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Concomitant acute lower extremity arterial and deep vein thrombosis developing in a patient under anticoagulant therapy after COVID 19 infection.

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Key words: Covid 19; thrombosis; hypercoagulability; thromboprophylaxis.

Abstract. The hypercoagulable state continues after the Coronavirus 2019 (Covid 19) infection and prophylactic anticoagulants are recommended in this period. However, arterial and venous thromboembolic events can be observed during the convalescence period after the Covid 19. Here, we present the case of acute lower extremity arterial and venous thromboembolism developed in the post-Covid 19 period in a 77-years-old patient, under therapeutic doses of anticoagulant therapy (enoxparin 1mg/kg of weight every 12 hours). The patient, who had no previous history of arterial or venous thrombosis, was taken to emergency surgery with the diagnosis of ALI (acute limb ischemia) due to acute arterial thrombosis. An arterial thrombectomy was performed with the help of a 4F Fogarty catheter inserted from the left femoral artery under local anesthesia. All distal pulses of the patient were palpable in the postoperative period. After the platelet count became >100,000 mm^3, 100 mg of acetylsalicylic acid daily was added to the therapeutic dose of enoxaparin sodium treatment. The patient was discharged, uneventfully, except for a minimal diameter increase secondary to deep venous thrombosis (DVT) on the fifth postoperative day, with a combination of enoxaparin and acetylsalicylic acid treatment. Endothelial injury, chronic immuno-thrombogenicity, and increased platelet aggregation in the post-Covid 19 recovery period can cause major thrombotic events, even weeks after the recovery. Anticoagulant therapy is recommended for thromboprophylaxis when the following statuses exist: ≥65 years, critical illness, cancer, prior VTE, thrombophilia, severe immobility, and elevated D-dimer. Combination treatment with long-term antiaggregant therapy may be prudent in thromboembolic events developed under anticoagulant therapy.

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Trombosis arterial aguda y trombosis venosa profunda concomitantes de extremidad inferior en un paciente bajo terapia anticoagulante después de infección por COVID 19.

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Palabras clave: COVID 19; trombosis; hipercoagulabilidad; tromboprofilaxis.

Resumen. El estado de hipercoagulabilidad continúa después de la infección por Coronavirus 2019 (Covid-19) y la anticoagulación profiláctica se recomienda durante este período. Sin embargo, eventos tromboembólicos arteriales y venosos se pueden observar durante el período de convalecencia posterior al Covid-19. Se presenta el caso de trombosis venosa profunda (TVP) y arterial agudas de una extremidad inferior en una paciente de 77 años, bajo terapia anticoagulante (enoxparin 1mg/kg de peso, cada 12 horas), en el período post-Covid 19. La paciente, sin historia previa de trombosis arterial ni venosa, fue llevada a cirugía de emergencia con el diagnóstico de isquemia aguda de extremidades por trombosis arterial aguda. Se le realizó trombectomía arterial con la ayuda de un catéter Fogarty 4F insertado desde la arteria femoral izquierda bajo anestesia local. Todos los pulsos distales del paciente fueron palpables en el periodo postoperatorio. Después de que las plaquetas llegaron a ser mayores a100.000 mm^3, 100 mg de ácido acetilsalicílico diarios se añadieron a la dosis terapéutica del tratamiento con enoxaparina sódica. La paciente fue dada de alta sin incidencias, excepto por un mínimo aumento de diámetro secundario a la TVP, al quinto día postoperatorio con la combinación de enoxaparina y ácido acetilsalicílico. La lesión endotelial, la inmunotrombogenicidad crónica y la agregación plaquetaria aumentada en el período de recuperación posterior a Covid-19 pueden causar eventos trombóticos importantes incluso semanas después de la recuperación. La combinación con terapia antiagregante a largo plazo puede ser prudente en los casos de eventos tromboembólicos desarrollados en pacientes con terapia anticoagulante.

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INTRODUCTION

Due to Coronavirus 2019 (Covid 19) infection, mostly pulmonary and cardiovascular complications develop. It has been demonstrated that patients with Covid 19 infection are in a hypercoagulable state, which causes arterial and venous thrombosis[1]. The hypercoagulable state continues after Covid 19, and long-term anticoagulant therapy is recommended for its treatment [2]. Acute limb ischemia (ALI) and venous thromboembolism are among the most common vascular complications seen after Covid 19 infection [1,3]. Especially in the patients that develop ALI, high amputation and mortality rates are reported [3].

Here, we present a case of concomitant lower extremity arterial and venous thrombosis that developed under anticoagulant therapy in the early period after Covid 19 infection. A written informed consent was

obtained from the patient for the report of the details and images related to her case.

CASE REPORT

On September 27, 2021, a 77-year-old female patient was referred to us from the emergency department of the Isparta City Hospital with complaints of tightness and swelling in the left leg that had been present for a day, and sudden coldness, pallor, and severe pain below the knee for the last two hours. As a result of physical examination, signs of coldness, pallor, prolongation of capillary refill time, tightness, increase in diameter and Homans sign were found in the left lower extremity (Fig. 1). While all pulses were palpable in the right lower extremity, only the femoral pulse was palpable in the left lower extremity. Monophasic flow pattern was determined with manual Doppler in the popliteal artery, but flow could not be determined with manual Doppler in the distal pulses. An electrocardiogram revealed sinus tachycardia at a rate of 105 per minute. Urgent blood test results were found as follows: white blood cell 10,720/mm^3 (normal range <10,000), lymphocyte 680/mm^3 (normal range 800-4,000), eosinophil 10/mm^3 (normal range 20-50), platelet 84,000/mm^3 (normal range 100,000-400,000), hemoglobin 9.5 g/dL (normal range 12-16), D-dimer value 0.92 mg/L (normal range 0-0.55), prothrombin time 12.4 seconds (normal range 10.5-14.5), activated partial thromboplastin time 21.6 seconds (normal range 21.6-35), and international normalized ratio 1.11 (normal range 0.8-1.2). Other biochemical parameters were found normal. A computed tomography angiogram (CTA) taken on the patient revealed an intraluminal thrombus extending from the distal part of the left superficial femoral artery to the tibioperoneal trunk (Figs. 2a, 2b). In addition, calibration increases were observed in the main and superficial femoral veins (Fig. 2c). Acute deep venous thrombosis (DVT) extending from the popliteal vein to the external iliac vein was determined by venous Doppler ultrasound.

Fig. 1. Significant increase in the diameter and cyanotic areas in patches in the left lower extremity.

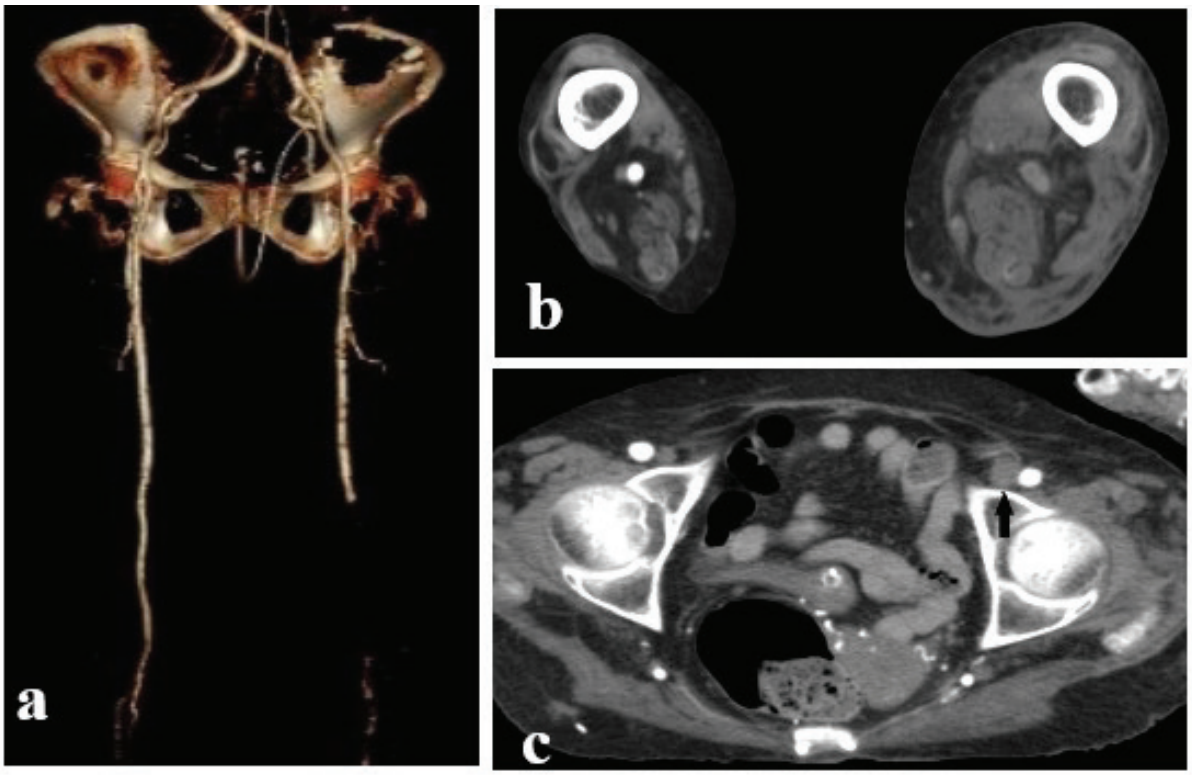

Fig. 2. Computed tomography angiogram a) and b) acute thrombus material in the left superficial femoral artery c) Calibration increase in the left common femoral vein due to acute thrombus material.

In the patient's medical history, there was a diagnosis of Covid 19 pneumonia confirmed by reverse transcription-polymerase chain reaction test and chest computed tomography 36 days before the thrombotic event. After 21 days of intensive care and 11 days of chest diseases service follow-up, the patient was discharged from the hospital a with therapeutic dose of enoxaparin sodium treatment (1mg/kg of weight every 12 hours) (Fig. 3). D-dimer value was found as 0.78 mg/L (normal range 0-0.55) and platelet was found as 202,000 mm3 (normal range 100,000-400,000) at discharge. The patient had not been vaccinated against Covid 19 infection prior to the event.

The patient, who had no previous history of arterial or venous thrombosis, was taken to emergency surgery with the diagnosis of ALI due to acute arterial thrombosis. An arterial thrombectomy was performed with the help of a 4F Fogarty catheter inserted from the left femoral artery under local anesthesia. The catheter was introduced to a 70 cm distal length. Abundant and fresh thrombus material was removed. All distal pulses of the patient were palpable in the postoperative period. After the platelet count became >100,000 mm3, 100 mg of acetylsalicylic acid daily was added to the therapeutic dose of enoxaparin sodium treatment. Leg elevation was applied. The patient was discharged from the cardiovascular surgery service uneventfully on the fifth postoperative day with the combination of enoxaparin and acetylsalicylic acid, except for a minimal diameter increase secondary to DVT.

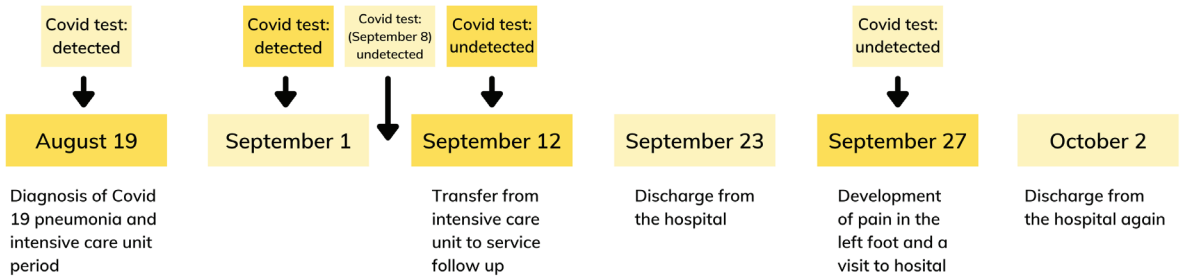

Fig. 3. Timeline of patient of this article.

DISCUSSION

Apart from pulmonary involvement, coagulopathy and cardiovascular effects, which cause significant increases in morbidity and mortality rates due to Covid 19 infection, are relatively common [4]. As detected in our case, increased fibrin degradation products, as well as high D-dimer and low platelet levels, may be an indicator of thrombotic complications that develop or may develop [5].

ALI is less common than venous thrombosis in patients with Covid 19. ALI due to arterial thrombosis can be seen after Covid 19 infection as well as during the acute infection period. Borrelli et al. reported cases of arterial thrombosis that developed 15-45 days after respiratory symptoms in the patients whose Covid 19 treatment was completed and nasopharyngeal swab test was negative [6], and Bozzani *et al* reported cases of arterial thrombosis that developed after 41-149 days in the patients with the same conditions [7]. In our case, the swab test was negative during the convalescence, and arterial and venous acute thrombosis was detected under therapeutic dose of anticoagulant therapy on the 19th day.

Virchow's classic triad for thrombosis consist of stasis, endothelial injury, and a hypercoagulable state. Hypercoagulability and stasis particularly affect acute thrombogenesis. This may play a lesser role in the arterial and venous events seen in convalescent Covid 19 patients. The most important mechanism here may be endothelial injury and dysfunction. The multisystem inflammatory syndrome, which includes myocarditis and inflammatory vasculopathy and seen in the recovery period after Covid 19 in children, is an indicator of endothelial dysfunction and injury [8]. Chronic immuno-thrombogenicity, which develops and accumulates especially after mild or asymptomatic Covid 19 infection, may also cause major thrombotic events even weeks later [2]. Another cause of thrombogenicity may be increased platelet aggregation. Zaid *et al* showed severe acute respiratory syndrome coronavirus 2 RNAs and high platelet-associated cytokine levels in platelets in their 115 cases studied. In this study as well, platelet aggregation occurred at lower concentrations of thrombin than it was expected [9].

There is no consensus on long-term thromboprophylaxis following Covid 19 infection. Guidelines for COVID 19 are derived from recommendations in medically ill populations. Although therapeutic doses of low molecular weight heparin (LMWH) have been recommended for the patients with Covid 19 and standard thromboprophylaxis, by taking the high incidence of venous thromboembolism (VTE) into consideration, the American College of Chest Physicians recommends standard prophylactic LMWH due to the lack of clinical trial data [10]. On the other hand, the International Society on Thrombosis and Hemostasis (ISTH)

guidelines recommend thromboprophylaxis with LMWH and a direct oral anticoagulant (DOAC) in patients with low bleeding and high VTE risks. ISTH has identified as high-risk factors the age older than 65 years, critical illness, cancer, prior VTE, thrombophilia, severe immobility, and elevated D-dimer. The ISTH suggests a duration of 14 to 30 days for post discharge thromboprophylaxis, although optimal duration remains unclear [11]. Although prophylaxis was initiated with a therapeutic dose of LMWH treatment in our case, who was considered with high risk due to high D-dimer level and advanced age, antiaggregant agent was added to the treatment in the postoperative period, considering possible increased platelet aggregation due to the simultaneous occurrence of arterial and VTE.

More systematic, randomized controlled studies on Covid 19-related thrombosis are needed. Results of ongoing clinical trials, such as the ACTIV-4 trial (NCT04498273), which have specifically evaluated prophylactic antiaggregant and anticoagulant therapy, are awaited.

In conclusion, anticoagulant agents and thromboprophilaxis should be considered especially in high-risk patients after Covid 19 infection. The combination of anticoagulant and antiaggregant prophylaxis should also be kept in mind in patients with low bleeding risk. It may be rational to add a long-term antiaggregant to the treatment, especially in thromboembolic events developed under anticoagulant therapy.

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