Article

Case report: An unusual case of high-risk pulmonary embolism in a post-COVID 19 female under hormonal contraception

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Abstract: Coronavirus 19 disease (COVID-19) may be complicated by thrombotic events, particularly venous thromboembolism (VTE), which have been reported both in critically ill hospitalized patients and in individuals with mild symptoms. It is known that the chronic use of oral contraceptive pills (OCPs) is associated with higher risk of VTE. To date, there are only few reports concerning the association of OCPs and VTE/pulmonary embolism (PE) in COVID-19 patients. Given that during the convalescent phase of disease, a state of endothelial dysfunction, hypercoagulability and a low-grade inflammation may be persistent, the occurrence of thromboembolic events following acute COVID-19 infection may be not surprising. Herein, we report a case of high-risk PE detected in a post-COVID-19 young woman under hormonal contraception, which required thrombolytic treatment. A number of prothrombotic phenomena, such as overweight, hormonal contraceptive therapy, recent COVID-19 infection and prolonged immobilization, might have synergically contributed to the development of a sublethal thromboembolic event.

Keywords: COVID-19 Coagulopathy; hormonal contraception; COVID-19; venous thromboembolism; pulmonary embolism; thrombolysis

1. Introduction

During the current Coronavirus 19 disease (COVID-19) pandemic, it has been documented that hospitalized patients, especially those under critical care, have an increased risk for thrombotic events, particularly venous thromboembolism (VTE) [1]. The occurrence of VTE in critically ill COVID-19 patients is associated with a significantly increased mortality rate, due to the rapid progression to pulmonary embolism (PE) [2-6]. The association between VTE/PE and COVID-19 infection has been also reported in patients with mild symptoms of COVID-19 disease [7-10], and in post-COVID patients, especially during the first three months following the infection [11,12]. The most common risk factors for VTE are overweight/obesity, previous thrombotic event, history of malignancy, smoking, uncontrolled diabetes, older age or frailty, prolonged immobilization, and chronic diseases [11]. Another risk factor for VTE is the chronic use of oral contraceptive pills (OCPs) [12]. During the last few years, OCPs have become increasingly prescribed [13]. The use of OCPs is

associated with a general two- to three-fold increase in the risk of deep vein thrombosis and PE, especially for estrogenic-containing therapies, such as ethinylestradiol [14]. Currently, there are only few reports describing the association of oral hormonal contraceptives and VTE/PE in acute COVID-19 patients [15,16]. As far as we know, significant thromboembolic complications, such as saddle PE, have never been described in post-acute COVID women who did a chronic use of OCPs. Herein, we present a case of extensive PE, which occurred four weeks after mild COVID-19 disease, in a young woman under hormonal contraception. In the present case, several prothrombotic phenomena, such as overweight, chronic OCP assumption, recent COVID-19 infection and prolonged immobilization, might have synergically contributed to a sublethal thromboembolic event.

2. Results

Case presentation

A 29-year-old, nulliparous, non-smoker, overweight (body surface area 1.97 m^2; body mass index 29.4 Kg/m^2) female, who had received 3 doses of mRNA COVID-19 vaccine, presented to the emergency room of our hospital for ongoing dyspnea, tachycardia and general malaise. She had recent COVID-19 infection, presenting with mild symptoms (pharyngodynia only), which occurred four weeks before and lasted one week. During the post-acute phase of disease, the patient was immobile at bedside for three weeks, due to muscle weakness. Moreover, she had a history of chronic OCP (levonorgestrel 0.10 mg and ethinylestradiol 0.02 mg daily) use for 6 years. At hospital admission, blood pressure was 90/60 mmHg, heart rate was 132 bpm, arterial oxygen saturation was 88% and body temperature was 36.5°C. The electrocardiogram revealed sinus rhythm with S1Q3T3 pattern (Figure 1).

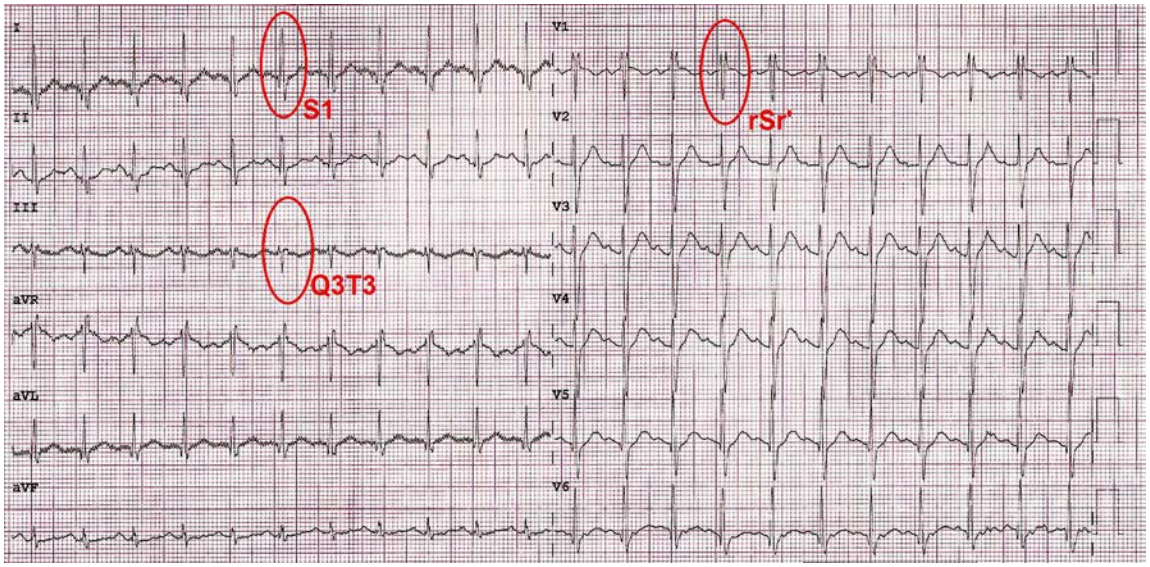

Figure 1. 12-lead ECG, showing mild right ventricular delay and S1Q3T3 pattern, indicative of acute pulmonary embolism.

Laboratory test results showed leukocytosis [white blood count (WBC) 12.3 x 10^9/L], hemoglobin 13.5 g/dl, hematocrit 42% and elevation of neutrophil-to-lymphocyte ratio (NLR) 7.8 (normal range between 1 and 3), serum levels of D-dimer (9546 ng/ml; normal range 0.0-682 ng/ml), troponin I (0.07 ng/ml; normal range 0-0.04 ng/ml) and C-reactive protein (CRP) (2.3 mg/dl; normal range 0-0.5 mg/dl); in addition, brain natriuretic peptide (BNP) and coagulation profile, assessed by prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalized ratio (INR), were normal (Table 1).

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Table 1. Biochemical parameters recorded at hospital admission and discharge. aPTT, activated partial thromboplastin time; BNP, brain natriuretic peptide; CRP, C-reactive protein; Hb, hemoglobin; HCT, hematocrit; INR, international normalized ratio; NLR, neutrophil-to-lymphocyte ratio; PLTs, platelets; PT, prothrombin time; WBC, white blood count.

Biochemical parameters	Hospital admission	Hospital discharge
Hb (g/dl)	13.5	12.8
HCT (%)	42	39
WBC (x 10^9/L)	12.3	6.9
NLR	7.8	1.5
PLTs (x 10^9/L)	198	281
Creatinine (mg/dl)	0.8	0.9
CRP (mg/dl)	2.9	0.2
D-dimer (ng/ml)	9546	1763
Troponin I (ng/ml)	0.07	0.02
BNP (pg/ml)	19	6
PT (sec)	11	12.5
aPTT (sec)	23.4	19.5
INR	1.0	1.1

Arterial blood gases analysis showed hypocapnia (pCO2 of 27.6 mmHg) and hypoxemia (pO2 of 66 mmHg) with mild respiratory alkalosis (pH of 7.48). An urgent computed tomography (CT) pulmonary angiography revealed extensive saddle pulmonary embolism (Figure 2). CT venography documented concurrent thrombosis of the left saphenofemoral junction and great saphenous vein (Figure 3). Transthoracic echocardiography (TTE) confirmed the saddle pulmonary embolism (Figure 4, Movie) and showed a moderate right ventricular (RV) dilatation (RV to left ventricular basal diameter ratio = 1.2) and dysfunction (tricuspid annular plane systolic excursion = 15 mm) (McConnell's sign positive) with severe pulmonary hypertension (tricuspid regurgitation velocity >3.4 m/sec).

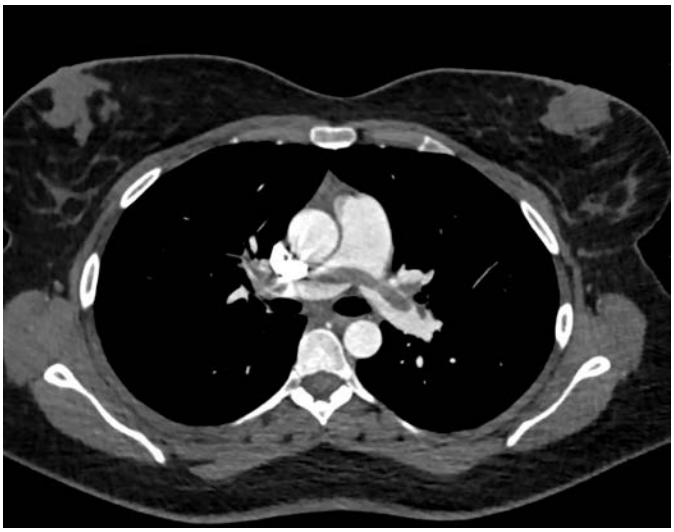

Figure 2. Axial view of the computed tomographic pulmonary angiography, showing a saddle pulmonary embolism extending in both the right and left pulmonary arteries.

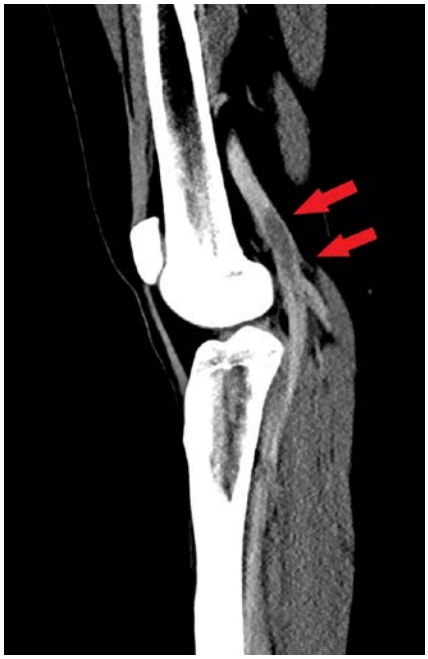

Figure 3. Computed tomography venography in sagittal reconstruction, showing concurrent thrombosis of the left saphenofemoral junction and great saphenous vein (red arrows).

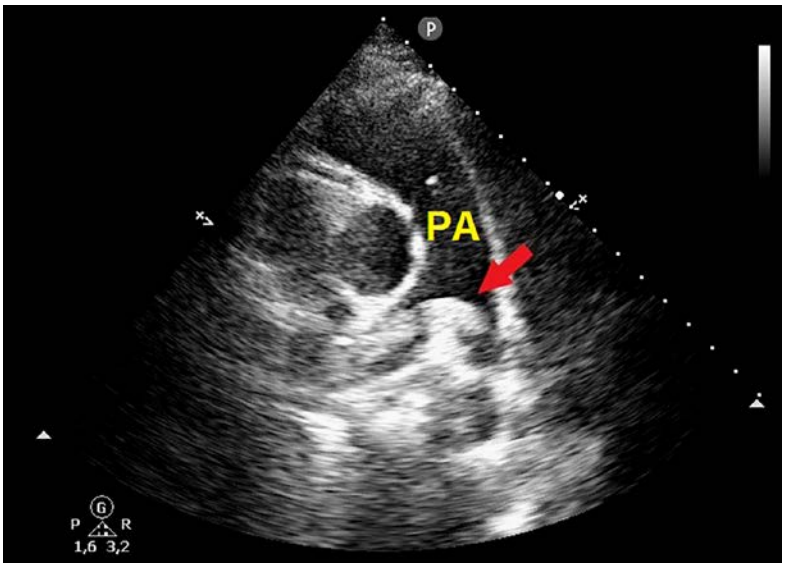

Figure 4. Two-dimensional transthoracic echocardiography. Basal short-axis view, demonstrating a saddle pulmonary embolism (red arrow) extending in both the right and left pulmonary arteries. PA, pulmonary artery.

Reverse Transcription-Polymerase Chain Reaction (RT-PCR) test for SARS-CoV-2 was negative and the patient was transferred to the respiratory intensive care unit. Given the arterial hypotension secondary to extensive PE, the patient underwent systemic thrombolysis with recombinant tissue plasminogen activator (rtPA) 100 mg infusion over 2 h. After treatment, she showed a rapid improvement in her hemodynamic and ventilatory patterns, the ECG quickly normalized and saddle pulmonary embolism disappeared on TTE (Figure 5). During hospitalization the patient underwent a thrombophilia screening, who did negative results. Notably, protein C activity (86%; normal range 70-130%), protein S activity (88%; normal range 65-145%), antithrombin III activity (96%; normal range 80-120%) and serum homocysteine (11 micromol/L; normal values <15 micromol/L) were within normal ranges. Factor V Leiden gene mutation (G1691A), prothrombin gene mutation (G20210A) and MTHFR mutation were negative. Finally, antibodies anticardiolipin and lupus

anticoagulant were not detected; accordingly, antiphospholipid syndrome was excluded. On repeated blood tests, normalization of serum inflammatory biomarkers (WBC, NLR, CRP) and troponin I was observed, whereas serum D-dimer levels were significantly decreased (Table 1).

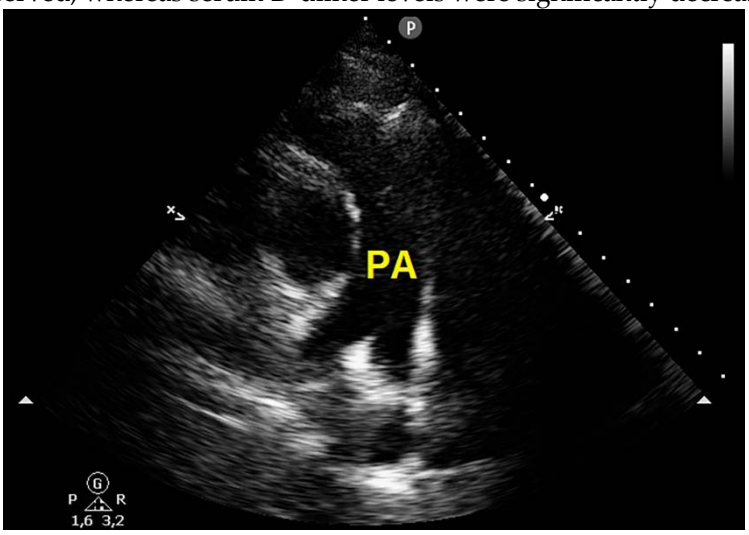

Figure 5. Basal short-axis view from transthoracic echocardiography, demonstrating total regression of mobile saddle thrombus after thrombolytic treatment. PA, pulmonary artery.

The further use of OCP was contraindicated and the patient was discharged from our institution with the indication to a 6-months of anticoagulant therapy with a factor-XA inhibitor (apixaban 5 mg twice a day).

3. Discussion

Venous thromboembolism is a leading cause of mortality in the world [17]. Risk factors for VTE can be permanent (such as thrombophilia) or temporary (such as infections or prolonged immobilization). Accordingly, hospitalized patients with acute infectious diseases have a significantly increased risk of developing VTE [3,5,17]. An increased prevalence of VTE has been documented in COVID-19 patients, both in those with severe disease, and even among those who are not critically ill [18-20]. The main factors responsible for hypercoagulability and thrombogenesis associated with COVID-19 infection are the following: endothelial cell activation and injury, activation of the renin-angiotensin-aldosterone system and hyperimmune response [21-24]. The endothelial dysfunction resulting from the binding of angiotensin-converting enzyme 2 receptors to the virus [25,26] may induce the activation of the coagulation cascade and increase the risk of thrombotic manifestations such as VTE, mediated by the endothelial release of procoagulant plasminogen activator inhibitor (PAI-1) and inflammatory cytokines, such interleukin (IL)-6, IL-2, IL-7, interferon-gamma, and TNF-alfa [21-23].

Another risk factor for VTE is the chronic assumption of hormonal contraceptives. The OCPs-related pro-thrombotic affects are more frequently observed in women older than 35 years, smokers, women with diabetes, women with body mass index >25 Kg/m^2, women with polycystic ovary syndrome or women with history of thrombophilia, particularly during the first year of treatment [27].

The literature data concerning the association between hormonal contraception and VTE/PE in COVID-19 patients are scanty. To date, only two authors have described the association between chronic OCP use and VTE/PE in the acute phase of disease [15,16]. Differently from the above-mentioned case reports, we described a case of extensive saddle PE detected during the post-acute phase of COVID-19 disease, in a young woman who did a chronic use of OCP. In our case, the patient was younger than 35 years, had never smoked, was not diabetic, did not have thrombophilia and used OCP for more than one year. The main mechanisms which could explain the development of VTE in the present case are the persistent inflammation caused by SARS-CoV-2 infection and a

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possible pro-thrombotic association between the virus and OCPs use [15,28]. In addition, a state of prolonged immobilization during the post-acute phase of COVID-19 disease may have exacerbated the potential risk for developing VTE/PE [29].

We reported a case of proximal PE; this finding was in contrast with the majority of reports which described segmental or subsegmental cases of PE in COVID-19 patients [5,30].

Current reasons for COVID-19-associated hypercoagulability include hypoxia and systemic inflammation secondary to COVID-19 infection, leading to high levels of inflammatory cytokines and activation of the coagulation pathway. Following mechanisms have been proposed to explain the occurrence of thromboembolic events in COVID-19 patients: 1) endothelial inflammation with very high levels of von Willebrand factor antigen and factor VIII; 2) hypoxemia-induced vasoconstriction promoting vaso-occlusion; 3) activation of hypoxia-inducible factors (HIFs) resulting in the induction or inhibition of tissue factor (TF) and plasminogen activator inhibitor 1 (PAI-1); 4) elevated levels of lupus anticoagulant; 5) direct activation coagulation cascades; and finally 6) endothelial injury by the virus [31].

Considering that the virus' spike protein binds to the Angiotensin-Converting Enzyme 2 (ACE2) receptor to enter the cell and infect the body [32] and that recent studies have demonstrated that estrogens stimulate ACE2 activity in the atrial tissue of the human heart [33], it is likely that hormonal steroid contraceptives may increase the risk of becoming infected with SARS-CoV-2 [34]. Moreover, the estrogenic component of hormonal contraception may increase the risk of venous thrombosis due to its ability to activate the coagulation system [35].

Given that during the convalescent phase of COVID-19 disease, a state of endothelial dysfunction, hypercoagulability and a low-grade inflammation may be persistent [36,37], it is likely that OCP may have exerted an additive prothrombotic effect on a substrate of chronic immuno-thrombogenicity related to COVID-19 infection. Indeed, the patient was diagnosed with increased serum levels of serum inflammatory biomakers, such as WBC, NLR and CRP, thus confirming a state of persistent inflammation during the post-acute phase of COVID-19 disease.

In the present case, serum D-dimer levels were strongly correlated with the extent of PE on CT pulmonary angiography, as observed by previous Authors [38]. According to literature data [39], the increase in serum D-dimer levels may be persistent in approximately 25% of convalescent COVID-19 patients up to 4 months following the resolution of the acute infection; these increased D-dimer levels have been observed in both hospitalized and nonhospitalized COVID-19 patients [40]. Moreover, sustained prothrombotic changes related to elevated thrombin-generating capacity have also been reported [41]. The persistent procoagulant effects following acute COVID-19 infection are likely modulated by persistent endotheliopathy and coagulation activation, independently of the acute phase response [42].

Although the present case was only a case report, it highlights the risk of sublethal PE following COVID-19 infection, even in patients with mild-to-moderate disease and confirms the wide interindividual variability of SARS-CoV-2 infection. The main clinical implication of our findings is that, for convalescent patients, regardless of the severity of infection, clinicians need to be vigilant for possible post-infective thrombotic sequelae as well as consider the importance of differentiating the immunologic and genetic characteristics of each patient [43]. In individuals at increased risk of thrombotic events, the thromboprophylaxis should be considered, even after resolution of mild-to-moderate forms of COVID-19 disease [31]. Moreover, frequent mobilization should be encouraged in patients with mild COVID-19 disease who can functionally perform activities of daily life. In addition, the discontinuation of prothrombotic drugs such as OCPs and selective cyclooxygenase-2 (COX-2) inhibitors [44] and weight loss in individuals with obesity [45] should be considered. Finally, it could be useful to employ individualized risk stratification for non-critical COVID-19 patients, by using scores that still need validation [46].

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

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