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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.

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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 QuantiTana 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 (PaO2/FiO2) ratio: 175] and sepsis. Laboratory results showed normal coagulation profile, leukocytosis with lymphocytopenia (0.41 × 10⁹/l; normal: 1.1–3.2 × 10⁹/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...
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 empirical 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 (PaO2/FiO2: 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 H20 to 8 cm H20) 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 PaO2/FiO2 increased to 290. Follow-up POCUS showed no right heart thrombi, and restored right ventricular function (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 tachyarhythmia 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 adminis-
tered 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 Faqhi: Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing; John Papanikolau: 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, Funding acquisition, Investigation, Methodology, Project administration, 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, IORG010374#, 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 com-
peting 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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