Acute pulmonary embolism in a patient with mild COVID-19 symptoms: a case report

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Background
The venous thromboembolism (VTE) is a frequent condition, which may worsen the prognosis of hospitalized COVID-19 patients. Nevertheless, the incidence of this complication is unknown in patients with mild COVID-19 symptoms.

Case summary
A 26-year-old female nurse, who had been taking oral contraceptive pills (OCPs) treatment for the last 2 years, developed mild COVID-19 symptoms (rhinitis and anosmia). She underwent isolation at home and was subsequently followed up with telehealth visits. Fifteen days after her initial presentation, she developed acute onset sudden dyspnoea. On physical examination, she was found to be tachycardic with normal pulse oximetry. The initial risk score for VTE was moderate and laboratory results showed increased D-dimer level without other relevant findings. Computed tomography pulmonary angiography was performed, which confirmed low-risk subsegmental pulmonary embolism.

Discussion
Venous thromboembolism in patients who present with severe COVID-19 symptoms has already been described in the literature; its incidence is greater in patients hospitalized in intensive care units. Efforts to prevent VTE based on risk scores are widely recognized. However, the relationship in patients who present with mild COVID-19 symptoms and VTE is still unknown. Recently, experts on this field have introduced thromboprophylaxis guidelines including ambulatory patients based on the severity of COVID-19 symptoms and pro-thrombotic risk. Our patient showed no major risk for developing VTE; therefore, the VTE could be associated with SARS-CoV-2 infection or the eventual pro-thrombotic association with the concomitant use of OCPs.

Keywords
COVID-19 • Venous thromboembolic disease • Oral contraceptive pills • Pulmonary embolism • SARS-CoV-2 • Case report

Learning points
• Thrombotic events are related to COVID-19. Although the association with moderate and severe cases has been described, the relationship in mild COVID-19 is still unknown. Further studies are needed to establish such association in this population.
• Venous thromboembolism should be suspected even in mild cases of COVID-19, whenever new symptoms such as dyspnoea or tachycardia appear and cannot be explained by other causes.
• Pro-thrombotic risk stratification in patients with COVID-19 infection who present with mild symptomatology could be considered.
Introduction

COVID-19 is a new infectious disease caused by the SARS-CoV-2 virus. Subjects who have contracted this disease may be asymptomatic, but may also present with a wide range of symptoms, including serious conditions such as acute respiratory distress syndrome. In addition, this infection is frequently related to thrombotic events, including venous thromboembolism (VTE). To date, the association between VTE and COVID-19 disease in hospitalized patients who need critical care has been described, with a significant increase in the mortality rate of this population. However, there are few descriptions of cases of thrombotic pulmonary embolism (PE) in patients who develop only mild symptoms of COVID-19 infection. Additionally, the use of oral contraceptive pills (OCPs) is associated with a two to six times higher risk of developing VTE.

We present the case of a patient who was taking OCPs and developed mild symptomatology due to COVID-19 infection, who was later found to have a PE, defined by the criteria stated in the 2019 European Guidelines for the diagnosis and management of acute PE.

Timeline

| Day | Event |
|-----|-------|
| 0   | The patient presented to the emergency department with rhinitis and anosmia symptoms. Reverse transcription–polymerase chain reaction SARS-CoV-2 virus was performed with a positive result. COVID-19 disease was diagnosed without hospitalization criteria. Self-isolation was indicated with routine telehealth follow-up. |
| 1–13 | The patient improves clinically. |
| 14  | The patient presented with dyspnoea (NYHA class II) and palpitations, with no associated oxygen desaturation. Electrocardiogram showed sinus tachycardia. A chest X-ray ruled out any infiltrate compatible with pneumonia. Laboratory results demonstrated an elevated D-Dimer level (1778 ng/mL), with no other significant findings. Both echocardiogram and compression ultrasonography of lower extremities were normal. Computed tomography pulmonary angiography was requested which confirmed bilateral subsegmental pulmonary embolism. Oral contraceptive pills were discontinued. Anticoagulant treatment with low-molecular weight heparin(s) was initiated. |
| 20  | Pregnancy and antiphospholipid syndrome were ruled out. Anticoagulation was switched to Apixaban with a treatment goal of at least 3 months. |

Case presentation

A 26-year-old previously healthy female nurse, who was working on a COVID-19 inpatient unit, presented to the emergency department (ED) with rhinitis and anosmia. Of note, she had been taking OCPs for the previous 2 years. On physical examination, she was afebrile with a normal heart rate and blood pressure and no respiratory distress. Her body mass index (BMI) was normal at 20 kg/m². Reverse transcription–polymerase chain reaction was performed, confirming the diagnosis of SARS-CoV-2 infection. Due to symptoms compatible with mild COVID-19 infection, she subsequently isolated at home with routine telehealth follow-up.

COVID-19 disease evolved favourably over the following 14 days that she spent on isolation; therefore, she was instructed to discontinue quarantine at the end of that period.

On the 15th day after the onset of the disease, the patient presented with NYHA class 2 dyspnoea. By using a digital pulse oximeter, she noted an oxygen saturation of 99% and a rapid heart rate, which led her to a cardiology consultation. Physical examination revealed: temperature: 36.5°C, blood pressure: 110/60 mm Hg, respiratory rate: 16 breaths per minute, oxygen saturation (SpO₂): 99% on room air, and heart rate: 120 b.p.m. Chest X-ray was normal (Figure 1). The electrocardiogram revealed sinus tachycardia without any other abnormalities (Figure 2).

Based on 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of acute PE, the Geneva score was used to estimate the probability of PE, which showed an intermediate risk of 20–30%. Therefore, a complete blood work was ordered including a D-dimer level (Table 1). The use of this predictive tool and an elevated level of D-dimer in blood led to performing a computed tomography pulmonary angiography, which confirmed a bilateral inferior subsegmental PE (Figure 3). Echocardiography and compression ultrasonography of lower limbs veins were normal. The patient’s OCPs treatment was suspended and she was initially started on anticoagulation with low-molecular weight heparin. Her anticoagulation
Figure 2 The electrocardiogram calibration speed 25 mm/seg—10 mm/mV shows sinus tachycardia 120 b.p.m., axis preserved 60 degrees, PR segment 160 ms, QRS Wave 80 ms, without ischaemic alterations in St and T waves.

Table 1 First laboratory requested

| First laboratory request       | Normal values |
|--------------------------------|---------------|
| Glucose 90 mg/dL              | 70–110 mg/dL  |
| Haematocrit 38.3%             | 37–47%        |
| Haemoglobin 12.8 g/dL         | 11.5–16 g/dL  |
| Leucocytes 6293/mm³           | 5000–1000/mm³ |
| Neutrophils 52%               | 50–60%        |
| Lymphocytes 35%               | 30–40%        |
| Monocytes 7.14%               | 4.00–12.00%   |
| Eosinophils 4.65%             | 2.00–4.00%    |
| Basophils 0.32%               | 0–1.00%       |
| Platelets count 156 600/mm³   | 150 000–450 000/mm³ |
| Erythrosedimentation 20 mm    | 2–20 mm       |
| D-Dimer 1778 ng/mL            | 0–500 ng/mL   |
| APTT 26 seg.                  | 25–40 seg.    |
| Ferritin 168 ng/mL            | 6–137 ng/mL¹  |
| Ultra-sensitive C reactive protein 0.7 mg/L | Normal³ |
| Creatinine 0.49 mg/dL         | 0.5–1.20 mg/dL|
| Urea 27 mg/dL                 | 20–50 mg/dL   |
| Plasma sodium 144 mmol/L      | 135–145 mmol/L|
| Plasma potassium 3.9 mmol/L   | 3.5–5.0 mmol/L|
| Plasma chlorine 108 mmol/L    | 95–106 mmol/L |

¹In premenopausal women.
²Population values in healthy people: 50th percentile: up to 18 years: <0.97 mg/L, from 25 to 44 years: 0.70 mg/L.
³APTT, activated partial thromboplastin time.
treatment was switched to Apixaban 5 mg twice a day with a minimum 3-month treatment goal once other causes of VTE such as pregnancy or anti-phospholipid syndrome, which would contraindicate the use of novel oral anticoagulants were ruled out. Additionally, antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), and viral serologies tests were performed, all of them with negative results (Supplementary material online, Table S1).

Clinically, the patient progressed favourably without dyspnoea though she continued to have tachycardia on mild to moderate exertion until the 1st week of anticoagulant treatment.

**Discussion**

Venous thromboembolism represents the 3rd acute cardiovascular syndrome, being one of the main causes of mortality in the world. This disease is associated with several predisposing conditions, which could be permanent (e.g. thrombophilia) or temporary (e.g. infections), and the diagnosis is essential for the correct treatment. Hospitalized patients with infectious diseases are at high risk of developing VTE. This complication is common among patients who present with severe COVID-19 symptoms, but the incidence of VTE in ambulatory patients is quite unknown. A retrospective study including 72 non-hospitalized COVID-19 patients with pneumonia who were admitted to the ED due to worsening respiratory symptoms reported a PE prevalence of 18%. Venous thromboembolism was associated with old age and elevated D-dimer levels in this population. The authors concluded that PE development is not limited only to critically ill COVID-19 infected patients. Nevertheless, further studies are needed to confirm these findings. The role of thromboprophylaxis in ambulatory patients with a COVID-19 diagnosis is yet unknown. According to Bikdeli et al., it could be reasonable to employ individualized risk stratification for thrombotic and haemorrhagic risk in this population using scores that still need validation.

In this case report, we describe a thrombotic event in a patient with COVID-19 infection with two temporary predisposing factors for VTE development: SARS-CoV-2 infection and OCPs treatment. However, the patient’s individualized thrombotic risk stratification was low since most of VTE risk assessment models do not include the variables mentioned before. As a result, the patient was not eligible for pharmacological prophylaxis. Therefore, further studies are needed to determine the association of these factors with VTE development.

The factors, which might explain the association between VTE and COVID-19 infection, are inflammation and hypercoagulability triggered by SARS-CoV-2 virus. Regarding the mechanisms involved, the activation and endothelial cell damage resulting from the binding of angiotensin-converting enzyme 2 receptors to the virus may increase the risk of VTE mediated by the release of inflammatory cytokines such as interleukin (IL)-6, IL-2, IL-7, granulocyte colony stimulating factor, interferon-γ, and TNF-α. This mechanism could play an important role in the activation of coagulation,
Acute pulmonary embolism in a patient with mild COVID-19 symptoms

Table 2  Laboratory tests to rule out other probable secondary predisposing causes of VTE and biomarkers for PE stratification.

| Laboratory results |
|-------------------|
| Pro-BNP           | 20.7 pg/mL\(^a\) |
| High-sensitivity cardiac troponin | <3.00 pg/mL |
| Pregnancy test    | Negative          |
| Anticardiolipin antibodies (IgM-IgG) | Negative |
| Anti-beta2-glycoprotein (IgM-IgG) | Negative |
| Anti-phospholipid antibodies | Negative |
| Lupus anticoagulant antibodies | Negative |
| ANCA C and P      | Negative          |
| Antinuclear antibodies | Negative |
| Anti-double-stranded DNA (anti-dsDNA) | Negative |
| C3 complement     | 134 mg/dL\(^c\) |
| C4 complement     | 25 mg/dL\(^d\)  |
| VIH serotypes 1 + 2 | Non-reactive |
| Hepatitis B antibodies | Non-reactive |
| Anti-HBs          | Reactive\(^f\)   |
| HBsAg             | Non-reactive     |
| Anti-HCV          | Non-reactive     |
| VDRL              | <2 pg/mL         |
| Interleukin-6     |                 |

\(^a\)Pro-BNP Healthy patients under 74 years: up to 125 pg/mL.
\(^b\)by indirect immunofluorescence testing.
\(^c\)C3 normal range 83–177 mg/dL.
\(^d\)C4 normal range 10–40 mg/dL.
\(^e\)Anti-HBc, anti-IgM, IgG.
\(^f\)Anti-HBs positive in context of vaccine immunization.

Increased blood viscosity, and micro-vascular thrombosis, although this is yet an area under study.\(^{13,14}\) This would explain the coagulation profile abnormalities found in patients with SARS-CoV-2 infection, including elevated levels of D-dimer, fibrinogen, fibrin, and fibrinogen degradation products, as well as decreased levels of antithrombin.\(^{13,14}\) A recently published study showed an increase in platelet activation and aggregation in patients infected with SARS-CoV-2, which could also contribute to thromboinflammation in this disease.\(^{15}\) This suggests that one of the potential mechanisms of VTE in our patient could have been caused by SARS-CoV-2 virus triggered inflammation, even in this case with mild symptoms of COVID-19 infection at presentation.

Although there is evidence that OCPs increase the risk of VTE in women of reproductive age, this does not seem to be the only precipitating factor in this study case.\(^1\) Firstly, the patient did not have any of the known risk factors, which increase OCPs-related pro-thrombotic effects, such as age greater than 35 years old, smoking, diabetes, BMI > 25 kg/m\(^2\), or history of thrombophilia. Secondly, she had been taking OCPs for more than 2 years. According to epidemiological data, the risk of VTE is greater during the 1st year of OCPs treatment.\(^{11}\) Thirdly, there is a temporal relationship between the development of VTE and SARS-CoV-2 infection. Thus, the two mechanisms, which could explain the development of VTE, are the inflammation caused by SARS-CoV-2 infection or a probable pro-thrombotic association between this virus and OCPs use.\(^12\)

Further studies are needed to support the hypothesis raised in this document, considering that PE worsens the prognosis of patients with COVID-19.

Lead author biography

Norberto B. Fiorini is born in 1986 in Berazategui, Buenos Aires, Argentina. He received his medical degree from the University of Buenos Aires in 2012. He always had a great interest in critical medicine; therefore, he specialized in intensive care medicine at the Italian Hospital in Buenos Aires. Later on, he decided to continue his training in critical cardiac care. He is currently in his last year as a cardiology resident at the same institution.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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