

COVID-19 associated pulmonary embolism with D-dimer values within the referent range: a case report and review of the literature

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Abstract. – OBJECTIVE: COVID-19 is associated with an increased incidence of pulmonary embolism (PE). Elevated D-dimer levels are linked to an increased risk of PE and poor clinical outcome. We reported a case of PE in a COVID-19 patient with normal D-dimer levels and conducted a review of the literature on the subject.

CASE REPORT: A 38-year-old man with no prior comorbidities returned to the COVID-19 outpatient clinic 36 hours after being discharged from the hospital, where he had been treated for COVID-19 pneumonia. He reported a sudden feeling of dyspnea and chest pain. The physical examination was unremarkable. No new changes were detected on the chest X-ray. D-dimer and cardiac-specific markers values were within the referent range. The patient underwent an urgent computerized tomography pulmonary angiography which revealed signs of bilateral arterial thrombosis. He was treated with a therapeutic dose of low molecular weight heparin and discharged after 15 days, with a recommendation to use a direct oral anticoagulant.

CONCLUSIONS: Healthcare professionals should be aware that PE can occur as a late complication of COVID-19. Clinical suspicion of PE should lead physicians to use additional diagnostic methods to confirm or rule out PE, even if D-dimer levels are within the referent range.

Key Words:

COVID-19, Pulmonary embolism, D-dimer.

Introduction

After nearly two years of the Coronavirus Disease 2019 (COVID-19) pandemic, it is safe to

say that this disease is a hypercoagulable state, with an increased risk of venous thromboembolism (VTE) – a clinical entity that includes deep vein thrombosis (DVT) and pulmonary embolism (PE)¹. Coagulation abnormalities are commonly encountered in all severe infections and inflammations², but they appear to occur more frequently and with a worse clinical prognosis in patients infected with severe acute respiratory syndrome-related Corona Virus 2 (SARS-CoV-2)³.

The true prevalence of PE in COVID-19 patients is still unknown, varying in the research conducted so far from less than 10% to more than 30%, with a higher prevalence among Intensive Care Unit (ICU) patients^{4,6}. The association between high D-dimer values and risk of PE has been found in almost all studies conducted thus far^{4,7}. D-dimer levels are linked with not only the possibility of PE but also the severity of COVID-19, with higher levels predicting a worse outcome⁸.

Considering this, the purpose of this paper was to report a rare case of pulmonary embolism in a COVID-19 patient whose D-dimer values were within the referent range. We then conducted a review of the literature on this topic.

Case Report

A 38-year-old Caucasian male with no prior comorbidities was admitted to the hospital in early October 2021 with COVID-19 bilateral interstitial pneumonia and associated respiratory insufficiency. Upon admission, high levels of

pro-inflammatory markers were detected, while D-dimer values were within the referent range. During his 12-day hospital stay, he was treated with continuous oxygen therapy (via an oral-nasal mask), antibiotics, parenteral corticosteroid, prophylactic dose low molecular weight heparin (LMWH), and other supportive and symptomatic treatment. He was discharged after his general condition had stabilized and recommended for further treatment (oral corticosteroids, acetylsalicylic acid and vitamins). The patient signed the informed consent to participate in the study.

The patient returned to the COVID-19 outpatient clinic 36 hours after discharge due to a sudden feeling of dyspnea and chest pain. Physical examination revealed that he was afebrile (36.6°C), eucardic (88 beats/min), normotensive (130/90 mmHg), and eupneic (respiratory rate 20/min). No new changes were detected in the lung parenchyma on chest X-ray, while the pulmonary gas exchange was preserved. Electrocardiography showed sinus rhythm, incomplete right-sided branch block, and a negative T wave in lead DIII. In laboratory analyses, D dimer values remained within the reference range (0.29 mg/L FEU, values < 0.5 mg/L FEU are normal), as did pro-inflammatory markers: CRP value was 1.4 mg/L (reference < 5.0 mg/L), procalcitonin 0.02 ng/ml (reference < 0.05 mg/L), fibrinogen 3.86 g/L (normal range 2.00-4.00 g/L). Cardiac-specific markers were not significantly elevated: CK-MB 39 U/L (normal range 0-24 U/L), NT-proBNP 42.70 pg/mL (reference for those under 75 years < 125 pg/mL), and high sensitivity Troponin I below 10 ng/L (reference for male < 25 ng/L). Computerized tomography pulmonary angiography (CTPA) was urgently performed as pulmonary embolism was suspected, and signs of bilateral thrombosis in the branches of the pulmonary arteries were detected (Figure 1). Additional findings of ground-glass opacities that matched COVID-19 pneumonia were also found.

The patient was re-hospitalized and given therapeutic doses of subcutaneous LMWH (nadroparin-calcium 86 IU/kg/12h), continuing the oral corticosteroid therapy with prednisolone and vitamin supplementation for COVID-19 pneumonia. Throughout the hospitalization, the patient's hemodynamic stability was maintained, and serial 3rd-day monitoring of D-dimer yielded constant values within the reference range (0.27; 0.27; 0.38; 0.27 mg/L FEU, respectively). He was discharged in a good general condition after 15 days of treatment, with a recommendation for the

use of a direct oral anticoagulant (apixaban 5 mg, twice daily, with a treatment recommendation for a minimum of 3 months).

Discussion

COVID-19 is a hypercoagulable disorder, with an increased risk of venous and arterial thrombosis⁶. Numerous studies have been conducted to investigate the frequency of PE among COVID-19 patients, and their findings clearly and unambiguously show that the incidence of PE is higher than in non-COVID-19 patients. However, the PE incidence significantly varied across different research. Even though retrospective studies from the beginning of the pandemic reported the incidence of PE usually between 20-30%^{4,7,9}, in a recent meta-analysis by Longchamp et al³, the PE incidence was estimated to be smaller - 8% overall and 17% in ICU patients. Compared to those in the medical ward and outpatients, patients in ICU had a higher incidence of PE in the majority of other research^{3,9}. In several studies, the presence of PE in COVID-19 patients was associated with a worse clinical outcome, resulting in more frequent ICU admission, mechanical ventilation, and a longer hospital treatment^{4,5,9}. Table I summarizes the most important findings from several meta-analyses^{3,6,10-12} that investigated PE in COVID-19 patients.

Elevated D-dimer levels have been linked to pulmonary embolism and poor prognosis in patients with COVID-19 in almost every study that investigated this topic^{5,9}. D-dimer values over 500 µg/L and greater than 1000 µg/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%, respectively) for the diagnosis of PE in COVID-19 patients in a meta-analysis by Suh et al¹⁰. Even though some studies have suggested using conventional cut-off D-dimer values when considering CTPA in COVID-19 patients suspected of pulmonary embolism¹⁰, such an approach should be used with caution. Even though there have been previously a few reports of pulmonary embolism with D-dimer values within the referent range in the literature¹³, to the best of our knowledge, our report is the first such case description in a patient with COVID-19. In other words, during the COVID-19 pandemic, clinical suspicion of PE is more important than ever in the diagnostic algorithm and should serve as the foundation for implementing other diagnostic methods.

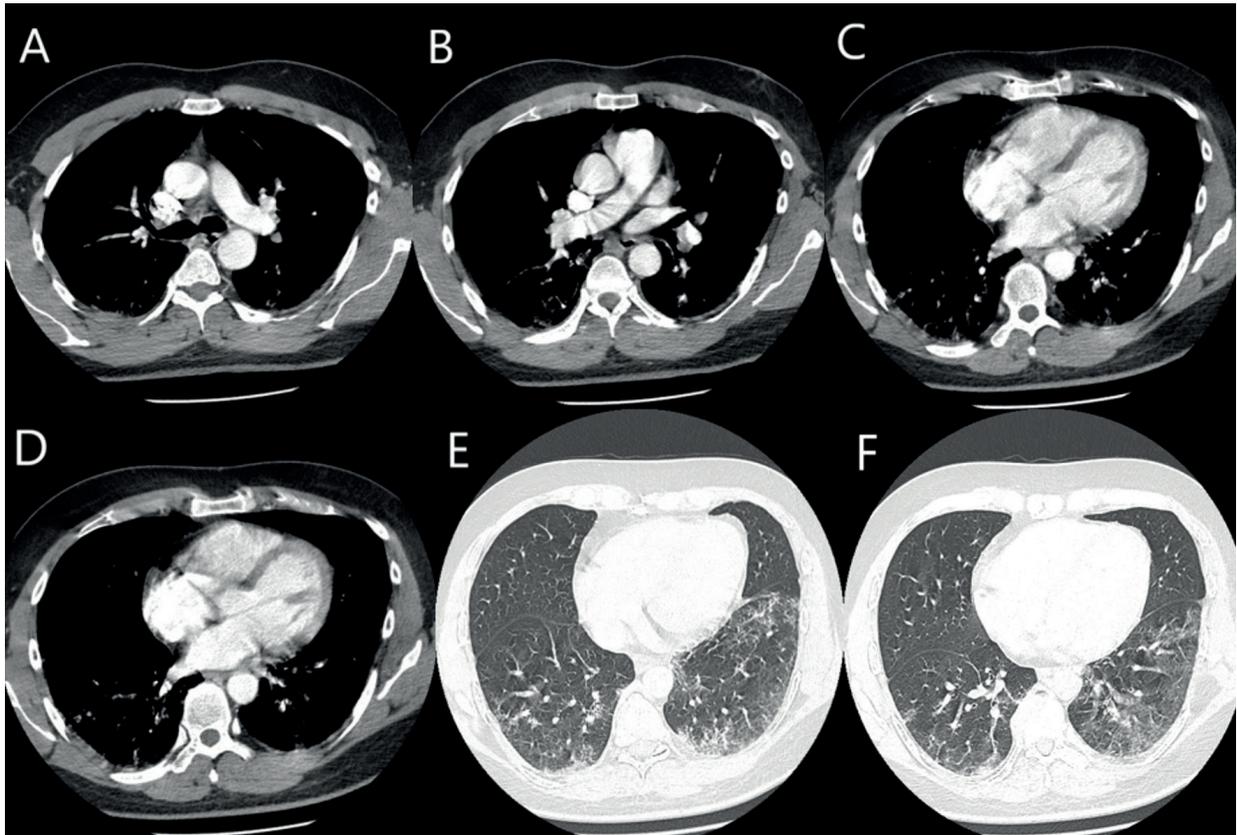


Figure 1. **A**, No signs of thrombosis in the truncus pulmonalis or the left pulmonary artery; **B**, in the distal part of the right pulmonary artery, inhomogeneous contrast filling of the lumen was observed, most likely due to partial thrombosis; **C**, Thrombosis at the lobar, segmental, and subsegmental branches of the pulmonary artery in the left lower lung lobe; **D**, Thrombosis in certain segmental and subsegmental branches of the right pulmonary artery; **E-F**, Additional findings of bilateral ground glass opacities that matched COVID-19.

Table 1. Findings from several meta-analyses that investigated VTE/PE in COVID-19 patients.

Study	No of participants	Gender	Age	Observed period	Study design	VTE/PE incidence	Other important findings
Longchamp et al³ 2021	4.009	The range of males was 51.7-86.2%; The range of females was 13.8-48.3%;	The range of mean age was 57-69 years	January 1- June 15 2020	Meta-analysis (33 studies analyzed)	The pooled VTE incidence was 9% overall (95% CI 5-13%, I ² = 92.5), and 21% (95% CI 14-28%, I ² = 87.6%) for ICU patients Overall PE incidence was 8% overall (95% CI 4-13%, I ² = 92.1%) and 17% for ICU patients (95% CI 11-25%, I ² = 89.3%)	Screening and absence of anticoagulation were associated with a higher VTE incidence When restricting to medically ill inpatients, the VTE incidence was 2% (95% CI 0-6%)
Fontelo et al⁶ 2021	2.554	The range of males was 46-81%; The range of females was 19-54%;	The range of mean age was 60-74 years	January 1- July 1 2020	Meta-analysis (19 studies analyzed)	The pooled incidence rate of development of VTE was 28% (95% CI 21-36%)	The pooled estimates of the odds ratios from the random effect meta-regression analyses for effect of four variables of interest on developing VTE (age, thromboprolylaxis, ICU admission and sex) were not significant
Suh et al¹⁰ 2020	3.342	65% males 35% females	The range of mean age was 69-70 years	January 1- June 15 2020	Meta-analysis (27 studies analyzed)	The pooled PE incidence was 16.5% (95% CI: 11.6, 22.9; <i>p</i> =0.93) PE was more frequently found in patients who were admitted to the ICU (24.7% [95% CI: 18.6, 32.1] vs. 10.5% [95% CI: 5.1, 20.2] in those not admitted to the ICU) and in studies with universal screening using CTPA	D-dimer levels of 500 and 1000 mg/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%, respectively) for development of PE Greater disease severity and universal screening with CTPA were significantly associated with a higher incidence of PE <i>p</i> <0.001 for both)
Di Minno et al¹¹ 2020	1.988	67% males 33% females	64.3 years mean	The last search was performed on May 19 2020	Meta-analysis (20 studies analyzed)	The weighted mean prevalence (WMP) of VTE was 31.3% (95% CI: 24.3-39.2%); WMP of PE was 18.9% (95% CI: 14.4-24.3%, <i>p</i> <0.001)	When specifically analyzing studies on ICU patients, WMP for VTE was 16.1% , 95% CI: 13.1-19.6%; <i>p</i> =0.330) and in studies on patients receiving antithrombotic prophylaxis WMP was 5.4% , 95% CI: 11.2-20.8%, <i>p</i> =0.002;
Nopp et al¹² 2020	28.173	60.1% males 39.9% females	62.6 years mean	The last search was performed on August 26 2020	Meta-analysis (66 studies analyzed)	The overall VTE prevalence estimate was 14.1% (95% CI: 11.6-16.9%) - 7.9% (95% CI, 5.1-11.2) in non-ICU and 22.7% (95% CI, 18.1-27.6) in ICU patients; Prevalence of PE in non-ICU and ICU patients was 3.5% (95% CI, 2.2-5.1) and 13.7% (95% CI, 10.0-17.9), retrospectively;	Patients developing VTE had higher D-dimer levels (weighted mean difference, 3.26 µg/mL; 95% CI, 2.76-3.77) than non-VTE patients VTE prevalence was 40.3% (95% CI, 27.0-54.3) with ultrasound screening and 9.5% (95% CI, 7.5-11.7) without screening

VTE - venous thromboembolism, CI - confidence interval, ICU - Intensive Care Unit, PE - pulmonary embolism, CTPA - computed tomography pulmonary angiography, WMP - weighted mean prevalence.

Conclusions

Healthcare professionals should be aware that PE can occur as a late complication of COVID-19. Although standard D-dimer cut-off levels could exclude the possibility of DVT and PE in outpatients with a low or intermediate clinical probability of PE, such an approach in COVID-19 patients may be inappropriate in some situations. Clinical suspicion of PE should lead physicians to use additional diagnostic methods to confirm or rule out PE.

Conflict of Interests

The authors declare that they have no conflict of interests.

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