JACC: CASE REPORTS VOL. 2, NO. 9, 2020

THROMBOEMBOLIC EVENTS

BEGINNER

CASE REPORT: CLINICAL CASE SERIES

Difficulties of Managing Submassive and Massive Pulmonary Embolism in the Era of COVID-19

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ABSTRACT

Acute pulmonary embolism (PE) is a potentially life-threatening manifestation of venous thromboembolic disease. Severe acute respiratory syndrome-coronavirus-2, a novel coronavirus that causes coronavirus disease-2019 (COVID-19), has been associated with an increased risk of thrombosis. We describe the therapeutic challenges of 3 patients presenting with PE and suspected or confirmed COVID-19. (**Level of Difficulty: Beginner.**)

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Pulmonary embolism (PE) is a life-threatening condition responsible for up to 15% of in-hospital deaths annually in the United States. Clinical deterioration results from right-sided heart failure, obstructive shock, hypoxia, and death in the most severe cases (1). With a diverse range of clinical presentations, diagnosis and timely risk stratification is important. Low-risk PE is defined by normotension, normal right ventricular function on computed tomography (CT) or transthoracic echocardiography (TTE), and no evidence of ischemia with biomarkers (troponin/B-type natriuretic peptide [BNP]). Submassive PE manifests with right ventricular (RV) dysfunction on imaging and/or abnormal biomarkers with normotension. Massive PE is characterized by hemodynamic collapse, defined as systolic blood pressure (BP) <90 mm Hg or a >40 mm Hg decrease in systolic BP for more than 15 min, or requiring inotropic support with associated RV dysfunction and ischemia (2).

LEARNING OBJECTIVES

- To suspect PE early in the disease process in confirmed or suspected COVID-19 patients.
- To identify high-risk patients early and to offer appropriate therapies while mitigating patient and provider risk.

In December 2019, a novel coronavirus originating in Wuhan, China, identified as severe acute respiratory syndrome-coronavirus-2 was implicated as the causative agent in cases of severe pneumonia with acute respiratory distress syndrome (ARDS). The virus has since been deemed a global pandemic by the World Health Organization (3). Data published on its clinical manifestations and disease course have shown that patients with the most severe cases

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received April 9, 2020; revised manuscript received April 21, 2020, accepted April 24, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.05.017

ABBREVIATIONS AND ACRONYMS

ARDS = acute respiratory distress syndrome

CDT = catheter-directed thrombolysis

PE = pulmonary embolism

PUI = patient under investigation

RV = right ventricular

RV/LV = right ventricular to left ventricular diameter ratio

TTE = transthoracic echocardiography

UFH = unfractionated heparin

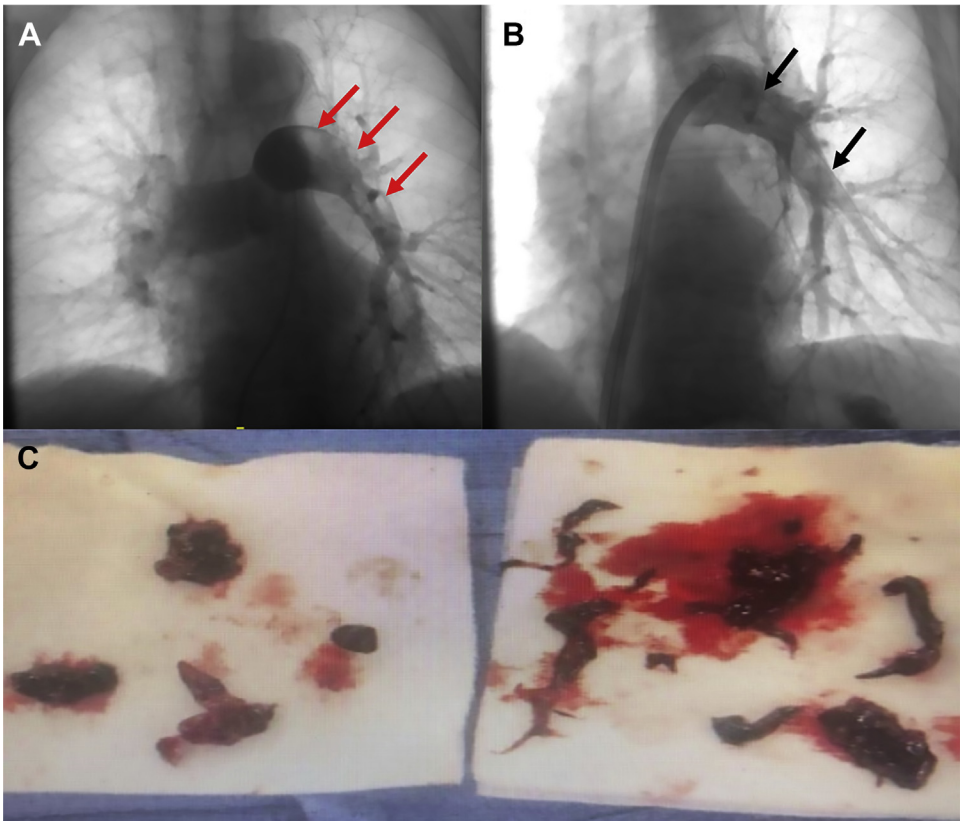
develop severe ARDS, sepsis-induced disseminated intravascular coagulation, and cytokine storm. Disseminated intravascular coagulation manifests with elevated levels of D-dimer, which are associated with increased mortality (4). Hemorrhagic infarction and microthrombi formation in the pulmonary vasculature can be found in postmortem analyses of these patients (5). Throughout the world, clinicians modified their management strategies for suspected and confirmed PE in coronavirus disease-2019 (COVID-19) patients. We describe the therapeutic challenges of 3 patients presenting with PE and suspected or confirmed COVID-19.

CASE 1: MASSIVE PE IN A COVID-19 PATIENT UNDER INVESTIGATION

A 75-year-old woman with history of PE in 2018 treated with 6 months of apixaban was transferred to our institution after presenting to an outside hospital with pleuritic chest pain and dyspnea. She was found to have hypotension and large, central PE extending into bilateral pulmonary arteries with a right ventricular to left ventricular diameter ratio (RV/LV) of 1.6. A head CT identified a new brain lesion. Because of massive PE, shock, and contraindication to tissue plasminogen activator, the patient was started on norepinephrine and transferred. On arrival to our institution, the patient was afebrile with BP of 109/80 mm Hg, pulse of 99 beats/min, saturating 99% on 2 l nasal cannula, and breathing 26 breaths/min. D-dimer was elevated at 7,348 ng/ml (normal <500 ng/ml), lactate of 2.1 mmol/l (normal <1.7 mmol/l), BNP of 614 pg/ml (normal <100 pg/ml), and troponin I of 0.52 ng/ml (normal <0.02 ng/ml). A rapid COVID-19 assay was drawn on arrival. Lower extremity Doppler ultrasound revealed a mobile thrombus in the left common femoral vein (Video 1).

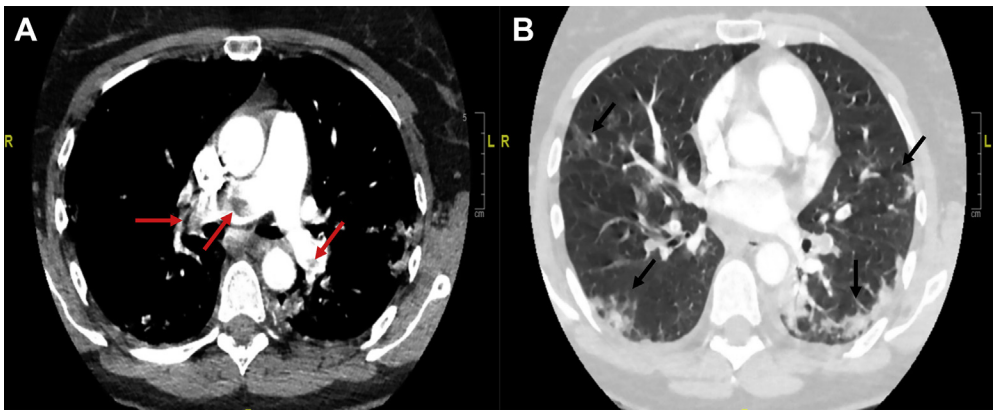
The patient was managed with intravenous unfractionated heparin (UFH) and dobutamine;

FIGURE 1 Mechanical Thrombectomy of Massive Pulmonary Embolism



(A) Left pulmonary artery (PA) angiogram showing thrombus burden **(red arrows). (B)** Angiogram following mechanical thrombectomy with restoration of blood flow **(black arrows)**. **(C)** Clots aspirated from bilateral PA.

FIGURE 2 Chest CT Demonstrating Pulmonary Artery Thrombi and Lung Infiltrates



(A) Axial plane demonstrating pulmonary embolism in the bilateral main pulmonary artery **(red arrows)**. **(B)** Axial plane lung window demonstrating ground glass opacities **(black arrows)**.

however, lactate continued to rise. In the interim, her COVID-19 assay came back negative, so the decision was made to proceed with mechanical thrombectomy. She underwent successful aspiration thrombectomy of bilateral pulmonary arteries (Figure 1). She was continued on anticoagulation, underwent workup of her brain mass, and was discharged home.

This case identifies a therapeutic dilemma for the interventionalist in the era of COVID-19. There is paucity of data demonstrating clear association of interventional techniques with improvement in survival for acute PE. It is not clear when to safely escalate care to the catheterization laboratory, while limiting staff exposure to a patient under investigation (PUI) with COVID-19. Aerosolized particles travel long distances, which may explain the extent of viral spread over the last few months (6). A patient's clinical condition must be weighed against the evidence of therapeutic approaches offered and safety of the health care team in determining the best course of action.

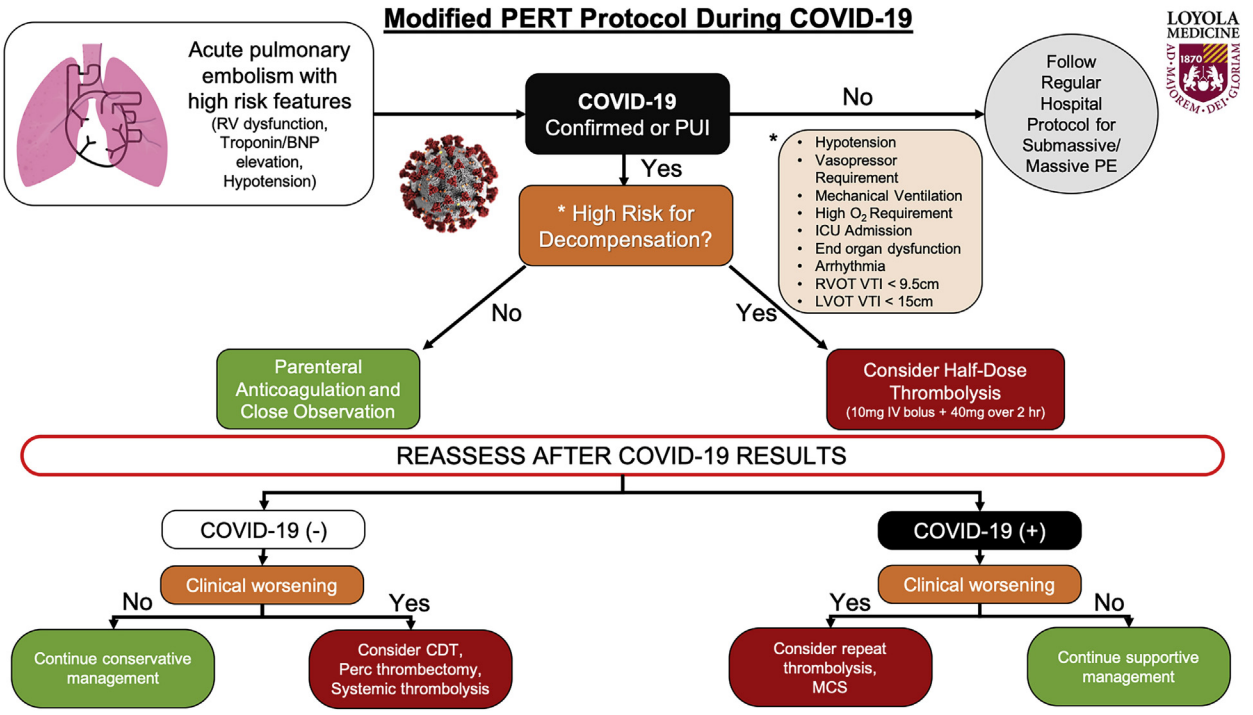
CASE 2: SYSTEMIC FIBRINOLYSIS IN A COVID-19 PUI

A 65-year-old woman with a history of PE treated with 6 months of warfarin presented to our institution with sudden-onset dyspnea, subjective fevers, and 1 day of diarrhea. She was afebrile with a BP of 159/102 mm Hg, pulse of 122 beats/min, oxygen saturation of 86% on 100% nonrebreather mask, and respiratory rate of 20 breaths/min. Troponin I was elevated at 0.16 ng/ml, lactate was elevated at 3.9 mmol/l, BNP was normal at 59 pg/ml, and D-dimer was elevated at 6,629 ng/ml. A chest CT confirmed multiple central PEs with extension into the bilateral lobar and subsegmental branches with an RV/LV of 2.6. Her COVID-19 assay was drawn upon presentation. Based on clinical status, catheter-directed thrombolysis (CDT) was considered but was deferred as she was a PUI for COVID-19.

Management involved initial airway stabilization with escalation to bilevel positive airway pressure and intravenous (IV) UFH for anticoagulation. Despite medical management, the patient had worsening hypoxia. In an attempt to stave off intubation, which can be associated with acute RV decompensation due to increased RV afterload and risk of aerosolizing the COVID-19 virus if the patient was infected, we proceeded with half-dose systemic fibrinolysis consisting of an IV alteplase 10-mg bolus followed by 40 mg over 2 h (7). Following fibrinolysis, her work of breathing significantly improved and oxygen requirements decreased to 6 l/min via nasal cannula. The patient did not experience any bleeding. Her RV/LV normalized on follow-up echocardiogram and was discharged home.

This case of submassive PE highlights the difficulties of managing patients suspected of COVID-19 infection. CDT is associated with early improvement in RV function and hemodynamics in deteriorating patients with lower doses of tPA (8,9); however, PUI

FIGURE 3 PERT Protocol for Management of PE in the COVID-19 Era



Algorithm detailing clinical decision tree for PE management in suspected or confirmed COVID-19 patients. BNP = B-type natriuretic peptide; CDT = catheter-directed thrombolysis; COVID-19 = coronavirus disease-2019; ICU = intensive care unit; IV = intravenous; LVOT = left ventricular outflow tract; MCS = mechanical circulatory support; PE = pulmonary embolism; Perc = percutaneous; PERT = pulmonary embolism response team; RV = right ventricular; RVOT = right ventricular outflow tract; VTI = velocity time integral.

for COVID-19 warrant infection rule out prior to proceeding with invasive procedures as already mentioned. Nevertheless, half- or full-dose systemic fibrinolysis is available in a physician's armamentarium to stabilize high-risk PE in PUI for COVID-19 without significantly increased risk of bleeding.

CASE 3: SUBMASSIVE PE IN COVID-19 CONFIRMED PATIENT

A 58-year-old woman with history of asthma presented with dyspnea, pleuritic chest pain, diarrhea, and productive cough. She had exposure to COVID-19 at work 16 days before presentation with a positive viral assay 13 days prior. She was afebrile with a BP of 137/85 mm Hg, pulse of 117 beats/min, oxygen saturation of 99% on a 2-l nasal cannula, and respiratory rate of 24 breaths/min. Troponin I was elevated at 0.38 ng/ml, D-dimer was elevated at 16,400 ng/ml, and BNP was elevated at 151 pg/ml. Lactate was normal at 1.2 mmol/l. CT chest revealed saddle PE with extension into bilateral pulmonary arteries. Lung windows demonstrated bilateral consolidations and ground glass opacities consistent with COVID-19 pneumonia (Figure 2). She was diagnosed with submassive PE and was started on IV UFH. Her respiratory status improved on medical management alone and she was transitioned to apixaban prior to discharge.

The care of patients diagnosed with PE is complex and relies on risk stratification with biomarkers and imaging with CT and echocardiography to guide management. At our institution, all PE patients undergo TTE. However, TTE was deferred for this patient given her COVID-19 status. Patient isolation is vital to limit exposure and possible transmission. However, this practice can interfere with comprehensive patient care. Physicians managing venous thromboembolism must rely on clinical status, laboratory markers, and CT markers of severity in lieu of TTE to make appropriate clinical decisions.

CONCLUSIONS

Although pneumonia complicated by ARDS remains the primary etiology of hypoxia in COVID-19, emerging data suggest that venous thromboembolism may also play a significant role, adding an extra layer of complexity to management of acute PE. The appropriate therapeutic strategy must weigh the patient's risk of decompensation, potential benefit of intervention, risk of provider exposure and infection, and availability of hospital resources during this pandemic. At our institution, the pulmonary embolism response team rapidly evaluates COVID-19 PUIs or confirmed patients and assesses their risk of decompensation based on several clinical, laboratory, hemodynamic, and echocardiographic markers (**Figure 3**) (8,10). Half-dose systemic thrombolysis is given to patients at high risk for decompensation. Conversely, stable patients are medically managed with close observation. If new high-risk features develop, either a half-dose systemic thrombolytic or CDT strategy is employed based on results from the COVID-19 assay.

In summary, as data continue to emerge in the COVID-19 pandemic, PE management algorithms must be revised to mitigate risks while maximizing patient care.

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KEY WORDS anticoagulation, computed tomography, pulmonary circulation, right ventricle, thrombus

APPENDIX For a supplemental video, please see the online version of this paper.