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## Successful treatment of warfarin-induced skin necrosis using oral rivaroxaban: A case report

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### Abstract

#### BACKGROUND

Heparin is commonly recommended for warfarin-induced skin necrosis; however, there is currently no established therapy for this disease. We present a serious case of warfarin-induced skin necrosis that was successfully treated with oral rivaroxaban, a factor Xa inhibitor.

#### CASE SUMMARY

A 48-year-old woman was admitted to the hospital for cellulitis of the right lower extremity. After antibiotic treatment, she developed pain and swelling of the left lower extremity, and deep vein thrombosis of both lower extremities was diagnosed. She was treated with a continuous heparin injection; subsequently, oral warfarin was concomitantly administered. Heparin was terminated after the therapeutic range was reached. On the following day, the patient had swelling and pain in the left lower extremity. In addition to decrease in protein S activity due to systemic lupus erythematosus, warfarin also reduced protein C activity, resulting in further hypercoagulation and skin necrosis. Warfarin was discontinued, and continuous heparin injection was resumed. Although the patient had to undergo amputation of the distal end of her left foot, continuous heparin injection was switched to oral rivaroxaban, and she was eventually discharged from the hospital in remission.

#### CONCLUSION

Administration of direct oral anticoagulants instead of warfarin is important in patients with decreased protein S and C activity.

**Key words:** Skin necrosis; Warfarin; Heparin; Rivaroxaban; Systemic lupus erythematosus; Case report

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**Core tip:** We present a serious case of warfarin-induced skin necrosis that was successfully treated with oral rivaroxaban, a factor Xa inhibitor. Administration of direct oral anticoagulants instead of warfarin is important in patients with decreased protein S and C activity.

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## INTRODUCTION

In warfarin-induced skin necrosis, the production of protein C and S is inhibited in an early stage after warfarin administration, which increases coagulability and thrombosis formation in the capillaries and venules of the dermis or subcutaneous tissue, leading to skin ischemia or necrosis<sup>[1]</sup>. Although there is currently no established treatment for warfarin-induced skin necrosis, heparin is commonly recommended<sup>[1]</sup>. However, the use of non-vitamin K antagonist anticoagulants is recommended in some case reports<sup>[2-6]</sup>.

We report the case of a patient who developed serious warfarin-induced skin necrosis as well as protein S deficiency caused by systemic lupus erythematosus (SLE), who was then successfully treated with oral rivaroxaban.

## CASE PRESENTATION

### Chief complaints

A 48-year-old woman presented to the emergency room with chief complaints of swelling of the right lower extremity and pyrexia.

### History of present illness

Regarding her present illness, pyrexia and redness, and swelling of the right lower extremity developed 10 and 5 d before hospitalization, respectively. She visited our hospital because the pyrexia was unresolved, and the symptoms of the lower extremity worsened.

### History of past illness

Her medical history included paronychia of the right big toe. She was gravida 3 and para 3, with no history of abortion.

### Personal and family history

Her father had a history of cerebral infarction.

### Physical examination upon admission

The patient's physical examination findings during examination were as follows: Body temperature, 39.4 °C; blood pressure, 107/65 mmHg; pulse rate, 81 beats/min and regular; respiratory rate, 13 breaths/min; and oxygen saturation, 97% (room air). Physical findings included swelling, warmth, redness, and pain in the right lower extremity as well as tinea unguis in the right foot.

### Laboratory examinations

Blood test findings on admission were as follows: White blood cell count, 4800 cells/ $\mu$ L; C-reactive protein, 9.51 mg/dL; prothrombin time (PT), 13.5 seconds; activated partial thromboplastin time, 34.5 s; and D-dimer, 6.9  $\mu$ g/mL (Table 1).

The patient was admitted to the hospital for cellulitis of the right lower extremity. Cefazolin (1 g) was administered every 8 h; subsequently, pyrexia declined. However, she redeveloped pyrexia (temperature, 39 °C). Considering the possibility of drug fever, we switched the antibiotic to clindamycin (600 mg) and administered it every 8 h from day 4 of hospitalization. As skin findings improved, the treatment of cellulitis was completed after 8 d.

**Table 1** Laboratory data upon admission

Parameter	Recorded value	Standard value
White blood cell count	4800/ $\mu$ L	4500-7500/ $\mu$ L
Lymphocyte count	1300/ $\mu$ L	
Red blood cell count	$327 \times 10^3$ / $\mu$ L	$380-480 \times 10^3$ / $\mu$ L
Hemoglobin	9.4 g/dL	11.3-15.2 g/dL
Hematocrit	31.3%	36%-45%
Platelet count	$10.6 \times 10^3$ / $\mu$ L	$13-35 \times 10^3$ / $\mu$ L
International normalized ratio	1.05	0.80-1.20
Activated partial thromboplastin time	34.5 s	26.9-38.1 s
Fibrinogen	374 mg/L	150-400 mg/dL
D-dimer	6.9 $\mu$ g/mL	$\leq 1.0$ $\mu$ g/mL
C-reactive protein	9.51 mg/L	$\leq 1.0$ mg/L
Total protein	7.5 g/dL	6.9-8.4 g/dL
Albumin	3.6 g/dL	3.9-5.1 g/dL
Total bilirubin	0.6 mg/dL	0.2-1.2 mg/dL
Aspartate aminotransferase	22 U/L	11-30 U/L
Alanine aminotransferase	24 U/L	4-30 U/L
Lactate dehydrogenase	262 U/L	109-216 U/L
Creatine phosphokinase	75 U/L	40-150 U/L
Blood urea nitrogen	7.6 mg/dL	8-20 mg/dL
Creatinine	0.43 mg/dL	0.63-1.03 mg/dL
Sodium	137 mEq/L	136-148 mEq/L
Potassium	3.6 mEq/L	3.6-5.0 mEq/L
Chloride	103 mEq/L	98-108 mEq/L
Glucose	146 mg/dL	70-109 mg/dL
Hemoglobin A1c	5.7%	$\leq 5.8\%$

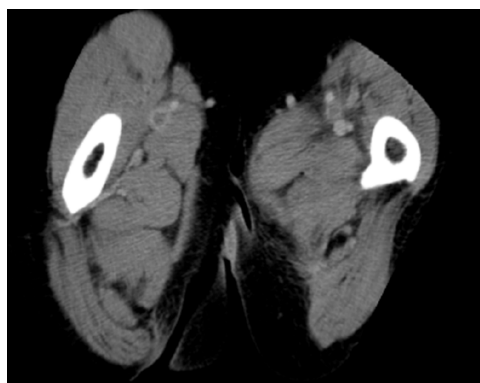
### Imaging examinations

On day 8 of hospitalization, the patient developed swelling of the left lower extremity. Deep vein thrombosis was suspected because she was on bed rest for the treatment of cellulitis. Contrast-enhanced computed tomography revealed deep vein thrombi in both femoral veins (Figure 1); she was diagnosed with bilateral deep vein thrombosis of the lower extremities. Blood tests for the evaluation of thrombophilia as a risk factor for the development of deep vein thrombosis revealed decreased protein S activity (Table 2); therefore, the patient was diagnosed with deep vein thrombosis caused by protein S deficiency.

Continuous intravenous infusion of heparin was initiated for deep vein thrombosis on day 8 of hospitalization, and oral warfarin was concomitantly administered from day 14 of hospitalization. Continuous heparin injection was completed on day 19 of hospitalization when the PT-international normalized ratio (INR) reached the therapeutic target range (1.6-2.5). Immediately after heparin cessation, the patient developed pain, swelling, redness, and blisters in her left lower extremity, as well as cold peripheries and skin necrosis (Figure 2). The activities of protein S and C at this time were both  $< 10\%$ . Warfarin administration during the period of low protein S activity subsequently led to decreased protein C activity, and discontinuation of the heparin injection caused hypercoagulation, leading to the onset of skin necrosis. The patient had a score of 7 points on the Naranjo adverse drug reaction probability scale<sup>[7]</sup>. Accordingly, we diagnosed her with warfarin-induced skin necrosis.

When evaluating the cause of decrease in protein S activity in this patient, we observed that she developed pleurisy approximately at the same time as the onset of bilateral deep vein thrombosis of the lower extremities. Along with lymphopenia, the patient fulfilled 2 clinical and 3 immunologic criteria of the Systemic Lupus International Collaborating Clinics classification<sup>[7]</sup>: Antinuclear antibody-positive (640-fold, homogeneous); low complement C4 (10 mg/dL; reference value, 17-45 mg/dL), C3 (56 mg/dL; reference value, 86-160 mg/dL) and CH50 (25 U/mL; reference value, 30-45 U/mL) levels; and direct Coombs test-positive. Therefore, the patient was diagnosed with SLE.

The activities of protein S and C over time are shown in Figure 3. Protein S activity



**Figure 1** Contrast-enhanced computed tomography on hospitalization day 8. Deep vein thrombi in both femoral veins were observed.

was normalized with 30 mg of prednisolone (PSL). Based on these results, the decrease in protein S activity in this patient was attributed to SLE. Warfarin was discontinued on the day 22 of hospitalization, and continuous heparin injection was resumed for warfarin-induced skin necrosis, and protein C activity was normalized. Necrotic tissue debridement was performed on day 35 of hospitalization (Figure 4), and left side toe amputation and free flap surgery were performed on day 67 of hospitalization (Figure 5). Subsequently, heparin was discontinued, and the patient was switched to oral rivaroxaban (15 mg/d) on day 68 of hospitalization. She was admitted to another hospital for rehabilitation on day 86 of hospitalization. At the 2-year follow-up, no aggravations of skin necrosis were observed, and the activities of both proteins S and C remained normal.

## FINAL DIAGNOSIS

Decreased protein S activity caused by systemic lupus erythematosus, and warfarin-induced skin necrosis decreased with protein C activity.

## TREATMENT

Prednisolone and rivaroxaban.

## OUTCOME AND FOLLOW-UP

At the 2-year follow-up, no aggravations of skin necrosis were observed, and the activities of both proteins S and C remained normal. Activity of systemic lupus erythematosus was stable.

## DISCUSSION

In this report, the patient developed warfarin-induced skin necrosis as well as decreased protein S activity secondary to SLE. Warfarin-induced skin necrosis occurred after discontinuation of heparin; however, the skin necrosis was not aggravated by the SLE treatment or oral administration of rivaroxaban, a direct factor Xa inhibitor. Only three other cases showing response to rivaroxaban for warfarin-induced skin necrosis have been previously reported<sup>[4-6]</sup>.

Our patient developed bilateral deep vein thrombosis of the lower extremities during the treatment for cellulitis. A detailed examination for thrombophilia revealed markedly decreased protein S activity. Protein S deficiency can occur due to the following: Congenital factors, pregnancy, oral hormonal contraceptive use, disseminated intravascular coagulation, acute thromboembolism, human immunodeficiency virus infection, nephrotic syndrome, liver disease, L-asparaginase chemotherapy, varicella recovery, antiphospholipid antibody syndrome, oral steroid use, and vitamin K deficiency (*i.e.*, decreased food intake, biliary obstruction, and oral warfarin administration)<sup>[8]</sup>. Protein S deficiency has been rarely reported in patients

**Table 2 Tests of thrombophilia**

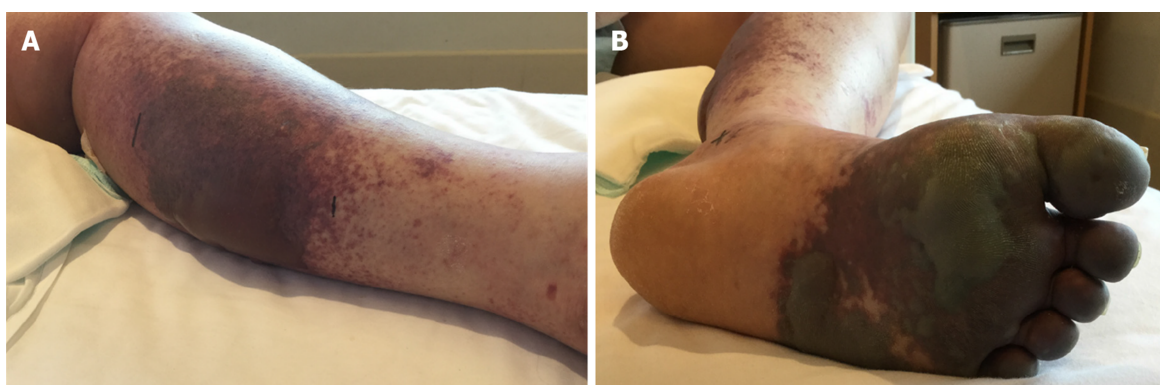
Parameter	Recorded value	Standard value
Anti-cardiolipin $\beta$ 2-glycoprotein I complex antibody	2.0 U/mL	< 3.5 U/mL
Lupus anticoagulant	1.3	< 1.3
Protein S activity	< 10%	56%-126%
Protein C activity	83%	64%-146%
Antithrombin III	79%	79%-121%

with SLE<sup>[9,10]</sup>. Our patient developed pleurisy during the clinical course. She was diagnosed with SLE after she fulfilled the Systemic Lupus International Collaborating Clinics classification criteria (*i.e.*, clinical criteria of pleurisy and lymphopenia as well as the immunologic criteria of positive antinuclear antibody, low complement, and positive direct Coombs-test)<sup>[7]</sup>. She had no family history, history of abortion, hepatic dysfunction, or renal dysfunction suggestive of congenital diseases. After initiating PSL treatment, protein S activity returned to normal as SLE improved, indicating that decreased protein S activity was caused by SLE.

Warfarin induced skin necrosis develops when proteins C and S production is inhibited in the early stage after the administration of warfarin, a vitamin K antagonist, resulting in increased coagulability and hypercoagulation<sup>[11]</sup>. Our case demonstrated that serious skin necrosis can occur in the early stage of treatment despite achieving a PT-INR within the therapeutic range. Onset of skin necrosis can occur within a few hours or several weeks after warfarin administration<sup>[11]</sup>. There are no currently established anticoagulant therapies for patients with decreased proteins S and C activities. Heparin, which is not a vitamin K antagonist, is commonly used for the treatment of warfarin-induced necrosis<sup>[11]</sup>. However, direct oral anticoagulants, such as dabigatran and rivaroxaban, have been found to be more effective for our patient based on previous findings<sup>[2-6]</sup>. We could find only three studies reporting that oral rivaroxaban was effective<sup>[7-9]</sup>. Heparin requires continuous intravenous injection, and its administration is not suitable for patients with deep vein thrombosis who require long-term anticoagulant therapy, such as our patient, because of the route of administration and necessity of hospitalization.

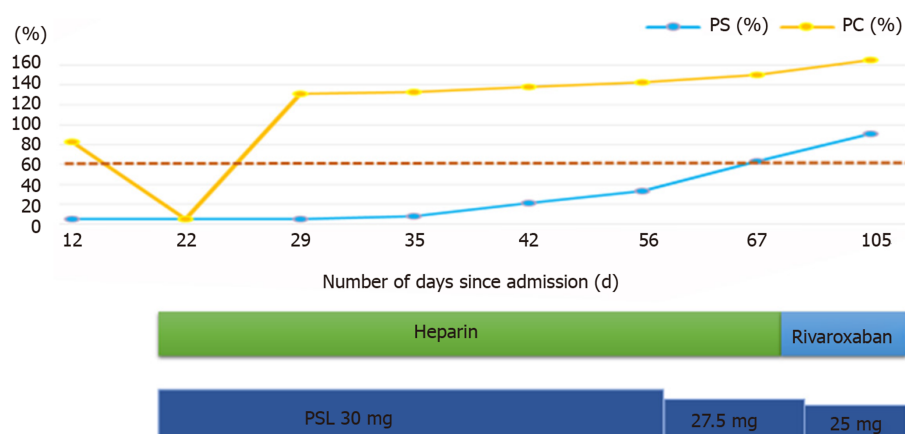
## CONCLUSION

We report the case of a patient with warfarin-induced skin necrosis who was successfully treated with oral rivaroxaban, a factor Xa inhibitor. It is important to administer DOACs instead of warfarin in patients with decreased activities of protein S and C, which are vitamin K-dependent coagulation inhibitors. During treatment of bilateral deep vein thrombosis of the lower extremities, it is necessary to closely examine the patient for the presence of thrombophilia and avoid warfarin administration until confirmation of the examination results. Furthermore, continuous heparin injections should be carefully discontinued when warfarin is administered.

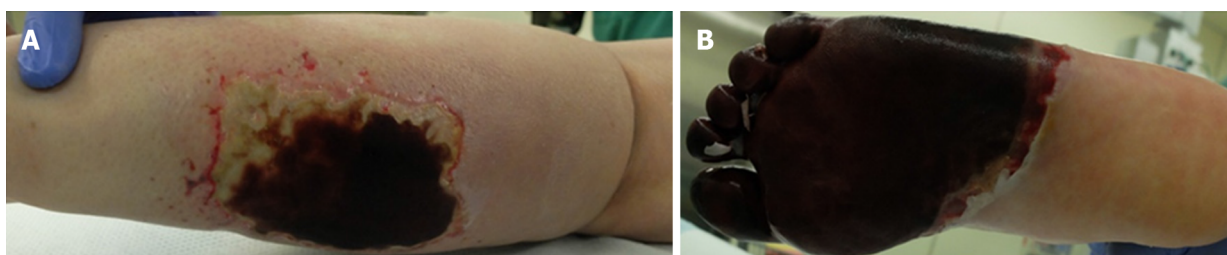


**Figure 2** Skin necrosis observed in the left lower extremity on hospitalization day 19. A: Left calf; B: Left foot.

Days	12	22	29	35	42	56	67	105
PT-INR	1.25	5.19	1.33	1.15	1.17	1.17	1.07	0.99
APTT (s)	41.7	76.6	96.8	73.0	111.3	73.5	35.8	29.6



**Figure 3** Clinical course of the patient. The course of treatment with prednisolone and anticoagulants as well as the activities of proteins C and S are shown. PSL: Prednisolone.



**Figure 4** Debridement of necrotic tissue in the left lower extremity (hospitalization day 35). A: Left calf; B: Left foot.

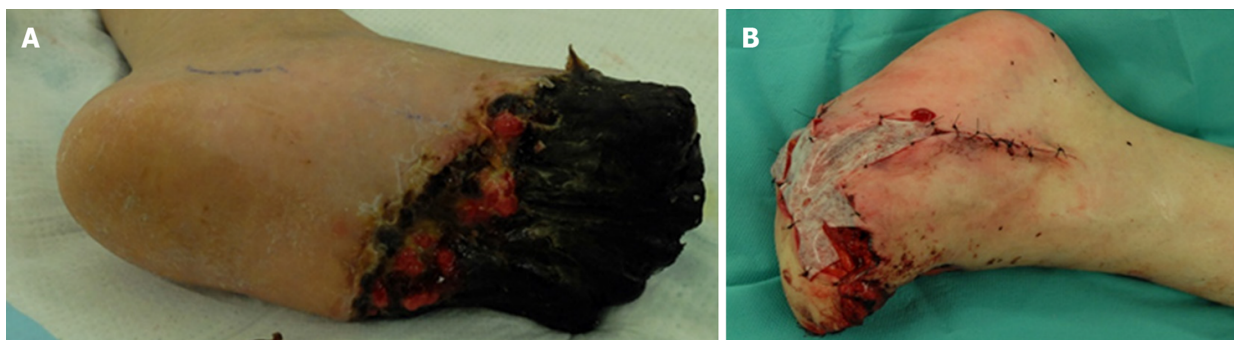


Figure 5 Left toe amputation and free flap surgery were performed on hospitalization day 67. A: Pre-surgery of left foot; B: Post-surgery of left foot.

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