Purple Toes Syndrome Related to Warfarin Therapy: A Case Report
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Citation

Abstract
Background: Purple toes syndrome is an rare adverse effect of warfarin. It is characterized by a painful purple to blue discoloration of the toes. The syndrome usually develops 3-8 weeks after the start of warfarin therapy.

Case Report: A 65-year-old woman was admitted to the hospital with deep vein thrombosis (DVT) in her right leg. Heparin and then warfarin was started because of the appearance of a painful purple lesion on her right leg. Warfarin was discontinued and heparin was restarted. One week later, under heparin therapy, she experienced pulmonary embolism and heparin could not rise the PTT, so warfarin was begun again and in 24 hours the right leg became edematous and painful so warfarin was stopped. Because the antithrombin III level was low, enoxaparin was started and her symptoms improved in a week. The interesting thing in this case was that our patient experienced recurrent purple toes syndrome with reexposure to warfarin.

This study happened in Department of Anesthesiology and Critical Care Medicine, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

BACKGROUND
Warfarin is an oral anticoagulant that decreases the production of Vitamin K dependent coagulant factors (II,VII,IX,X)\[1\]. Adverse effects of warfarin are categorized into hemorrhagic and nonhemorrhagic complications. Although, GI bleeding is the most common hemorrhagic related complication of warfarin, less common nonhemorrhagic complication such as allergic maculopapular eruptions, urticaria, eosinophilic pleuritis, vasculitis, toxic hepatitis, skin necrosis and purple toes syndrome have also been reported.\[1\]

Skin necrosis is a rare adverse effect of warfarin, occurring in about one of every 5000 or more patients treated with warfarin, and in about 3% of subjects affected by protein C deficiency.\[1\] Skin necrosis usually develops 3 and 8 days after the start of warfarin and the occurrence is characterized by a painful maculo-papular rash in those parts of the body rich in adipose panniculus, quickly changing into hemorrhagic and then necrotizing blebs.\[1\] Histology shows thrombosis in dermal vessels. Skin necrosis usually happens in protein C deficiency subjects. Purple toes syndrome is a very rare adverse effect of warfarin and it was first described in 1961 by Auerbach.\[1\] It happens in patients with vascular atherosclerosis who are receiving the drug. It usually develops 3-8 weeks after the start of warfarin therapy and is characterized by development of painful purple lesions on the toes. This syndrome is thought to be secondary to cholesterol crystal emboli released as a result of warfarin-induced bleeding into atherosclerotic plaques.\[1\] If warfarin therapy is discontinued, the toe pain will resolve, but purple discoloration will persist.

CASE REPORT
A 65-year-old woman with a 20 years history of type II diabetes was admitted to a university hospital with diagnosis of deep vein thrombosis (DVT) of her left calf. A loading dose of 80 units/kg heparin followed by a continuous infusion of 1000u/hr was initiated and at the third day of the heparin therapy, warfarin (5mg/day) was also started for that patient. Three days later, heparin was discontinued once an INR of 2.5 had been achieved. On the 8th day of oral anticoagulation therapy, the left calf and thigh became painful and edematous with reddish discoloration. Doppler ultrasonography showed no reportable abnormalities.

On the 12th day of warfarin therapy, it was found that the
color of the 1st-3rd toes on her left foot was changed to a blue-black discoloration. With diagnosis of purple toes syndrome warfarin was discontinued and heparin infusion was started again. One week into heparin therapy she experienced dyspnea and was admitted to Intensive Care Unit (ICU) with diagnosis of pulmonary emboli that was confirmed by ventilation/perfusion scan. Heparin infusion (1500U/hr) was continued while PTT was still at normal limit. Although the dose of heparin was increased to 2500U/hr, the PTT remained within the normal range.

Additional laboratory tests such as Antithrombin III, Antinuclear Antibody, ANCA, Anticardiolipin and protein S,C were ordered. Protein C was deficient and Antithrombin III was low. Other tests were normal. Since heparin therapy did not seem to be useful, warfarin at 5 mg/day was restarted. One day later, the left leg became edematous and painful and with the warfarin continuation they became worse. Three days later, warfarin was stopped and because of low activity of Antithrombin III and elevation of FDP and D-dimer and decrease in platelet count, heparin infusion was stopped and enoxaparin (a low molecular-weight heparin (LMWH), was started at a dose of 1 mg/kg/day.

The pain and edema resolved within a week and she was discharged while she was symptom free and on subcutaneous enoxaparin (40 mg/ day).

Figure 1
Figure 1: Painful purple discoloration of the left foot developed in a sixty five year old woman seven days after beginning of warfarin therapy due to DVT in her left leg.

DISCUSSION
Skin necrosis is one of the rare complications of warfarin. It happens in 0.1-1% of patients who receive warfarin. In patients with protein C deficiency and the history of skin necrosis, heparin is started first and 72 hours later it is followed by warfarin. In our patient, who had protein C deficiency, despite of heparin infusion before warfarin, skin necrosis happened and purple toes syndrome was appeared by continuation of warfarin. So we had to discontinue warfarin immediately. In this patient, treatment of pulmonary emboli with heparin infusion was not successful. Therefore, additional tests were performed and they revealed a low level of antithrombin III and protein C deficiency.

Since antithrombin III is a co-factor for heparin, high doses of heparin would not be effective in this patient and despite of her past drug history of skin necrosis, warfarin was cautiously started. Unfortunately, a skin necrosis reoccurred. Because of the poor previous response to heparin and the presence of warfarin complications, enoxaparin was started for our patient. This drug is not dependent on antithrombin III for activation and only inhibits factor Xa. Therefore, the prothrombin activation is intact and prothrombin time and partial thromboplastin time are remains in normal range. Factor X activity must be checked to evaluate LMWH efficacy.

CONCLUSIONS
In conclusion we had a patient who developed purple toes syndrome under the treatment of warfarin. As the patient was antithrombin III deficient, after the change of warfarin to heparin, she developed pulmonary emboli. Therefore, heparin was discontinued and enoxaparin was started. By starting of enoxaparin skin necrosis and manifestations of pulmonary emboli were resolved. Thus we continued enoxaparin for the next three months.

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