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Late pulmonary embolism in a patient with mild COVID-19 An association with reinfection and the instituted treatment

Tomasz Czerski[1], Monika Landzberg[1], Kamil Mytkowski[1], Krzysztof J. Filipiak[2]

[1]Internal Medicine and Cardiology Department, Wegrow Hospital, Węgrów, Poland
[2]Maria Skłodowska-Curie Medical Academy in Warsaw, Warsaw, Poland

Abstract

A case is presented of a 49-year-old patient without risk factors for venous thromboembolism hospitalized with pulmonary embolism after COVID-19 infection, previously treated with amantadine for a short period. The patient underwent successful medical treatment with resolution of embolic material at 3 months. The authors discuss potential causes of embolism and possible recommendations for prevention.

Key words: pulmonary embolism, computed tomography, pulmonary fibrosis, COVID-19, prevention

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Introduction

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, multiple cases of pulmonary embolism have been reported, particularly in patients hospitalized in intensive care units, with fewer reports of late thrombotic complications in patients with mild severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and/or bacterial superinfection without other risk factors. Less data are also available regarding a potential association between thromboembolism and the treatment instituted for COVID-19.

Case report

A 49-year-old non-obese (body mass index 26 kg/m^2) man without any remarkable past medical history was hospitalized on day 20 after the initial symptoms of SARS-CoV-2 infection. He was admitted due to mild dyspnoea, haemoptysis for 3 days, and a high level of C-reactive protein (CRP) with a negative result of an antigen test (BIONOTE® Rapid MERS-CoV Ag Test Kit) ordered by a family physician. The patient was not vaccinated against COVID-19. Eight days before the admission, he completed his home quarantine ordered by a family physician. He was treated with amantadine for 4 days starting from day 5 after the onset of symptoms, followed by azithromycin for 5 days. On admission, the patient appeared generally well, with normal blood pressure (systolic 130 mm Hg, diastolic 90 mm Hg), oxygen saturation of 94%, and tachycardia (heart rate of 115 beats per minute). Crackles at the base of the right lung were noted on auscultation. High-resolution chest computed tomography without administration of a contrast agent was performed on admission, showing massive pulmonary fibrosis with particularly advanced lesions in the inferior lobe of the right lung, interpreted as secondary to inflammation in the course of COVID-19 disease, and mediastinal and right hilar lymphadenopathy (Figure 1). Laboratory blood tests showed CRP level 119 mg/dL, leukocyte count 11.2 × 10^9/L, platelets 409 × 10^9/L, D dimer 9496 ng/mL, troponin 32.6 ng/L, N-terminal pro-B-type natriuretic peptide (NT-proBNP) 74 pg/mL, SARS CoV-2 IgG

Address for correspondence: Tomasz Czerski MD, Oddział Internistyczno-Kardiologiczny, Szpital w Węgrowie, ul. Kościuszki 201, 07–100 Węgrów, Poland, e-mail: czerski4@2com.pl

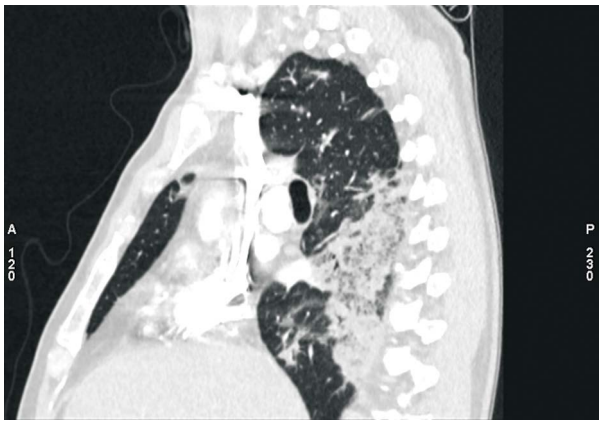

Figure 1. Massive pulmonary fibrosis with particularly advanced lesions in the inferior lobe of the right lung, secondary to previous inflammation in the course of COVID-19 disease

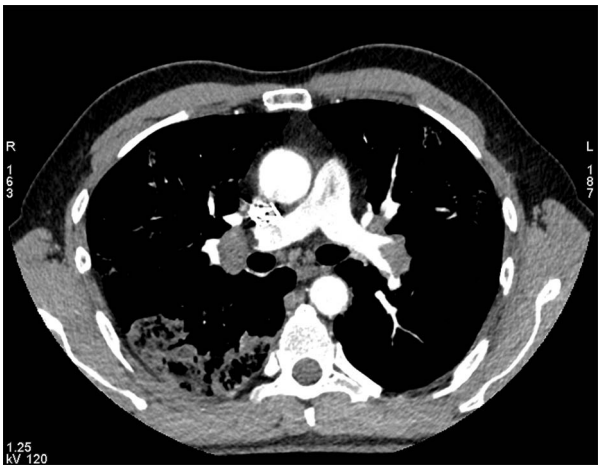

Figure 2. Massive pulmonary embolism. A large amount of embolic material in the bifurcations of both pulmonary arteries and in all lobar branches in both lungs

> 40 000 AU/mL, SARS CoV-2 IgM 10.98, and a negative SARS CoV-2 polymerase chain reaction test. The patient underwent computed tomography pulmonary angiography which showed a large amount of embolic material in the bifurcations of both pulmonary arteries and in all lobar branches in both lungs, mostly in the lower lobar branches and in segmental branches to the lower lobe of the right lung. Small amount of embolic material was noted in segmental branches to the middle lobe of the right lung and the lower lobe of the left lung (Figure 2). Echocardiography showed right ventricular dimension 28 mm, right ventricle to left ventricle diameter (RV/LV) ratio 0.8, pulmonary artery dimension 23 mm, tricuspid annular plane systolic excursion (TAPSE) 28 mm, mild tricuspid regurgitation with pulmonary artery systolic pressure (PASP) 55 mm Hg, pulmonary acceleration time (AcT) 71 ms, and peak pulmonary regurgitation velocity (PRV_{max}) 1.5 m/s. The calculated Pulmonary Embolism Severity Index (PESI) was 79 (low risk) and thus the Pulmonary Embolism Response Team (PERT), providing rapid evaluation and treatment for patients with acute pulmonary embolism, was not activated. The patient was admitted to a coronary care unit. He was administered enoxaparin 1 mg/kg subcutaneously twice daily, ceftriaxone intravenously, and clarithromycin intravenously. Rivaroxaban 30 mg/24 h was initiated on day 5. Follow-up laboratory tests showed CRP level reduction to 17 mg/dL on day 5, with normal values of other inflammatory markers, and follow-up echocardiography on day 7 showed a reduction of PASP to 40 mm Hg and an increase in pulmonary AcT to 82 ms. Anticoagulation was continued according to the typical schedule, with rivaroxaban dose reduction to 20 mg/24 h. Follow-up echocardiography at 3 months showed resolution of pulmonary hypertension, and follow-up computed tomography pulmonary angiography showed no filling defects in the pulmonary arterial vasculature (Figure 3). In view of the above, a decision was made to stop rivaroxaban after 3 months and initiate chronic sulodexide therapy at the dose of 2 capsules twice daily.

Discussion

The reported case of pulmonary embolism complicating COVID-19 may seem typical but when discussing it at a remote time, with expanded knowledge about the consequences of this pandemic, we believe that four specific aspects merit consideration.

First, thromboembolic complications may occur also in mild SARS-CoV-2 infection. It may be of importance in the context of future pandemic waves, likely to be cause by less virulent mutants. A direct prothrombotic effect of SARS-CoV-2 cannot be excluded but haemostasis abnormalities related to systemic inflammation in COVID-19 seem a more important factor, particularly with bacterial superinfection, as in the presented case [1]. The reported patient was treated at home, was not immobilized, had no additional risk factors, and the disease was initially mild, so an anticoagulant was not prescribed. However, pulmonary embolism was reported also in such patients, on average at 19 days since the beginning of the infection [2]. It is a disturbing finding, suggesting that the prothrombotic effect of COVID-19 may extend beyond the usual 5–7 days of patient isolation and self-observation. Thus, it may be reasonable to extend indications for thromboprophylaxis in some patients, as suggested in some expert consensus statements [3].

Second, additional risk factors for thromboembolic complications may exist that are not taken into consideration in the world's literature but may be important in the reported Polish patient. The fact of being unvaccinated and

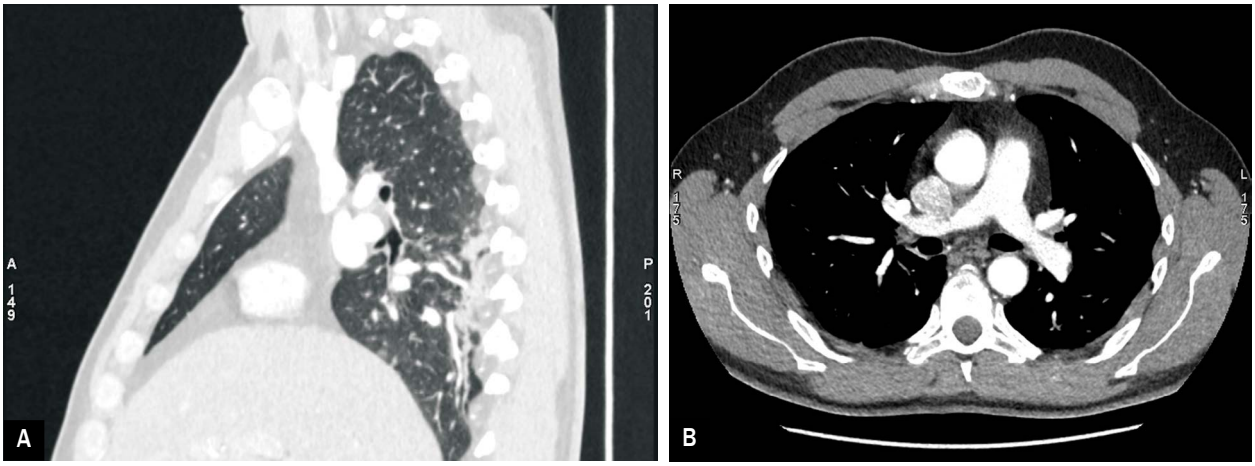

Figure 3. A. Patchy and streaky consolidations are seen in the dorsal part of the lower lobe of the right lung; **B.** No evidence of pulmonary embolism. Complete resolution of embolic lesions noted in the previous imaging study

dwelling in a low-vaccinated population might have additionally worsened the disease course even in a young, healthy individual without other risk factors for thrombosis. Polish patients who have not been fully vaccinated against COVID-19 or have not been vaccinated at all (currently 40% of the Polish population, predominantly in the eastern regions of the country), rarely protected by an additional dose (currently 70% of the Polish population have not been administered a booster dose, again predominantly in the eastern regions of the country), are potentially at a higher risk of COVID-19 complications, including thromboembolic events. In addition, Polish patients with a profile similar to the reported case often take amantadine, a therapy without any medical rationale, which is not supported by evidence-based medicine. Amantadine administered to patients with SARS-CoV-2 infection may cause cardiovascular deaths [4]. Until today, this drug has no credible research evidence supporting its use in SARS-CoV-2 infection [5], and publishing the results of uncontrolled observations without a bioethics committee approval in Polish scientific journals [6] should be considered outrageous and violating good scientific practice. In addition, there are observations suggesting an increased mortality rate in COVID-19 in those Polish voivodships where high sales of amantadine were recorded during the pandemic peaks [7]. It remains unclear whether this has been a result of amantadine use leading to prolongation of the prehospital phase and thus worsening outcomes in patients who were hospitalized too late, or a direct, e.g. proarrhythmic, amantadine effect.

Third, increasing evidence indicates a need for long-term anticoagulant use in such patients. In the reported patient, oral anticoagulation for the secondary prevention of pulmonary embolism was discontinued at 3 months in accordance with the current guidelines, considering SARS-CoV-2 infection a transient risk factor. However, sulodexide was initiated instead to continue anticoagulation. It is an agent which exerts a mild anti-Xa action, neutralizing the effect of this clotting factor but not leading to an increased bleeding risk. Use of this drug was first supported in the 2019 European Society of Cardiology guidelines on the management of acute pulmonary embolism [8]. This was a result of the SURVET study, a prospective, randomized, multicentre, double blind, placebo-controlled trial which showed that additional 2-year treatment with sulodexide after discontinuation of conventional anticoagulation used for a thromboembolic event resulted in halving the risk of a recurrent event without an increase in the bleeding risk [9]. Data collected during the COVID-19 pandemic also indicate that sulodexide may be useful for pharmacological repair and regeneration of endothelium, in particular its external glycocalyx layer [10]. Early reports also suggest that sulodexide may mitigate post-COVID or long COVID symptoms [11, 12].

Fourth, new algorithms have been suggested in early 2022 to search for late complications after mild/moderate COVID-19, which also increase the credibility of the management approach used in the reported patient. An interesting approach has been recently suggested in the Hamburg City Health Study COVID programme [13]. In this algorithm, a routine evaluation is suggested in all patients at 6–9 months after the infection, even after moderate or mild COVID-19. Thus the reported patient, after the 3-month follow-up required for the decision-making regarding continuation or discontinuation of oral anticoagulant therapy, should be reevaluated again 3–6 months later, with focus on the heart, lungs, kidneys, and the venous system, as suggested by the Hamburg approach. According to the algorithm, the minimum evaluation in this patient would

include full physical examination, history taking for post-COVID syndromes, evaluation of NT-proBNP and dimer D levels, estimation of the glomerular filtration rate, careful lung auscultation, and lower limb compression ultrasound, followed by other investigations if indicated based on the findings from this initial evaluation. A high clinical value of this "Hamburg algorithm", which could be employed in our patient during further follow-up, has been highlighted in expert commentaries [14].

Conflict of interest

None declared.

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