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Prikaz slučaja /
Case report

PULMONARY THROMBOEMBOLISM CAUSED BY SHORT-TERM USAGE OF COMBINED ORAL CONTRACEPTIVES (COCS) IN A YOUNG WOMAN WITH NEWLY DETECTED HOMOCYSTEINEMIA: WHEN THE HARM OUTWEIGHS THE BENEFIT, RARE AND INTERESTING - *Case report*

PLUĆNI TROMBOEMBOLIZAM UZROKOVAN KRATKOTRAJNOM PRIMENOM KOMBINOVANE ORALNE KONTRACEPTIVNE TERAPIJE KOD MLADE ŽENE SA NOVOOTKRIVENOM HOMOCISTEINEMIJOM: KADA ŠTETA PREVAZIĐE KORIST, REDAK I ZANIMLJIV - *Prikaz slučaja*

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Ključne reči
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Abstract

PTE and VTE are rare but serious side effects of COCs treatment, especially when they are associated with conditions that might lead to thrombosis. In our study, we presented the case of a 21-year-old nulligravida woman who developed PTE as a result of short-term endometriosis treatment with COCs therapy. The patient was hospitalized in the ICU and was given a heparin infusion to treat the severe PTE. A more thorough investigation revealed elevated homocysteine and LAC levels. Because of these high readings, it was agreed that warfarin medication would be continued once the condition stabilized. To provide the appropriate therapy, clinicians must consider all risk factors for the development of PTE.

INTRODUCTION

Pulmonary (PTE) and venous thromboembolism (VTE) are well known as rare but serious adverse effects of combined oral contraceptives (COCs), especially when they are associated with risk factors such as smoking, high blood pressure, blood clotting disorders, fat metabolism disorders, obesity, varicose veins, previous venous inflammation and thrombosis [1]. Since Jordan WM initially documented a case of venous thrombosis related to contraceptive usage in 1961[2] numerous writers have highlighted the increased risk of venous thromboembolism in contemporary COCs therapy[3]. According to published data, the incidence of VTE and PTE in women during the reproductive period is 3 per 10,000 woman-year[4], and the effect of oral contraceptives on VTE is estimated to be significant in a large number of their users[5], while the incidence of VTE during pregnancy is estimated to be 0,76 to 1,72 per 100.000[6]. Some writers link the estrogenic component to an increase in plasma coagulation factors and their gene expression, as well as a decrease in anticoagulant factors and a tissue factor pathway inhibitor[7]. Second-generation progestogens (levonorgestrel) had a reduced incidence of VTE development when compared to third- and fourth-generation progestogens[3]. We will present a case of PTE in a 21-year-old nulligravid Serbian woman who was using COCs (dienogest and ethinylestradiol) for newly discovered homocysteinemia. In this paper, we report on the case and provide a brief overview of the relevant literature.

Case report: A 21-year-old lady (gravida 0) presented to our emergency department complaining of tiredness, shortness of breath, and chest pain. She reported that she had experienced greater weariness throughout the exertion, shortness of breath, and an occasional sense of tightness in the chest that lasted for 10-15 minutes and then stopped after resting for the previous ten days. The symptoms worsened over time to the point that they would persist from the early hours, as well as on the day of admission to our facility. She recalls using contraceptive pills (dienogest and ethinylestradiol) for seven months to treat endometriosis. On admission, she was awake, afebrile, eupnoeic, and cyanotic; her pulse oximeter saturation was 99% on room air; her blood pressure

was initially 140/100 mmHg; her heart rate was 100 beats per minute. The auscultatory findings over the heart and lungs were consistent. Electrocardiogram (ECG) ECG showed a sinus rhythm, a frequency of 100 beats per minute with no change in the final axis. The laboratory results were within the normal range. D-dimer had a value of 1254 (normal range 0-250 ng/ml). We performed computed tomography (CT) pulmonary angiography based on the collected anamnestic data on the usage of COCs and high D-dimer levels.

CT showed massive PTE on the bifurcation of the right pulmonary artery with propagation into the artery for the upper lobe and the intermediate artery and both its branches as well as on the bifurcation of the left pulmonary artery with propagation into the artery for the lower lobe and its branches (Fig.1). Ultrasonography of the heart revealed right ventricular dilatation with hypokinesia of the free wall and borderline function. A vein doppler examination of the lower extremities revealed no indication of deep vein thrombosis. She was hospitalized in the intensive care unit (ICU) and given a heparin infusion following the PTE treatment protocol. She was moved to the ward after being stabilized with rivaroxaban. Because there was a suspicion of inherent risk factors for PTE, the hematologist recommended testing the homocysteine, antithrombin (AT), proteins C and S, activated protein C resistance (APCR), lupus anticoagulants (LAC), anti-beta 2-GPI, and anticardiolipin antibodies. Homocysteine levels were 21,38 (normal range 4-14 mol/L) and LAC levels were 1,56 (normal range 0,84-1,06), while all other markers were negative. Vitamin B12 levels were 181 (normal range 133-675 pmol/l) and folic acid levels were 8 (normal range 7-45 nmol/l). It was recommended that rivaroxaban should be avoided and warfarin be used as the optimum therapeutic choice. A gynecologist ultrasound was performed, and the results were within the normal range. The woman was discharged from the hospital, having been improved to the best of her abilities, with the recommendation to continue warfarin medication. The gynecologist strongly prohibited the use of COCs and recommended a nutritional supplement including alpha-lipoic acid, magnesium, and vitamin B6. It was suggested that the LAC, anti-beta2 GPI, and anticardiolipin antibodies be measured again in 12 weeks and that the results should be reported to the hematologist for management and future monitoring.

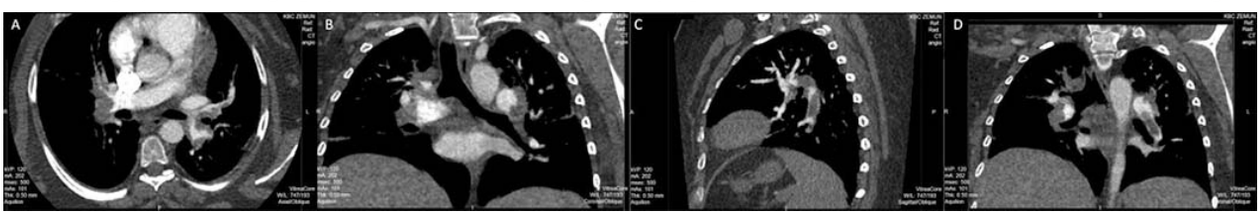

Fig. 1. *massive PTE on the bifurcation of the right pulmonary artery with propagation into the artery for the upper lobe and the intermediate artery and both its branches as well as on the bifurcation of the left pulmonary artery with propagation into the artery for the lower lobe and its branches.*

DISCUSSION:

According to several authors, in the last few decades, 50% of all VTE patients had one or more thrombophilic abnormalities, most notably deficits in antithrombin III, protein C, and protein S [8,9]. The discovery of several common inherited abnormalities has sparked renewed interest in inherited thrombophilic states: prothrombin (PT) gene G20210A, Factor V Leiden (FVL) mutation (Arg506Gln), hyperhomocysteinemia and homocystinuria, Wein-Penzing defect, Sticky Platelet Syndrome (SPS), Quebec platelet disorder (QPD), and Sickle Cell Disease (SCD)[10]. In this study, we presented a case of PTE in a 21-year-old woman who was using COCs and had an increased risk of thrombophilia due to elevated homocysteine and LA levels. Our patients complained of tiredness, shortness of breath, and chest tightness. PTE, regardless of the circumstances that produce it, is a condition with a high morbidity and death rate, particularly if misdiagnosed or undertreated[11].

According to one study, the most frequent PTE symptoms are dyspnea (78%to 81%), chest pain (39% to 56%), fainting (22% to 26%), and hemoptysis (5% to 7%). In a sample of 800 patients, 94% experienced at least one of the specified symptoms, while 1% had no issues before the diagnosis. Deep vein thrombosis occurred in 3% of the instances[12], which did not adhere to our patient. Our patient was hypertensive and tachycardic when she was admitted. Clinical symptoms such as tachycardia (>100 beats/min) and tachypnea (>20 beats/min) with a poor rate of sensitivity and specificity may suggest PTE, according to some evidence[13]. According to the American College of Cardiology, systematic thrombolytic therapy has been shown to reduce mortality, lower the risk of developing chronic thromboembolic pulmonary hypertension, and improve quality of life in patients with massive PTE, however, some studies showed a high risk of bleeding, including intracranial hemorrhage[14]. Our patient had a heparin infusion and remained hemodynamically stable throughout. Following stabilization, the therapy was maintained in the ward, and increased levels of homocysteine and LAC were found. Homocysteine levels above a certain level raise the risk of VTE, PTE, ischemic heart disease, and stroke. According to some studies, the increased risk of venous thrombosis in the general population due to moderate hyperhomocysteinemia is unknown. One of the hypotheses on the mechanism by which hyperhomocysteinemia induces thrombosis is the toxic impact of homocysteine on vascular endothelium[15]. Other authors reported that high levels of homocysteine increased tissue factor expression, increased platelet reactivity, increased thrombin generation, attenuated anticoagulant processes, enhanced factor V activity, impaired fibrinolytic potential, and vascular injury, including endothelial dysfunction[16]. When we detected homocysteinemia, we removed rivaroxaban and added warfarin. Why? According to research, therapy with coumarin derivatives had no significant effect on homocysteine concentrations[17].

We must not forget that our patient used COCs. One research on 50 healthy women who took oral contraceptives found that their homocysteine levels were substantially higher three months later[18]. Vitamin supplementation, primarily with folic acid, pyridoxine, and vitamin B12, is the most effective therapeutic option for lowering high levels of

plasma homocysteine [19]. In our patient, LACs antibodies were marginally elevated. The capacity of LACs antibodies to prolong phospholipid-dependent coagulation events allows them to be identified. Antiphospholipid antibodies may be linked with around 20% of cases with deep venous thrombosis with or without PTE[20]. LAC was reported to be a substantial risk factor for thrombosis in one research of 7000 individuals who did not have systemic lupus erythematosus (SLE) [odds ratio 5-16][21] but it is also important to mention that PTE can be possible manifestation at patient with SLE[22].

CONCLUSION:

In this study, we described a rare case of a young woman with endometriosis who, after being treated with COCs for a short period, developed massive PTE and, coincidentally, homocysteinemia was detected. In such cases, clinicians must constantly consider homocysteinemia or antiphospholipid syndrome to determine the best therapy for their patients in the future course of treatment.

Sažetak

Plućna i venska tromboembolija su retke ali ozbiljne neželjene reakcije usled primene kombinovane oralne kontraceptivne terapije posebno ako su povezane sa faktorima koji mogu da dovedu do tromboze. Mi smo prezentovali slučaj žene stare 21 godinu (bez porođaja) koja je razvila masivnu plućnu tromboemboliju usled kratkotrajne primene oralne kontrceptivne terapije u cilju lečenja endometrioze. Bolesnica je primljena u jedinicu intenzivnog lečenja gde joj je ordinirana heparinska infuzija. Tokom hospitalnog lečenja kod bolesnice su dokazane povišene vrednosti homocisteina i lupus antikoagulans antitela. S obzirom na prethodno pomenute povišene vrednosti bolesnici je ordinirana terapija varfarinom nakon stabilizacije stanja.Neophodno je da lekari uzmu u obzir sve faktore rizika koji bi mogli da dovedu do plućne tromboembolije kako bi odabrali odgovarajuću terapiju.

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