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CASE REPORT / *OLGU SUNUMU*

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A Fatal Case of COVID-19 with Diffuse Leukocytoclastic Vasculitis of Both Hips, Breasts, Feet, and Back

Kalça, Göğüs, Ayak ve Sırtta Diffüz Lökositoklastik Vasküliti Olan Ölümcül Bir COVİD-19 Olgusu

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ABSTRACT A 47-year-old female patient with no known disease other than rheumatoid arthritis in remission was admitted to the hospital with complaints of bruising on her feet, breasts, hips, and back. It was determined that her severe acute respiratory syndrome coronavirus-2 polymerase chain reaction test was positive 7 days ago and she received favipiravir treatment for 5 days. In the physical examination, ecchymotic lesions were detected in her both feet, breasts, trochanteric regions, and posterior thoracic regions, which were symmetrical and did not change color with pressure in varying sizes. There were diffuse bilateral ground glass and consolidation areas in the computed tomography of the lungs. Because of the histopathological examination of the biopsy taken from the skin lesions, the patient was diagnosed with leukocytoclastic vasculitis. In the lower extremity venous Doppler ultrasonography examination, there was complete occlusion due to thrombus in the subacute period in the right vena saphena parva. During the subsequent intensive care follow-up period, necrotic lesions progressed to amputation in the right foot, debridement in the left foot, and trochanteric regions, and bilateral mastectomy. Our patient required multidisciplinary management involving many specialties during her long-term stay in the intensive care unit. Here, we present a case of coronavirus disease-2019 leading to severe and diffuse leukocytoclastic vasculitis resulting in amputation.
Keywords: Coagulopathy, leukocytoclastic vasculitis, COVID-19, amputation

ÖZ Remisyon evresinde romatoid artrit dışında bilinen bir hastalığı olmayan 47 yaşında kadın hasta ayaklarında, göğüslerinde, kalçalarında ve sırtında morarma şikayetleri ile hastaneye başvurdu. Yedi gün önce şiddetli akut solunum sendromu koronavirüs-2 polimeraz zincir reaksiyonu testinin pozitif çıktığı ve beş gün favipiravir tedavisi aldığı öğrenildi. Fizik muayenesinde; her iki ayak ve memelerde, torakanterik bölgede ve sırtta simetrik ve basmakla renk değiştirmeyen değişen büyüklüklerde ekimotik lezyonlar görüldü. Akciğer bilgisayarlı tomografisinde diffüz bilateral buzlu cam ve konsolidasyon alanları mevcuttu. Deri lezyonlarından alınan biyopsinin histopatolojik incelemesi sonucunda hastaya lökositoklastik vaskülit tanısı kondu. Alt ekstremite venöz Doppler ultrasonografi incelemesinde sağ vena safena parvada subakut dönemde trombüs nedeniyle tam tıkanma mevcuttu. Takip eden yoğun bakım sürecinde; nekrotik lezyonlar sağ ayakta amputasyona, sol ayakta ve sırtta debridmana ve bilateral mastektomiye kadar ilerledi. Hastamız yoğun bakım ünitesinde kaldığı uzun süre boyunca birçok uzmanlığı içeren multidisipliner bir yönetime ihtiyaç duymuştur. Burada amputasyonla sonuçlanan şiddetli ve yaygın lökositoklastik vaskülite yol açan bir koronavirüs hastalığı-2019 olgusu sunuyoruz.
Anahtar Kelimeler: Koagülopati, lökositoklastik vaskülit, COVİD-19, amputasyon

Introduction

Since its identification in December 2019, coronavirus disease-2019 (COVID-19) has affected millions of people worldwide. Although COVID-19 is primarily viewed as a respiratory disease, it should be considered as a systemic disease that affects multiple neurological, cardiovascular, gastrointestinal, hematopoietic and immune systems (1). This case report presents a case with multisystemic involvement due to COVID-19 and skin involvement.

Case Report

A 47-year-old female patient, who had no other known disease other than rheumatoid arthritis (RA) in remission and did not use any medication other than colchicine and adalimumab, admitted to the hospital with complaints of bruising on her feet, both breasts, hips and back. In her medical history, it was found out that her severe acute respiratory syndrome coronavirus-2 polymerase chain reaction test was positive 7 days ago and she received favipiravir treatment for 5 days. Her bruising started on the 3rd day of the favipiravir treatment. As a result of the physical examination, ecchymotic lesions were detected in her both feet, breasts, trochanteric regions, and posterior thoracic region, which were symmetrical and did not change color with pressure in varying sizes (Figure 1a, b). The evaluation of vital findings were as follows: Body temperature 36.2 °C, pulse 96/min, blood pressure arterial 116/68 mmHg, respiratory rate 22/min, and partial oxygen saturation was 96% at 5 lt/min oxygen support with a reservoir mask. Her initial and subsequent laboratory findings of the patient are given in the table (Table 1). There were diffuse bilateral ground glass and consolidation areas in the computed tomography

Figure 1. Ecchymoses in the patient (**a.** Bilateral ecchymoses in both feet; **b.** Ecchymoses in the thoracentesis region and breast)

Table 1. Some laboratory findings of the patient since hospitalization

Day	Admission to the hospital	1	2	3	5	10	15	20	30	50	70
D-dimer mg/L (0-0.5)	>35.2	>35.2	15.4	5.4	5.6	3.4	2.52	2.79	2.6	1.93	13.7
WBC 10^9/L (4.5-10.5)	24.8	23.2	28.9	20.9	18.6	15.2	14.6	25.4	11.9	22.8	4.8
Neu 10^9/L (2-6.9)	18.3	19.6	24.7	18.7	14.1	13.6	11.6	16.1	9.2	20.2	0.3
Lym 10^9/L (06-3.4)	1.6	1.7	1.4	0.7	0.5	0.4	0.4	2	1.7	1.4	1.7
Plt 10^9/L (142-424)	195	198	275	237	283	158	124	279	162	213	28
PT sec (10-14)	12.5	12.8	12.4	13.4	12.1	12.8	13.1	12.9	11.1	11.1	69.9
aPTT sec (18-36)	27.3	27.1	27.6	27.7	24.3	28.1	26.3	26.6	23.3	18	124.7
INR (0.8-1.2)	1.18	1.13	1.09	1.18	0.98	1.1	1.08	0.99	0.76	0.97	6.8
Fibrinogen mg/dL (180-350)	365	342	288	322	296	317	308	369	376	133	54
CRP mg/L (0-5)	162	155	103	190	170	106	83.4	18.6		15	357.6
Procal. mg/L (0-0.046)	0.71	-	-	0.28	0.82	0.75	0.53	0.64	1.83	0.75	27.5
Ferritin µg/L (13-150)	698	692	586	395	439	443	717	623	572	602	>2000

WBC: White blood cell, Neu: neutrophil, Lym: lymphocyte, Plt: platelet, PT: prothrombin time, aPTT: activated partial thromboplastin time, CRP: C-reactive protein, procal.: procalcitonin, INR: international normalized ratio

(CT) of the lungs (Figure 2). There was a toxic granulation and a left shift in peripheral smear. In the lower extremity venous Doppler ultrasonography examination, there was complete occlusion due to thrombus in the subacute period in the right vena saphena parva. In the lower extremity arterial system Doppler ultrasonography, we found no evidence of arterial thrombosis.

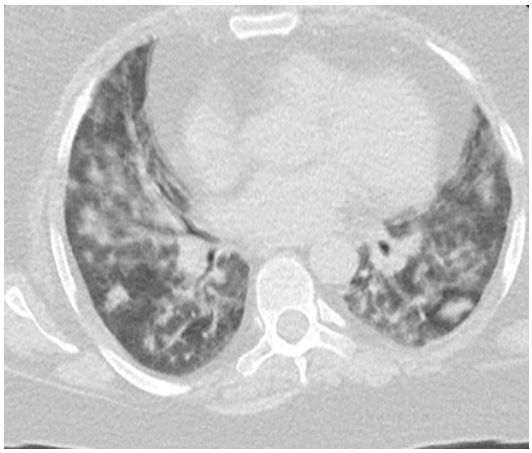

Figure 2. Thoracic CT image of the patient. Common ground glass and consolidation areas consistent with COVID-19 pneumonia
CT: Computed tomography, COVID-19: coronavirus disease-2019

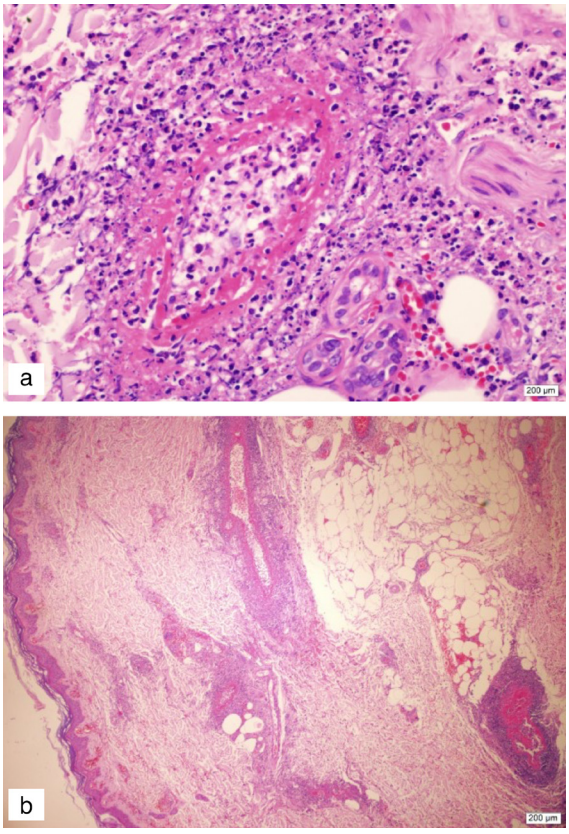

Figure 3. Histopathological image of the biopsy material. **a.** Fibrinoid necrosis of the relatively large vessel wall and surrounding leukocytoclastic are observed (H&E, x400). **b.** Subepidermal separation is observed in the epidermis secondary to diffuse vasculitis (H&E, x200)

According to peripheral smear and laboratory findings of blood, urine, and sputum cultures of the patient, empirical piperacillin-tazobactam (3x4.5 g), methylprednisolone (250 mg/day) and enoxaparin (1x0.6 mL) treatment were initiated, considering COVID-19-related pneumonia due to findings in lung CT. Due to high D-dimer and possible arterial microthrombosis, 0.5 ng/kg/min iloprost infusion was added to the treatment and the infusion was continued for six days. In addition, when it was reported that there was no growth in the cultures taken, de-escalation to ceftriaxone was performed. Both cytoplasmic type and myeloperoxidase type anti-neutrophil cytoplasmic antibody (p and c-ANCA) tests were negative. On the 3rd day of her hospitalization, a biopsy was taken from the dorsum of the right foot for pathological examination with the preliminary diagnosis of small vessel vasculitis. Histopathological examination was reported as leukocytoclastic vasculitis (Figure 3). Then, the dose of the methylprednisolone was increased to 1 g/day which was administered for 3 days and decreased gradually on the follow-up period. On the 12th day of her hospitalization, the patient had signs of hypoxia despite high-flow oxygen therapy and non-invasive ventilation support. After intubation invasive mechanical ventilation and sedation were started. On the 26th day of the intensive care follow-up, meropenem, vancomycin and colistin treatment was started according to the antibiogram results for *Klebsiella pneumoniae* in the tracheal aspirate culture and *Enterococcus faecalis* in the blood culture. On the 30th day of her admission to the intensive care unit, due to the development of significant necrosis of the lesions (Figure 4), amputation of the right foot below the knee, debridement of the left foot (Figure 5), and bilateral mastectomy were performed under general anesthesia. In addition, surgical tracheostomy was performed on the 18th day of intubation. Pathological examination of the mastectomy material was also reported as leukocytoclastic vasculitis. The patient, who could not wean from mechanical ventilator support during the intensive care follow-up, died on the 71st day of hospitalization due to sepsis associated multiorgan failure.

Informed consent was obtained from the patient.

Discussion

COVID-19 continues to be investigated in all its aspects since the day it was first identified. In this disease, coagulation abnormalities and skin findings can be observed alone or in combination with many systemic involvements. This is a very rare case due to the systemic manifestations such as severe pneumonia, coagulopathy, and leukocytoclastic vasculitis associated with COVID-19 being seen together.

Coagulopathy is one of the critical complications in COVID-19 and effects the mortality and morbidity of patients (1). Inflammatory response and vascular endothelial damage resulting from COVID-19 trigger the coagulation cascade

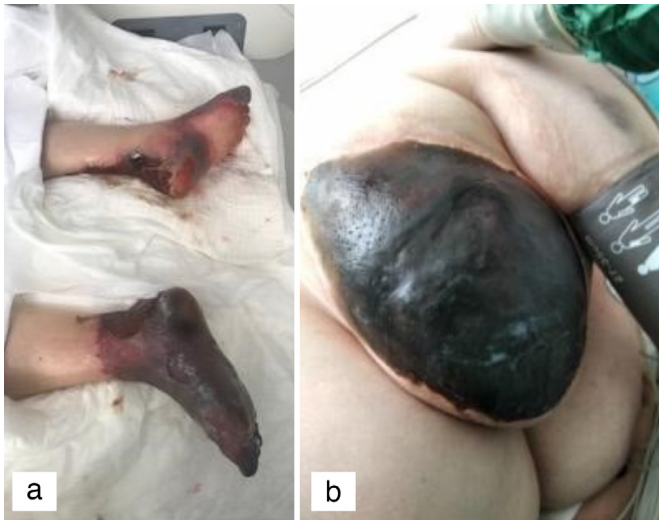

Figure 4. Necrotic lesions developed in the patient (**a.** both feet; **b.** right breast)

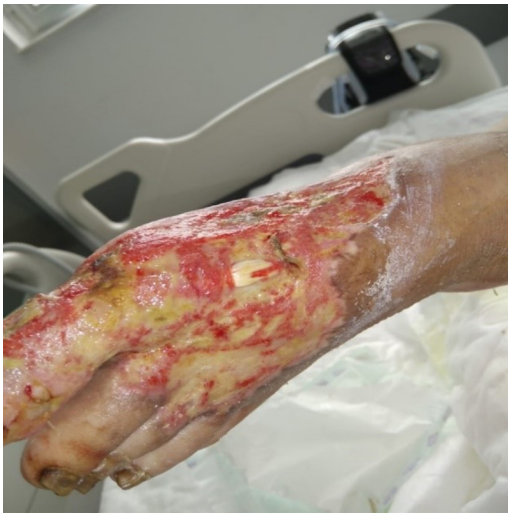

Figure 5. Debridement in the right foot

(2). The best laboratory test for the diagnosis of COVID-19 related hemostatic abnormalities is considered to be D-dimer (3). While circulating D-dimer levels are low in healthy individuals, high levels are found to be associated with increased coagulation and fibrinolytic activity (1). D-dimer is routinely used clinically for the diagnosis of diffuse intravascular coagulation (DIC), deep venous thrombosis, and pulmonary thromboembolism (4). D-dimer elevation has also been reported in COVID-19 patients and it is one of the most common laboratory findings in COVID-19 patients requiring hospitalization (1,5). An increase in D-dimer may indicate activation of the coagulation system due to infection/sepsis, cytokine storm or organ failure (6). High D-dimer levels are indicated as a reliable parameter in predicting mortality (1). In the case of COVID-19, although laboratory findings are similar, including a marked increase in D-dimer and, in some cases, mild thrombocytopenia, other coagulation parameters differ from DIC. In particular, high fibrinogen and high factor-VIII activity observed in the course of the disease indicate that coagulation pathologies do not occur and DIC does not develop in most patients (7). In our case, disseminated intravascular coagulation was not considered according to peripheral smear findings and DIC scoring results (8). In our case, D-dimer values were quite high, as observed in the literature. In addition to leukocytoclastic vasculitis detected in skin lesions, deep vein thrombosis was also present.

Leukocytoclastic vasculitis is a common histopathological term to describe small vessel vasculitis. Basic features of cutaneous leukocytoclastic vasculitis are palpable purpura, lower extremity localization, and small vessel involvement (9). About half of the cases are idiopathic. In cases with secondary development, infections and drugs are among the most common triggering factors. However, it may develop secondary to autoimmune diseases, chronic infections, and malignancies. Skin manifestations of leukocytoclastic vasculitis appear approximately 1-3 weeks after the triggering event. Lesions may present as purpura, erythematous macules, hemorrhagic bullae, or other clinical findings secondary to ischemia, such as ulcers (10). Lesions on the lower extremities and buttocks are usually symmetrical and not associated with trauma (11). A biopsy should be taken from the lesion area to confirm the diagnosis in cases with suspected vasculitis. Basic histological features in biopsy are evidence of tissue damage such as polymorphonuclear leukocyte infiltration, fibrinoid necrosis, extravasated red blood cells, and damaged

endothelial cells in and around the vessel wall (12). Our case had leukocytoclastic vasculitis, which developed during COVID-19 infection and was histopathologically proven in both skin biopsy and debridement samples. There are some case reports of leukocytoclastic vasculitis associated with COVID-19 in the literature. In a similar case report including findings of a 41-year-old male patient published by Alattar et al. (13), histopathological examination of the biopsies of skin lesions and skin debridements obtained from more than one region were compatible with leukocytoclastic vasculitis and left toe amputation was required. Like our case, Iraji et al. (14) described a case of cutaneous leukocytoclastic vasculitis in a 49-year-old male patient which started simultaneously with COVID-19-associated pneumonia and presented with purpuric skin rashes in the lower extremities. Gouveia et al. (15) reported the presence of leukocytoclastic vasculitis in a 27-year-old male patient with COVID-19 in the biopsies they obtained from purpuric lesions and hemorrhagic vesiculobullous lesions, which are more common in the lower extremity skin and less common in the back and upper extremities. Another feature of this case was microthrombi in small vessels revealed in histopathology. Camprodon Gómez et al. (16) published a case of leukocytoclastic vasculitis that developed in the 1st month of infection and presented with palpable purpura in a 29-year-old male patient who had COVID-19 and recovered completely. Similarly, Mayor-Ibarguren et al. (17) published a paper including leukocytoclastic vasculitis occurred during recovery from COVID-19 in an 83-year-old female patient. In a case-control study published by Kutlu et al. (18), it was reported that leukocytoclastic vasculitis accounted for 1.8% of all skin lesions in patients with COVID-19.

It is thought that approximately 20-30% of all vasculitis cases are due to drug use (19). Leukocytoclastic vasculitis has been suggested to have an association with many drugs, most notably beta-lactam antibiotics. If drug-induced vasculitis is considered as a diagnosis, new drugs and their associated comorbidities should be investigated. For most patients, symptoms or signs should be expected to develop usually 7-10 days after exposure due to the time for the formation of antigen-antibody complexes. Symptoms can be expected to regress upon discontinuation of the drug. In our case, favipiravir treatment was started for the treatment of COVID-19 three days before the onset of clinical symptoms, and it can be considered as a suspicious agent in terms of triggering the development of leukocytic vasculitis. However, favipiravir has a low side-effect profile, and to the best of our knowledge there is no report in the literature including vasculitis related to the use of favipiravir. In addition, vasculitis developed on the 3rd day of favipiravir treatment in our case. We believe that this period is not sufficient enough to trigger the vasculitic immune mechanism.

Autoimmune diseases are also important diseases to be considered in the etiology of leukocytoclastic vasculitis (20). Our case was a patient with a long-term diagnosis of RA who was in remission under adalimumab treatment. The development of a small vessel vasculitis associated with RA under the anti-tumor necrosis factor antagonist adalimumab treatment seems to be less likely in the presence of a risk factor such as COVID-19.

The data in the literature contains reports supporting that some cutaneous involvements may occur at the onset, during, and even after COVID-19. Some of these cutaneous involvements may be associated with leukocytoclastic vasculitis. Our case is crucial because it reveals a rare condition such as leukocytoclastic vasculitis, in addition to COVID-19-associated pneumonia and coagulopathy. Since there is no publication, it seems difficult to decide whether the use of favipiravir is a trigger for the development of leukocytoclastic vasculitis.

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Ethics

Informed Consent: Informed consent of the patient was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.E.Ö., E.M.Y., Concept: Ç.E.Ö., E.M.Y., Design: Ç.E.Ö., E.M.Y., Data Collection and/or Processing: Ç.E.Ö., E.M.Y., Analysis and/or Interpretation: Ç.E.Ö., E.M.Y., Literature Search: Ç.E.Ö., E.M.Y., Writing: Ç.E.Ö., E.M.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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