



## Late Onset of Warfarin-Induced Skin Necrosis: A Case Report with Review of the Literature

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### Abstract

Skin necrosis is a rare but serious complication of warfarin. A 68-year-old male patient was admitted with sudden chest pain, breathlessness and swelling of the left leg. The chest CT angiography showed thrombus both in the lower lobe pulmonary artery and its branches. Heparin and warfarin was administered. After a time, warfarin application was continued. Palpable petechiae and purpura developed the left leg and the knee in the 5th month of the treatment. Meanwhile, it was learned the patient had taken ibuprofen for 2 days before the development of the skin lesions. The examination showed that the patient had necrotic bullae on a dark erythematous surface around the front of the right leg tibia. Skin necrosis was thought to be due to warfarin, and warfarin was stopped. Enoxaparin was initiated. Because the skin lesions did not improve, rivaroxaban treatment was started, and lesions eventually disappeared. Skin lesions should be evaluated with care in patients taking warfarin.

**Key Words:** Skin Necrosis; Warfarin; Rivaroxaban; Enoxaparin.

### Geç Dönemde Warfarine Bağlı Gelişen Cilt Nekrozu: Literatür Eşliğinde Bir Olgu Sunumu

### Özet

Warfarine bağlı cilt nekrozu nadir, fakat önemli bir komplikasyondur. Altmışsekiz yaşında erkek hasta ani başlayan göğüs ağrısı, nefes darlığı ve sol bacakta şişlik ile başvurdu. Çekilen toraks bilgisayarlı tomografi anjiyografide, her iki alt lob pulmoner arter ve dalları içerisinde trombüs izlendi. Hastaya heparin ve warfarin başlandı. Tedavinin 5. ayında sol bacakta diz etrafında yaygın palpabl peteşi ve purpura gelişti. Sağ bacak tibia ön yüzünde koyu eritemli zemin üzerinde nekrotik kurut ve bül izlenen plak görüldü. Bu arada, cilt lezyonları başlamadan önce iki gün süre ile ibuprofen aldığı öğrenildi. Hastanın cilt nekrozunun warfarine bağlı geliştiği düşünüldü ve warfarin kesilerek enoksaparin başlandı. Cilt lezyonları düzelmediğinden, rivaroksaban tedavisi başlandı. Rivaroksaban'dan sonra, cilt lezyonları kayboldu. Warfarin alan hastalarda, yeni gelişebilecek cilt lezyonları açısından kontrollerde hastaların mutlaka iyi sorgulanması gerektiğini vurgulamak amaçlı olgu sunulmuştur.

**Anahtar Kelimeler:** Cilt Nekrozu; Warfarin; Rivaroxaban; Enoxaparin.

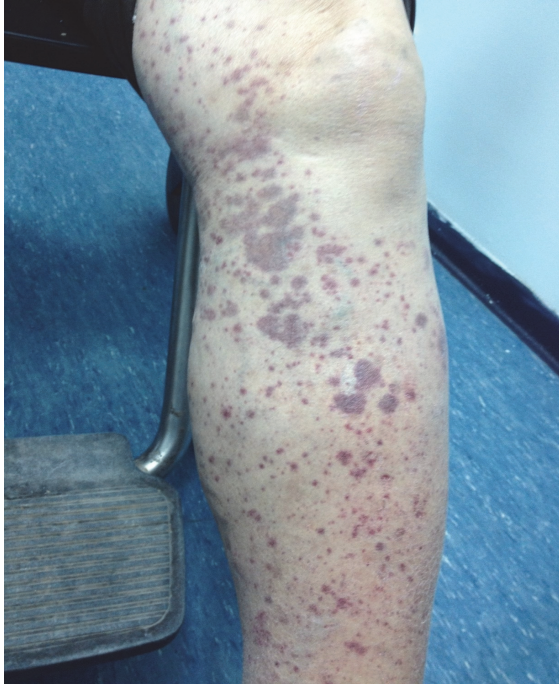
## INTRODUCTION

Warfarin sodium (Coumadin) is an oral anticoagulant that has been used for many years. It is widely used both in the treatment and prophylaxis of deep vein thrombosis and pulmonary thromboembolism as well as in the prevention of thrombus that may develop in some heart diseases such as prosthetic valve disease and atrial fibrillation. However, warfarin comes with several side effects such as bleeding, hepatitis, alopecia, pruritic macular-papular rash, purple toe syndrome (cholesterol microembolisation), and skin necrosis (1). Warfarin-induced skin necrosis (WISN) usually develops in the first 10 days of warfarin use. Nevertheless, literature also reports WISN cases even three years after warfarin application (2). A rare undesirable situation as it is, we would like to share our case with references to the literature.

## CASE REPORT

Sixty-eight-year-old male patient was admitted to our

clinic with sudden onset of chest pain, shortness of breath, and swelling in the left leg. In his medical history, we detected lower extremity surgery. Doppler ultrasonography of the venous system of the left leg showed deep femoral, superficial femoral thrombus appearances. We also observed thrombus appearances in popliteal veins consistent with the acute period. Computed tomography angiography revealed thrombus within the pulmonary artery and its branches of both lower lobes. Concurrent echocardiography findings did not show any sign of right heart strain. Then, intravenous heparin and warfarin sodium therapy was started. As international normalised ratio (INR) values reached to the desired level (2-3), heparin treatment was discontinued though the warfarin sodium therapy continued. In the 5th month of the treatment, we observed the development of palpable petechiae and purpura in the left leg, particularly around the knee (Figure 1).



**Figure 1.** Palpable petechiae and purpura in the left leg, particularly around the knee.

On the front side of the right leg tibia, there were plaques with necrotic scabs and bullae on a dark erythematous surface. Meanwhile the INR was 3.0. Including platelets and partial thromboplastin time values, laboratory results were normal. The patient did not have history of trauma before the skin lesions started. The patient, however, told us that he had been receiving ibuprofen 600 mg/day for two days before the skin lesions appeared. Assuming that the necrosis on the skin was a result of warfarin sodium, we cut off the warfarin therapy. Instead of warfarin, we started to give enoxaparin sodium. Observing no signs of decline in the skin lesions, an rivaroxaban treatment was started. Within two weeks after the rivaroxaban application, the skin lesions resolved (Figure 2).

## DISCUSSION

Warfarin-induced skin necrosis is a rare complication and it can be fatal if, following an early diagnosis, necessary precautions are not taken. It is observed in 0.01% to 0.1% of warfarin using patients (3). WISN was first defined by Mclean in 1916, and then by Flood et al. in 1943 (4,5). It usually occurs between the third and sixth days of warfarin therapy (in 90% of the cases). However, there are cases in the literature that report WISN development within the 15th-17th days, 3rd-17th months, and even 3rd year of warfarin treatment (2, 3). In our case, WISN developed in the 5th month of the warfarin therapy. As it was in our case, WISN is rather rare in late periods. Warfarin-induced skin necrosis often develops around the chest, thighs, buttocks, abdomen, and breasts in female patients. In addition, it can also be observed around the arms, legs, and penis (5). In our



**Figure 2.** The skin lesions resolved after the discontinuation of warfarin use.

patient's case, the skin lesions were in the bilateral lower extremities. As it occurred in our case, WISN generally starts with erythematous rashes and localised paresthesia, progresses with petechiae and hemorrhagic bullae, and eventually ends up with skin necrosis in its full-thickness. Capillary around the skin and subcutaneous regions, diffused microthrombi in the venules and deep veins, and dense erythrocytes outside the veins are among the important histopathologic findings to identify WISN. Lack of the involvement of the arterioles and the absence of vascular inflammation are important signs that help in distinguishing WISN from primary vasculitis. In case of the development of great skin necrosis or secondary infections, biopsies do not usually have diagnostic value since histopathological findings change rapidly in these cases (3). Tissue biopsy, therefore, is not necessary for diagnosis (3). Disseminated intravascular coagulation, heparin induced immune-mediated thrombocytopenia, erythema and pyoderma gangrenosum, cellulitis, and Fournier's disease should be considered for differential diagnosis of WISN (3). A carefully acquired medical history and physical examination can be of great help in distinguishing WISN from these pathologies. Without the need for biopsy, we diagnosed our patient with WISN as a result of the present clinical signs.

Inhibiting 2,7,9,10 clotting factors that are synthesised as vitamin K-dependent factors, warfarin shows anticoagulation effect. Warfarin also inhibits proteins C and S, which have natural anticoagulant effects. In warfarin-treated patients, protein C and S deficiency is an important risk factor for skin necrosis. As a result of the half-life duration differences between the

anticoagulant-effective protein C (half-life: 6-8 hours) and the procoagulant-effective prothrombin (half-life: 2-5 days), a temporary imbalance develops between procoagulant and anticoagulant factors at the beginning of warfarin therapy. This imbalance explains the current theory of WISN development (2). Apart from protein C and S deficiency, though less frequently, anti-thrombin III deficiency, the presence of factor V Leiden mutation or antibodies in anti-phospholipid syndrome (anticardiolipin antibodies and/or lupus anticoagulants) were also found to have relationship with WISN (1). Although WISN develops in its early stages as it has been explained, how the WISN mechanism develops in late stages, as it was in our case, is still unclear. The literature reports a case in which skin lesions developed for five times during the late follow-ups of a patient with WISN. It has been stated that, suffering from heart failure, the patient had WISN attacks during the same periods with his decompensated heart failures and that WISN development was probably a result of the imbalance of the procoagulant-anticoagulant factors secreted from the liver (7). However, our patient did not have protein C and S deficiency, anti-thrombin III deficiency, factor V Leiden mutation, anticardiolipin antibodies, or lupus anticoagulant; neither did he have any pathologies, such as heart failure or chronic liver disease, that would give way to protein C and S deficiency. In some cases, WISN take place when the patients on warfarin stop using the medication for a short time and restart using it again (2). We did not have a story of discontinued warfarin use in our case.

Some drugs can lead to procoagulant-anticoagulant imbalance by binding to albumin instead of warfarin or by altering warfarin metabolism in different ways. Cameron et al. report a case of late stage WISN after a sodium salicylate (4 mg/day) application for four days in a patient who had been using warfarin for three years when the patient (8). In another study, Essex et al. report WISN development on the 14th day of the warfarin therapy in a patient who used ibuprofen (400 mg/day) a day before the skin necrosis development (2). Similarly, our patient also had a history of ibuprofen (400 mg/day) use before the emergence of WISN. In vitro studies show that non-steroidal anti-inflammatory drugs, including ibuprofen, disconnect albumin-bound warfarin (9). Thus, it is possible that WISN occurred due to the increased interaction between warfarin and ibuprofen. Normally, there is no interaction concerning prothrombin time between propionate derivatives; ibuprofen and warfarin are no exceptions to this. In summary, although still uncertain, the late stage WISN

may be developing as a result of discontinuing and restarting the use of warfarin, a sudden reduction in some anticoagulant factors synthesised by the liver, and drug interactions. A quick recognition of the complications and taking the necessary measures will provide life and limb salvage. Early diagnosis and discontinuing warfarin use will stop the progression of skin necrosis. In addition to discontinuation of the drug, providing patients with vitamin K and fresh frozen plasma could prove to be supportive treatment methods. In some cases, local debridement of the region, grafting, and implementation of topical antibiotics may be required. Despite all these applications, the affected area may still require amputation in 50% of cases (1). In our patient, the discontinuation of warfarin was enough to bring recovery without any other intervention.

As a result, we believe that patients should be evaluated with care during warfarin use due to possible skin lesions. In this report, we aimed to highlight the development of WISN, a rare complication that arises from the use of warfarin, an oral anticoagulant, by drawing attention to warfarin-drug interactions.

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