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Deep Vein Thrombosis and Subsequent Pulmonary Embolism in A Patient Recovered from COVID-19

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ABSTRACT

A 45-year-old female patient with a previous SARS-CoV2 pneumonia suddenly presented with pain, swelling and cyanosis of the left leg, and severe dyspnea. Extensive deep vein thrombosis of the left leg and bilateral pulmonary embolism were diagnosed. The patient received standard treatment according to ESC 2019 Guidelines on Acute Pulmonary Embolism (Konstantinides et al., 2019). A study of the patient's cytokine profile was carried out, according to which an increase in several pro-inflammatory cytokines was detected. After a 3-week follow-up, partial recanalization of the deep veins of the left leg was revealed.

Keywords: *COVID-19, Pulmonary Embolism, Cytokines, Thrombosis*

Introduction

Despite active study of both the fundamental and the clinical features of the novel coronavirus disease (COVID-19) that the world has faced in 2020, there is currently a lack of data on the long-term prognosis of patients who have contracted this infection. A high prevalence of thrombotic complications in patients with COVID-19 has recently been described (Tang *et al*., 2020a). However, many questions regarding thromboembolism risk stratification, the choice of anticoagulant and its dose, and the duration of anticoagulant therapy in this group of patients are yet to be clarified. Although there is some consensus on these issues, further randomized clinical trials are needed (Spyropoulos *et al*., 2020a; Thachil *et al*., 2020).

We present a case of ileofemoral thrombosis and pulmonary embolism in a patient with a predisposition for thromboembolic events with previous novel coronavirus pneumonia.

Timeline

Time	Event
2 weeks before admission	Covid-19 along with bilateral pneumonia treatment in hospital
1,5 weeks before admission	Sudden onset of exertional dyspnea
1 day before admission	Left leg cyanosis along with pain and swelling
Admission date	Severe dyspnea
Primary inspection	Signs of segmentary pulmonary embolism on CT - pulmonary angiography along with left leg occlusive deep vein thrombosis
Day 1	Anticoagulation therapy with UFH was initiated
Day 5	Switch to NOACs treatment
3 weeks after release	Signs of left leg deep vein recanalization

Case Presentation

Anamnesis Morbi

A 45-year old woman was admitted to our hospital because of pronounced dyspnea, left leg cyanosis, and swelling. It was found that two weeks before then she had been treated in a hospital for viral pneumonia caused by SARS-CoV2. During her stay in the hospital (21/04/2020), the patient experienced exertional dyspnea. In blood tests, the level of D-dimer was increased to 1830 ng/ml. However, anticoagulant therapy was not carried out, because of hemorrhoidal bleeding. On 30/04/2020, the patient was discharged from the hospital after receiving double negative results on the PCR test for SARS-CoV-2.

01/05/2020 a sharp pain in the left inguinal region with further irradiation of pain on the inner surface of the thigh and lower leg was observed, followed by swelling and cyanosis of the left leg. The next day, the patient developed an attack of severe resting dyspnea, accompanied by decreases in blood pressure to 70/50 mm Hg and in SpO2 down to 91%. The patient was admitted to our hospital. It was noteworthy that the patient had taken combined oral contraceptives for a year and, moreover, she had used intravaginal gestagen-estrogen–containing rings because of endometriosis-associated dysmenorrhea.

Upon admission, the patient's respiratory rate was 20/min, SpO2 was 95%, and blood pressure

was 110/70 mm Hg; therefore thrombolysis was not performed.

Investigations

Laboratory studies revealed leukocytosis (18.5 * 109/L) and increased level of C-reactive protein (92.7 mg / L) and D-dimer (> 1500 ng/ml). The ECG was unremarkable. A contrast CT-scan revealed defects of the pulmonary artery contrasting at the segmental and subsegmental levels of both lungs as well as in the lower lobes of both lungs, together with areas of lung tissue opacity with involvement of the pulmonary parenchyma in the amount of 25%, which met the criteria for the severity of the lesion (CT-1) (Fig. 1). There were no echocardiographic signs of right heart failure. Ultrasonography of the lower-extremity veins revealed occlusive deep vein thrombosis of the left leg (Fig. 2).

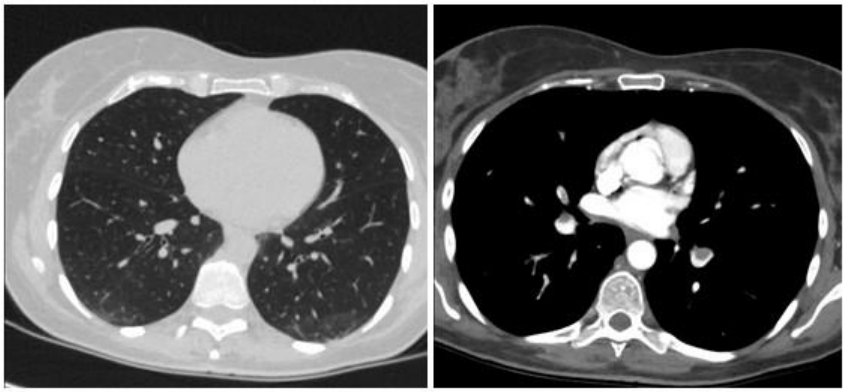

Figure 1: Contrast CT-scan

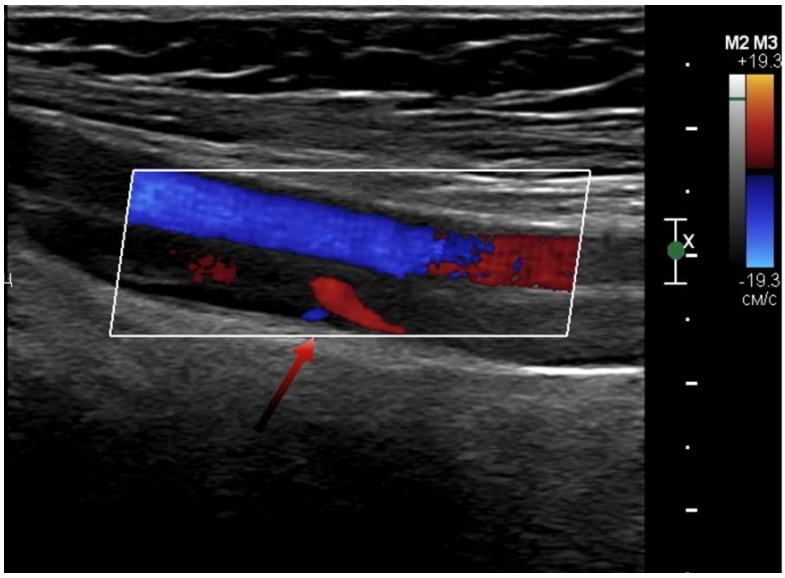

Figure 2: Ultrasonography of the lower extremity

In order to access endothelial function, we performed a flowmediated dilatation test. The test showed a normal value (13,1%).

Management

In the acute period of pulmonary embolism, the patient was treated with UFH under the control of the APTT. During treatment, the patient's condition remained stable, and echocardiographic parameters did not worsen in dynamics (PAP 35 mm Hg). Subsequently, the patient was switched to rivaroxaban (15 mg b.i.d. for 3 weeks), and a prolongation of anticoagulation for 6 months (rivaroxaban 20 mg q.d.) was recommended. Removal of the intravaginal ring was not carried out because of the high risk of developing menometrorrhagia due to ongoing anticoagulant therapy.

A follow-up examination was performed after 3 weeks, and partial recanalization of the deep veins of the left lower limb was noted. After discharge, the patient tolerated physical activity well without recurrence of dyspnea. An echocardiographic examination revealed no negative dynamics compared with anamnestic data.

Cytokine Study

We measured several proinflammatory cytokine concentration in the patient's plasma. According to our results, concentrations of IFN-ɣ, IL-1β, IL-6 (see full list of elevated cytokines in Suppl. Table 2) were more than 3 SD higher than the average concentrations of these cytokines in healthy controls.

Discussion

Viral infections are known to induce endothelial disfunction, inflammatory state, and hypoxemia which can lead to subsequent thrombosis (Gupta *et al*., 2019; Phillippe, 2017). COVID-19 is associated with hypercoagulation with a high risk of thromboembolic complications (Tang *et al*., 2020). According to our data, activity of COVID-19–induced coagulopathy correlates with disease severity, while generalized endothelial dysfunction was not observed (Kalinskaya *et al*., 2020). In this clinical case, the patient also had a normal FMD-test.

However, VTE is described mainly in the acute period of infection, and there are no robust data on the timing of anticoagulation after discharge from the hospital.

In this case report, in a patient with a procoagulant state (use of combined contraceptive vaginal ring,) tending to bleeding (hemorrhoidal and uterine), SARS-CoV2 infection provoked ileofemoral thrombosis and pulmonary embolism two weeks after the acute period of infection, despite normal endothelial function.

Several inflammatory cytokines have been previously shown to be risk factors for deep vein

thrombosis and pulmonary embolism (Christiansen *et al*., 2006; Halici *et al*., 2014).

Recently, plasma levels of numerous cytokines have been shown to be increased in COVID-19–infected patients (Rothan and Byrareddy, 2020; Spiezia *et al*., 2020) as well as in patients with pulmonary embolism. It has been shown that some of the cytokines we observed (IFN-ɣ, IL-1β, IL-6) may be associated with hypercoagulation and subsequent thromboembolic events (Bester and Pretorius, 2016). The mechanisms of their action include enhancing neutrophil extracellular trap (NET) formation, inducing platelet activation, and promoting vein wall inflammation) (Bertin *et al*., 2019; Nosaka *et al*., 2011; Zhang *et al*., 2020).

All these facts together correlate with our findings from this case: higher levels of pro-inflammatory cytokines involved in COVID-19 may also take part in hypercoagulation and deep vein thrombosis.

Thus, anticoagulation is the cornerstone of COVID-19 management (Bikdeli *et al*., 2020; Thachil *et al*., 2020). Various protocols of anticoagulant therapy have been developed. Current guidelines recommend the use of unfractioned heparin and low molecular weight heparins (Atallah *et al*., 2020; Connors and Levy, 2020; Rico-Mesa *et al*., 2020). At the same time, the issue of prolonged anticoagulant therapy and its duration remains controversial. The routine use of long-term anticoagulation after COVID-19 infection seems to be inappropriate because of the high risk of bleeding complications. However, there are certain high-risk patient groups that require long-term anticoagulation. The use of previously developed protocols for prolonged thromboprophylaxis was proposed in patients with a high risk of thromboembolic complications (active cancer, history of DVT, etc.), as well as a more than two fold increased level of D-dimer (Cohen *et al*., 2014; Spyropoulos *et al*., 2020). The use of direct oral anticoagulants may also be considered (Cohen *et al*., 2016), but there is currently no evidence comparing the effectiveness of oral and parenteral prolonged anticoagulation regimens for COVID-19 patients. Further research efforts are needed to develop criteria for prolonged anticoagulation and its duration.

Conclusion

In this case we observed a thrombotic complication in a patient recovered from SARS-CoV2-induced pneumonia. In addition to factors predisposing to hypercoagulation, a hyperproduction of several proinflammatory cytokines (IFN-ɣ, IL-1β, IL-6) induced by SARS-CoV-2 was also revealed. This case report demonstrates the necessity of careful hemostasis study in patients with COVID-19 and the development of anticoagulation algorithms after discharge.

Declaration of Competing Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval: Ethical approval to report this case was obtained from the local ethics committee.

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Informed Consent: Written informed consent was obtained from legally authorized representatives for anonymized patient information to be published in this article.

Author Contribution: EK, OD, PG contributed to the literature search, data interpretation and writing of the manuscript. DV, EM provided a cytokine study, contributed to the literature search, data interpretation and writing of the manuscript. PS, AS, EV critically reviewed the manuscript.

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References

Atallah B, Mallah SI, AlMahmeed W. Anticoagulation in COVID-19. *Eur Hear Journal Cardiovasc Pharmacother* 2020; 6: 260-261.

Bertin FR, Rys RN, Mathieu C, Laurance S, Lemarié CA, Blostein MD. Natural killer cells induce neutrophil extracellular trap formation in venous thrombosis. *J Thromb Haemost* 2019; 17: 403-414.

Bester J and Pretorius E. Effects of IL-1β, IL-6 and IL-8 on erythrocytes, platelets and clot viscoelasticity. *Sci Rep* 2016; 6: 1-10.

Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV. COVID-19 and Thrombotic or Thromboembolic Disease: Implications for Prevention, Antithrombotic Therapy, and Follow-Up: JACC State-of-the-Art Review. *J Am Coll Cardiol* 2020; 75: 2950–2973.

Christiansen SC, Næss IA, Cannegieter SC, Hammerstrøm J, Rosendaal FR, Reitsma PH. Inflammatory Cytokines as Risk Factors for a First Venous Thrombosis: A Prospective Population-Based Study. *PLoS Med* 2006; 3: e334.

Cohen AT, Harrington RA, Goldhaber SZ, Hull RD, Wiens BL, Gold A, Hernandez AF, Gibson CM. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med* 2016; 375: 534-544.

Cohen AT, Spiro TE, Spyropoulos AC, Desanctis YH, Homering M, Büller HR, Haskell L, Hu D, Hull R, Mebazaa A, Merli G. D-dimer as a predictor of venous thromboembolism in acutely ill, hospitalized patients: A subanalysis of the randomized controlled MAGELLAN trial. *J Thromb Haemost* 2014; 12: 479-487.

Connors JM and Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020.

Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. *Thromb Res* 2019; 181: 77-83.

Halici B, Ulasli SS, Günay E, Nural S, Sen S, Akar O, Celik S, Unlu M. Assessment of inflammatory biomarkers and oxidative stress in pulmonary thromboembolism: Follow-up results. *Inflammation* 2014; 37: 1186-1190.

Kalinskaya A, Dukhin O, Molodtsov I, Maltseva A, Sokorev D, Elizarova A, Sapozhnikova O, Glebova K, Stonogina D, Shakhidzhanov S, Nikonov E. Dynamics of coagulopathy in patients with different COVID-19 severity. *MedRxiv* 2020: 2020.07.02.20145284.

Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Respir J* 2019; 54: 1901647.

Nosaka M, Ishida Y, Kimura A, Kuninaka Y, Inui M, Mukaida N, Kondo T. Absence of IFN-γ accelerates thrombus resolution through enhanced MMP-9 and VEGF expression in mice. *J Clin Invest* 2011; 121: 2911-2920.

Phillippe HM. Overview of venous thromboembolism. *Am J Manag Care* 2017; 23: S376–S382.

Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, White A, Anderson AS, Chilton R. The Role of Anticoagulation in COVID-19-Induced Hypercoagulability. *Curr Cardiol Rep* 2020; 22.

Rothan HA and Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *J Autoimmun* 2020; 109: 102433.

Spiezia L, Boscolo A, Poletto F, Cerruti L, Tiberio I, Campello E, Navalesi P, Simioni P. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. *Thromb Haemost* 2020; 120: 998–1000.

Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, Douketis JD. Scientific and Standardization Committee Communication: Clinical Guidance on the Diagnosis, Prevention and Treatment of Venous Thromboembolism in Hospitalized Patients with COVID-19. *J Thromb Haemost* 2020a: jth.14929.

Spyropoulos AC, Lipardi C, Xu J, Peluso C, Spiro TE, De Sanctis Y, Barnathan ES, Raskob GE. Modified IMPROVE VTE Risk Score and Elevated D-Dimer Identify a High Venous Thromboembolism Risk in Acutely Ill Medical Population for Extended Thromboprophylaxis. *TH Open* 2020b; 04: e59–e65.

Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 2020a; 18: 844–847.

Thachil J, Tang N, Gando S, Falanga A, Levi M, Clark C, Iba T, Cattaneo M. Type and dose of heparin in COVID-19. *J Thromb Haemost* 2020.

Zhang Y, Zhang Z, Wei R, Miao X, Sun S, Liang G, Chu C, Zhao L, Zhu X, Guo Q, Wang B. IL (Interleukin)-6 Contributes to Deep Vein Thrombosis and Is Negatively Regulated by miR-338-5p. *Arterioscler Thromb Vasc Biol* 2020; 40: 323-334.