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## SARS-CoV-2 infection, hormonal contraception and pulmonary embolism in a 17-year-old female patient

Infekcja SARS-CoV-2, antykoncepcja hormonalna i zatorowość płucna u 17-letniej pacjentki

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### Abstract

The paper presents the history of a 17-year-old patient admitted to the paediatric cardiology department in a life-threatening condition with dyspnoea, blood desaturation up to 90% and chest pain. The patient contracted COVID-19 (she was not vaccinated), and additionally treated her acne with oestrogen hormonal drugs. Computed tomography of the chest revealed massive embolic changes in the pulmonary artery and its branches. After introduction of heparin under the control of activated partial thromboplastin time and then warfarin under the control of international normalised ratio (INR), regression of changes was achieved; however, the arterial vessel narrowed up to the upper lobe of the right lung. During cardiac catheterisation, the vessel was widened with a balloon and successfully opened. Follow-up echocardiography showed regression of changes, the dimensions of the right heart decreased, and the features of pulmonary hypertension disappeared. During the exercise test, she reached stage 4. After 2 months, to avoid patient exposure to radiation, follow-up magnetic resonance imaging of pulmonary vessels was performed instead of computed tomography, showing partial restoration of the artery. Currently, the patient is still taking warfarin (INR 2.5–3.5), is in good general condition and a lung scan is planned in the future.

**Keywords:** pulmonary embolism, hormonal contraception, SARS-CoV-2

### Streszczenie

W pracy przedstawiono historię choroby 17-letniej pacjentki, przyjętej na oddział kardiologii dziecięcej w stanie zagrożenia życia, z dusznością, desaturacją krwi do 90% oraz bólem w klatce piersiowej. Pacjentka przechorowała COVID-19 (nie była zaszczepiona), dodatkowo leczyła trądzik lekami estrogenowymi. W tomografii komputerowej klatki piersiowej stwierdzono masywne zmiany zatorowe w tętnicy płucnej i jej gałęziach. Po włączeniu heparyny pod kontrolą czasu kaolinowo-kefalinowego, a następnie warfaryny pod kontrolą międzynarodowego współczynnika znormalizowanego (*international normalised ratio*, INR) uzyskano regresję zmian, naczynie tętnicze uległo jednak zwężeniu do górnego płata prawego płuca. W czasie cewnikowania serca balonem poszerzono tętnicę i skutecznie ją udrożniono. Kontrolne badanie echokardiograficzne wykazało cofnięcie się zmian, zmniejszyły się wymiary prawego serca oraz ustąpiły cechy nadciśnienia płucnego. Podczas próby wysiłkowej pacjentka osiągnęła stopień wydolności 4. Po 2 miesiącach, ze względu na ochronę radiologiczną, zamiast kontrolnej tomografii komputerowej wykonano rezonans magnetyczny naczyń płucnych, stwierdzając częściowe udrożnienie tętnicy. Obecnie pacjentka nadal zażywa warfarynę (INR 2,5–3,5) i jest w dobrym stanie ogólnym; w przyszłości planuje się wykonanie u chorej scyntygrafii płuc.

**Słowa kluczowe:** zatorowość płucna, antykoncepcja hormonalna, SARS-CoV-2

## INTRODUCTION

**H**ypercoagulability, which can lead to formation of blood clots that can travel with blood flow and deposit in pulmonary, cerebral or coronary vessels, is one of the dangerous manifestations of coronavirus disease 2019 (COVID-19)<sup>(1)</sup>. The global incidence of acute pulmonary embolism (APE), which is the third leading cause of death in Europe, is about 1/1,000 adults per year<sup>(2-4)</sup>. The cause of death in APE is acute right ventricular failure caused by sudden mechanical pulmonary obstruction leading to a rapid increase in the right ventricle afterload<sup>(5,6)</sup>. Pulmonary embolism (PE) is very rare in children and most often develops as a consequence of congenital thrombophilia (e.g. Leiden *F5* mutation, *F2* mutation, congenital deficiencies of coagulation inhibitors, i.e. protein C, protein S, or congenital hyperhomocysteinaemia associated with *MTHFR* mutation). Embolism can also be promoted by trauma, surgery, overweight or smoking<sup>(7-9)</sup>. About 80% of patients develop deep vein thrombosis in their lower limbs, which can be suspected when lower limb oedema, tenderness (especially when walking) and redness or bruising appear within a short period of time. Migration of embolic material into the pulmonary artery causes sudden chest pain with rapidly increasing dyspnoea and blood desaturation. These are alarm signals that should not be ignored, and acute PE should always be ruled out in such cases<sup>(10)</sup>. There is also data showing an increased incidence of embolism in women using combined oral contraceptives (COCs) containing oestrogens<sup>(11,12)</sup>. In the presented case, PE may have been promoted by COVID-19 and the use of oestrogen contraception for the treatment of acne vulgaris. Treatment of PE should be initiated immediately to prevent dramatic complications<sup>(13-15)</sup>.

## CASE REPORT

A 17-year-old patient was transported by an emergency medical team to a district hospital due to repeated fainting episodes at home, acute chest pain and dyspnoea. On her visit to a general practitioner 7 days earlier, she manifested symptoms of upper respiratory tract infection, pharyngeal and chest pain, rhinitis and malaise, accompanied by gastroenteritis, general weakness, and breathing difficulties. Although she was not feverish, antibiotic therapy was introduced. During her visit to the toilet (urination), she experienced a dramatic episode of fainting without losing consciousness, preceded by the appearance of eye floaters. Importantly, the patient had used COCs (containing two active substances, i.e. ethinylestradiol and dienogest) prescribed by her dermatologist for acne vulgaris, for 4 weeks. On admission, she suffered from dyspnoea, with 90% oxygen saturation, which increased to 99–100% after oxygen supply at 6 L/min. Furthermore, there were signs of rhinitis, drying oral mucosa, reddened throat, single dry rales above the lung fields without signs of obstruction, and significant

respiratory effort. During her stay, temporary drops in saturation to 77% were also noted, especially in the supine position, which improved to about 99–100% upon lifting the torso while on passive oxygen therapy. Tachycardia of 120–130/min persisted. Laboratory findings included leukocytosis (81 thousand/ $\mu$ L), C-reactive protein (CRP) of 15 mg/L, blood smear indicative of neutrophilia, thrombocytopenia (140 thousand/ $\mu$ L), increased creatinine, abnormalities in the coagulation system, D-dimers of 13,000 ng/mL, and reduced activated partial thromboplastin time (APTT) of 23 s (normal: 26–40 s). Additionally, increased high-sensitivity cardiac troponin T was found (141 pg/L; normal: 0–14 pg/L). Electrocardiogram (ECG) on admission showed accelerated sinus rhythm of up to 130/min, right axis deviation, and negative T waves in leads V1–V3. Drug tests were negative. Computed tomography (CT) of the chest was performed, showing massive embolism in the pulmonary vessels. Diagnosed with PE, the girl was referred to the department of paediatric cardiology for further treatment (Fig. 1).

On admission, the patient was in moderately severe condition, with dyspnoea and chest pain reported as the main symptoms. Neither the patient nor her family were vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). PCR test for SARS-CoV-2, which was performed during her stay in the ward, was negative, while an increased titre of IgG antibodies was found, indicating a past infection with this virus. Passive oxygen therapy was initiated, tachycardia of 125–130/min and desaturation of 92–94% persisted. There were no pathological auscultatory findings over the lung fields, the liver was not enlarged, no oedema was observed, blood pressure was 114/76 mm Hg, leukocytosis – 8.1 thousand/ $\mu$ L, D-dimers – 16,467 ng/mL. ECG records indicated low

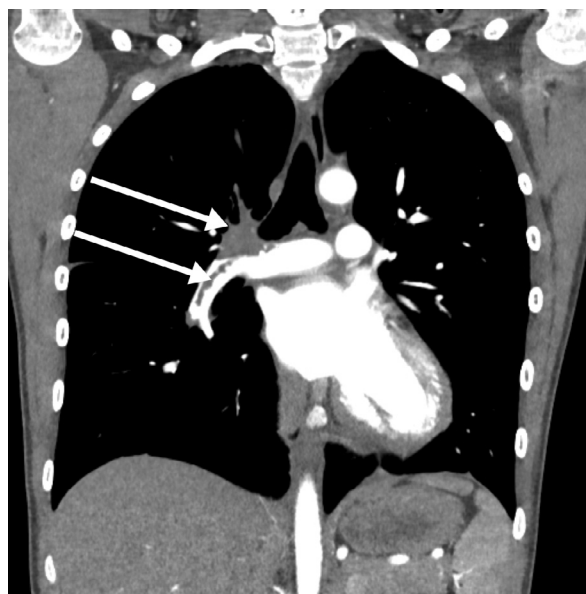


Fig. 1. Chest CT at the onset of the disease. Massive clots in the pulmonary artery and branches (arrows)

QRS voltage as well as disturbances in repolarization. Echocardiography revealed dominance of the right heart chambers, right atrial and right ventricular enlargement, low volumetric flow through the heart valves, grade II tricuspid valve regurgitation with a systolic gradient increased to 45 mm Hg, blood flow in the pulmonary trunk with signs of hypertension, and acceleration time (AcT) of 53 ms (normal: >100 ms). The patient was recommended bed rest, a clinical report card with fluid balance was set up, arterial pressure was measured every 2 hours, heart function, respiration and saturation were monitored, passive oxygen therapy and parenteral hydration were used, COC was discontinued and heparin infusion was started at a therapeutic dose of 15 U/kg/hour in 4-hourly doses, under the control of APTT. In addition, an antibiotic and enalapril maleate were included. Laboratory tests revealed APTT of 23 s and no significant change in D-dimers (16,000 ng/mL). In the hours that followed the patient's condition was stable, and the intravenous infusion of heparin and passive oxygen therapy were continued. After a few hours of treatment, the girl noticed a marked improvement in well-being, reduced dyspnoea and chest pain, but general weakness persisted. During passive oxygen therapy, the saturation remained within the range of 98–100%. At the time of heparin inclusion, on day 3 of heavy menstrual bleeding, the bleeding extended for another 3 days due to heparin. Systematic reduction of dyspnoea and chest pain, marked improvement in well-being, as well as in laboratory markers were a measure of the patient's improvement. Saturation remained constant at 98–100%. Thrombocytopenia was confirmed (up to 153 thousand/ $\mu$ L), inflammatory markers were negative. After 10 days, chest CT was repeated and showed a significant regression of PE. Treatment was changed, continuous heparin infusion was discontinued, enoxaparin sodium was administered at a dose of 100 IU/kg body weight (1 mg/kg body weight) twice a day and warfarin at a dose of 3–5 mg/day under international normalised ratio (INR) control. After making sure that the INR was in the range of 2.8–3.5, the girl was discharged home in good condition with instructions to use warfarin. On discharge, platelets and D-dimers were normal, the INR index was 2.94, and the prothrombin index was 34.7% (normal: 80–120%). Follow-up echocardiography revealed reduced size of the right heart and an increase in AcT from 53 ms to 132 ms. On the other hand, moderate tricuspid regurgitation with a regurgitation jet and a gradient of approximately 42 mm Hg persisted, indicating persisting pulmonary hypertension. Therefore, to assess therapeutic efficacy, the patient had a CT scan of the chest performed again after another 2 months, showing almost complete regression of the lesions; however, a significant narrowing of the artery to the upper lobe of the right lung was visible at a distance of about 6 mm (Fig. 2). Additionally, streaky areas of reduced aeration and accompanying fibrous bands were visible in the third segment of the right lung.

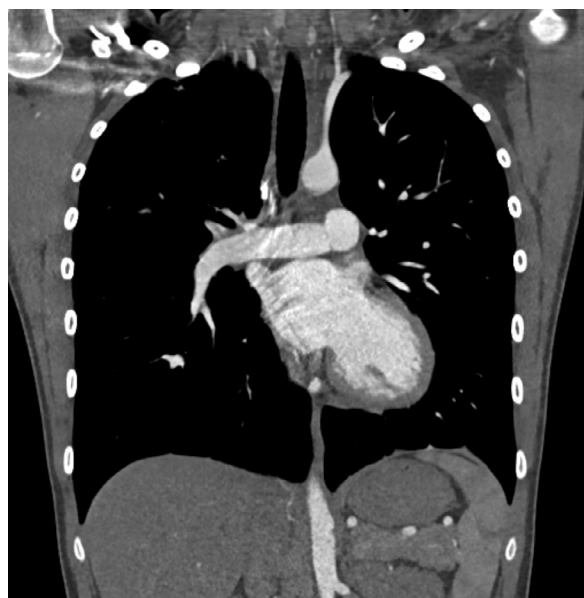


Fig. 2. Follow-up CT after 2 months. Partial restoration of the artery up to the upper lobe of the right lung (narrowing up to 1 mm over a 6 mm segment), weaker contrast enhancement of the branches of segmental arteries within the upper lobe of the right lung

During the patient's stay in the department, the laboratory parameters were normal, INR was 3.26, echocardiography revealed further reduction in right heart dimensions and reduced tricuspid valve regurgitation (trace) with a gradient of 30 mm Hg; AcT was 143 ms. ECG showed a changed heart axis, a normogram appeared, but the low amplitude of QRS complexes was still present. An exercise stress test was also performed according to a modified Bruce protocol, which was discontinued at stage 4 due to patient's fatigue. No cardiac arrhythmias or changes in the ST-T segment were observed during the test. The patient stopped losing hair (after previously heavy hair loss), which could have been related to the recent coronavirus infection. CT findings were consulted with an interventional cardiologist and the girl was qualified for cardiac catheterisation, during which successful percutaneous balloon angioplasty of the proximal part of the upper lobe of the right pulmonary artery was performed (Fig. 3). In order to avoid patient exposure to radiation, follow-up magnetic resonance (MR) of the heart and pulmonary vessels was performed instead of lung CT after 2 months, showing partial restoration of the right pulmonary branch (Fig. 4).

Currently, the patient remains in good general condition, continues warfarin (INR 2.9–3.5) and wishes to resume physical activity.

## DISCUSSION

The general practitioner who was first to see the patient presenting with dyspnoea, weakness, cough, and chest pain initially suspected an infection. However, as the symptoms

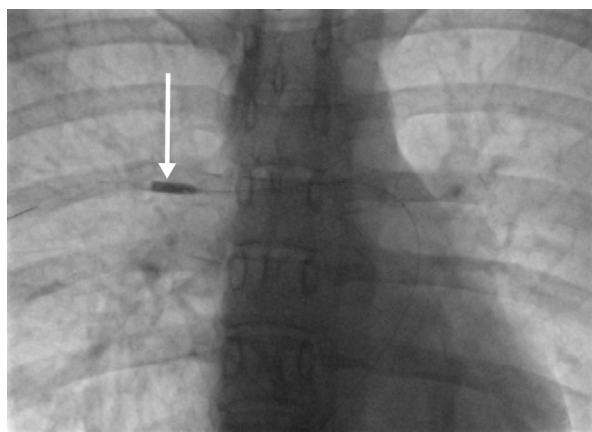


Fig. 3. Cardiac catheterisation. Percutaneous balloon angioplasty of the proximal part of the upper lobe branch of the right pulmonary artery with a 3.5 × 12 mm balloon catheter (arrow)



Fig. 4. MRI of the heart and pulmonary vessels showing partial restoration of the previously obstructed branch of the right pulmonary artery. A narrowing of approximately 2 mm (arrow) in the proximal part of the artery up to segment 3 of the right lung. The artery is 5 mm before the stenosis and 4.5 mm behind the stenosis. No other pulmonary stenosis or vascular obstruction was found. No residual embolic material was visualised

worsened over the next few days, the mother called an ambulance, and the girl was transported to the nearest hospital. There, a chest CT scan was performed and PE was diagnosed. Since this disorder is rare in children and adolescents, correct diagnosis may be challenging. Congenital defects of the clotting system (thrombophilia) that run in families are the most common aetiology of PE in children<sup>(2,4)</sup>. A well-collected history often reveals thrombotic events in the lower limbs, strokes or myocardial infarctions, often of a dramatic course, in family members.

So far, there are not many reports in the world literature on the use of COCs in the course of COVID-19 infection that would result in massive PE. Valenzuela-Vallejo et al. described a case of a 45-year-old overweight (another risk factor for thrombosis) woman infected with SARS-CoV-2, a long-term user of COCs, the active ingredients of which were levonorgestrel (synthetic progestogen and also a component of single-component or combined contraceptive pills) and oestradiol (one of the three natural estrogenic hormones), who presented with symptoms of shock due to massive PE requiring thrombolysis. The authors discussed the impact of risk factors on the development of embolism and emphasised the need for reporting similar cases<sup>(11)</sup>.

As shown in multicentre studies, the risk of thrombosis in COC users is approximately 3.5 times higher than in the group of women who do not use these agents, with the highest risk of thrombosis (as emphasized by Keenan et al.) in the first year of COC use. The same authors indicate that if thrombophilia is additionally detected in a woman using COCs, the risk of thrombosis increases 62-fold in the first year of COC use and 25-fold after the first year. In addition to COCs, other risk factors for thrombosis include age, obesity and smoking<sup>(12)</sup>.

In children, PE most often has a genetic background related to congenital thrombophilia, but it can also be promoted by past surgeries (fat embolism), overweight and injuries. Recently, this age group of risk factors was joined by SARS-CoV-2 infection.

In the described patient, the embolism was due to an overlap of several unfavourable circumstances, namely the girl had a history of coronavirus infection and was also on hormonal oestrogen contraceptives to treat acne vulgaris<sup>(11,12)</sup>. Significantly increased IgG antibodies, as well as hair loss, which may be one of the distant symptoms of COVID-19 disease, confirmed the past SARS-CoV-2 infection. As the pandemic progresses, we gather more data on the early and long-term effects of coronavirus infection and the symptoms based on which the infection is diagnosed, as well as the distant symptoms in children, i.e. the paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Massive PE is a life-threatening emergency and the patient's condition depends on which area of the pulmonary arteries will be blocked by blood clots and at what time. The more severe blood flow obstruction and the faster progression of this process, the more dangerous the course of the disease and the worse the prognosis. Acute chest pain in young people is most often due to trivial, insignificant causes, such as exhaustion, infection, trauma or incorrect body position (e.g. computer games or smartphone use), but there may also be more important circumstances, such as use of drugs or stimulants, etc. These causes can also be as serious as PE. Therefore, the presence of acute chest pain with dyspnoea and desaturation as well as reduced exercise tolerance always requires the utmost care and such a patient should be referred to a centre with specialist laboratory and diagnostic imaging

facilities, as the family doctors or primary care physicians have limited possibilities of providing proper, immediate help in their offices. Therefore, their role is to pre-identify the threat and assess the risk, since not every case of chest pain requires such engagement. In the event of thrombosis, heparin treatment should be initiated immediately; heavy menstrual bleeding lasting for several days in the described girl was not a contraindication to such therapy. Alteplase should also be considered in acute PE. This drug converts plasminogen into plasmin, which dissolves blood clots, but should be used in the early stages of thrombotic events. In our patient, the time elapsed from the onset of the first symptoms was several days and the inclusion of heparin as the first-line treatment proved to be effective<sup>(2)</sup>.

## CONCLUSIONS

Acute chest pain accompanied by dyspnoea and blood desaturation may be caused by PE. Family doctors may encounter young patients with such symptoms and, additionally, SARS-CoV-2 infection. In such a situation, the patient's fate will depend on how fast the correct diagnosis is established and appropriate treatment initiated.

### Conflict of interest

*The authors do not declare any financial or personal links to other persons or organisations that could adversely affect the content of this publication or claim rights thereto.*

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