



# Lab Lines

<http://pathology.uc.edu/LABLINES/index.asp>

An Educational Bulletin

Nov/December 2001  
Volume 7, Issue 6

A publication of the  
Department of  
Pathology and  
Laboratory Medicine  
at the University of  
Cincinnati

## Editor

G. Retzinger, MD, PhD



## Production

Jennifer Webb

## This Issue:

Warfarin-Induced  
Skin Necrosis

## Next Issue:

Idiopathic  
Thrombocytopenic  
Purpura (ITP)

## Warfarin-Induced Skin Necrosis

### Introduction

Warfarin-induced skin necrosis is a rare but serious complication of oral anticoagulant therapy. It has a prevalence of 0.01-0.1%. This condition was first recognized in 1943. It is of great clinical interest and raises a number of questions concerning pathological mechanisms and patient management.

### Clinical presentation

Warfarin-induced skin necrosis typically occurs in middle-aged women who are perimenopausal and obese, and are being treated with warfarin for thromboembolic disease. It is often associated with the administration of a large dose of the drug and develops within 1-10 days of initiating therapy. The majority of cases appear between day 3 and 6 of therapy. Late-onset warfarin-induced skin necrosis occurs occasionally from 15 days up to 15 years after onset of therapy. Skin necrosis usually appears in microcirculation-rich areas. In women, breast, buttocks and thighs are the most common sites; in men, the penile skin may be affected. The trunk, extremities and face can also be involved. Pathological changes include extensive thrombosis with microvascular injury and fibrin deposits in the postcapillary venules and small veins. Lack of vascular or perivascular inflammation and absence of arteriolar thrombosis are distinctive features. Clinically, patient's early complaints are paresthesia, sensation of pressure with an erythematous flush, or simply localized skin discomfort. The lesions are demarcated, painful, and initially erythematous or hemorrhagic. Hemorrhagic bullae and full-thickness skin necrosis with eschar formation are seen in the inevitable end stage. Both spontaneously heal after discontinuation of warfarin. Recurrence of skin necrosis in the absence of further anticoagulation therapy has been reported. Whether the condition reappears or not is unpredictable after restarting the drug.

### Etiology

The precise etiology of the disease is unclear. Protein C deficiency, protein S deficiency, factor VII deficiency, hypersensitivity, direct toxic effect of warfarin, and other mechanisms have all been proposed. Among these, protein C deficiency is a widely accepted major risk factor. The pathogenesis of this phenomenon may be explained by the rapid drop in factor VII and protein C levels (both have a half-life of ~5 h) following the initiation of warfarin. This transiently procoagulant/anticoagulant imbalance is further exaggerated in protein C deficiency, leading to a relative hypercoagulable state with thrombotic occlusion of the microvasculature. In addition to protein C deficiency, clinicians should be aware that other hypercoagulable conditions, such as protein S deficiency, resistance to activated protein C, antithrombin deficiency and lupus anticoagulants have been associated with warfarin-induced skin necrosis.

## Patient management

In general, large loading doses of warfarin should be avoided. Gradually increasing doses of warfarin (by 1-2 mg per day) over an extended period may be applied to patients with known existence of risk factors for skin necrosis. Careful monitoring of patients in this situation is mandatory. Rapid reversal of warfarin with high doses of parenteral vitamin K and therapeutic heparin anticoagulation may also prevent the progression of skin necrosis. Clinicians should also be aware that heparin itself can cause skin necrosis clinically indistinguishable from warfarin-induced skin necrosis. The heparin-induced version is more commonly seen in abdominal wall, extremities and nose, and usually appears between 5-10 days after onset of therapy. Screening of patients for protein C, protein S or antithrombin deficiency before beginning warfarin therapy may delay treatment and is not recommended. These tests are neither sensitive nor specific in predicting a risk of developing this condition. In patients with protein C deficiency, intravenous infusion of monoclonal antibody-purified protein C has shown promising results; however, its routine use is limited by high cost. Prostacyclin is another possible treatment choice for warfarin-induced skin necrosis.

Despite all the medical treatment, the associated morbidity is high. About half of the patients require surgical intervention with wide local debridement, skin grafting or even amputation. Failure of early diagnosis and treatment may result in death.

Finally, it is very important to realize that warfarin-induced skin necrosis is not specific for warfarin therapy as it has been associated with the use of other vitamin K antagonists. The condition may also be confused with other causes of acute thrombosis with associated skin necrosis, including disseminated intravascular coagulation with purpura fulminans, necrotizing fasciitis, cellulitis, venous gangrene and other dermatological entities.

## Summary

Warfarin-induced skin necrosis is a rare but serious complication of oral anticoagulant therapy. It is often associated with the administration of a large dose of the drug, and develops within 3-6 days of initiating therapy. One possible pathogenesis is transient procoagulant/anticoagulant imbalance caused by the rapid drop in factor VII and protein C levels following the initiation of warfarin. Avoiding a large loading dose, gradually increasing doses, and distinguishing

from other conditions associated with skin necrosis are critical in management of warfarin-induced skin necrosis.

**Authors:** Jun Mo, MD, Resident in Pathology, and Gregory S. Retzinger, MD, PhD, Associate Professor, Department of Pathology and Laboratory Medicine, University of Cincinnati.

## References

1. Rose VL, Kawada HC, Williamson K, Hoppensteadt D, Walenga J, Fareed J. Protein C antigen deficiency and warfarin necrosis. *Am J Clin Pathol* 1986; 86: 653-5.
2. Sternberg ML, Pettyjohn FS. Warfarin sodium-induced skin necrosis. *Ann Emerg Med* 1995; 26: 94-7.
3. Enzenauer RJ, Berenberg JL, Campbell J. Progressive warfarin anticoagulation in protein C deficiency : A therapeutic strategy. *Am J Med* 1990; 88: 697-8.
4. Essex DW, Wynn SS, Jin DK. Late-onset warfarin-induced skin necrosis: case report and review of the literature. *Am J Hematol* 1998 Mar; 57: 233-7.
5. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. *Br J Surg* 2000 Mar; 87:266-72.
6. Kelly RA, Gelfand JA, Pincus SH. Cutaneous necrosis caused by systemically administered heparin. *JAMA* 1981; 246:1582-3.