapy with empiric antivirals should be further explored [1,3]. In conclusion, thrombolysis appeared to be a

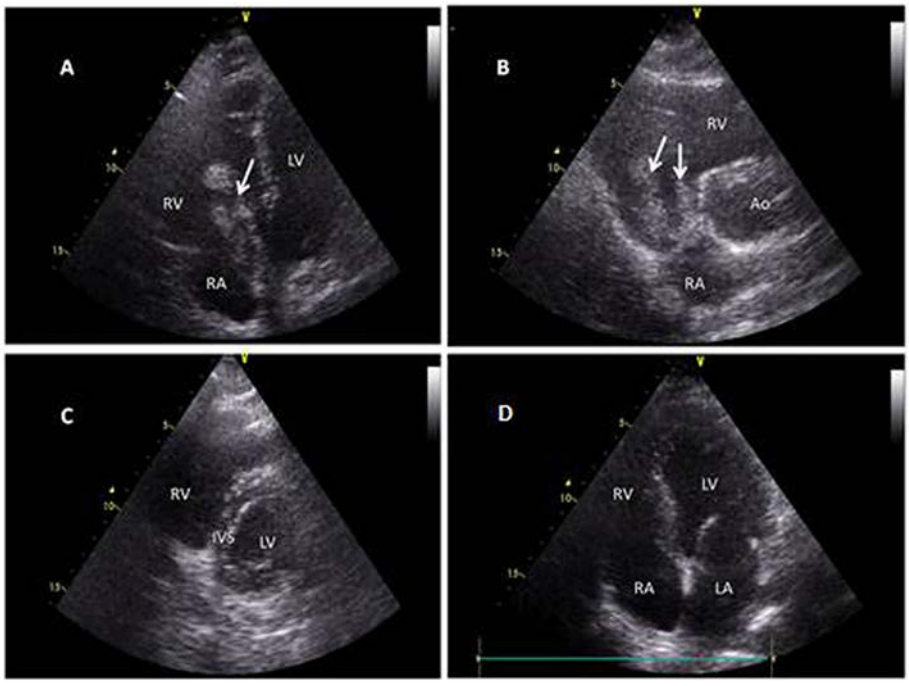

Fig. 1. Point-of-care-cardiac ultrasound (day-2) performed on our critically ill patient with COVID-19: modified four-chamber (A), and short-axis at the level of aortic valve (B) views depicting a large free-floating thrombus (white arrows) migrating to the pulmonary circulation along with severe RV dilatation/dysfunction. Also, on day-2, another short axis view (C) shows a D-shaped left ventricle in systole due to right ventricular pressure overload. On day-5 post-thrombolysis, four-chamber view (D) shows restored right ventricular function. Abbreviations: RA = right atrium, RV = right ventricle; LA = left atrium; LV = left ventricle; IVS = interventricular septum, Ao = aorta.

safe and effective therapy for massive PE in COVID-19 when administered under close ICU monitoring.

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Authors contributions

Abdulrahman Alharthy: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing; **Fahad Faqihi**: Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing; **John Papanikolaou**: Conceptualization, Data curation, Formal analysis, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing; **Abdullah Balhamar**: Conceptualization, Data curation, Formal analysis, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing; **Mike Blaivas**: Conceptualization, Data curation, Formal analysis, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing; **Ziad A Memish**: Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing; **Dimitrios Karakitsos**: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

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Ethical approval

The study was approved by the Institutional Review Board of King Saud Medical City, Riyadh, Kingdom of Saudi Arabia [H-01-R-053, IORG0010374#, H1RI-07 May-20-01]. Written informed consent was obtained from the patient's legal representative.

Declaration of Competing Interests

Authors AA, FF, JP, AB, ZAM, and DK declare that they have no competing interests. MB consults for EthosMedical, 410Medical, EchoNous and Sonosim; none of these companies were aware of the study or had influence on it.

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