Coumarin-induced skin necrosis

LLOYD W. BROOKS, JR, DO
FRANCIS X. BLAIS, DO

Coumarin skin necrosis is a rare and usually unpredictable complication of coumarin therapy, occasionally leading to death. Onset is usually between the third and sixth day of coumarin therapy. The patient most commonly complains of pain in a region of abundant subcutaneous fat, with progression to erythema, petechiae, and gangrenous necrosis. Thrombosis of the dermal and the subcutaneous veins is demonstrated pathologically. We describe a case and review the pathogenesis, treatment, and prevention of this lesion.

(Key words: Coumarin therapy, skin necrosis, anticoagulation therapy)

Coumarin skin necrosis is a rare and usually unpredictable complication of coumarin congener anticoagulant therapy (Table 1). Occasionally, this complication leads to death. The more common complications of coumarin therapy, such as subcutaneous hemorrhage, intramuscular hematoma, visceral intramural bleeding, and cutaneous reactions are directly related to anticoagulation, while coumarin-induced skin necrosis has well-defined histopathologic changes consistent with thrombosis and infarction (Table 2).

Report of a case

An 81-year-old woman with chronic dementia was admitted to the hospital from a nursing home, with deep venous thrombosis of the left thigh that was confirmed by venogram. Constant infusion of heparin was instituted, and anticoagulation was maintained at two times the control partial thromboplas-

At the time this article was written, Dr Brooks was a cardiology fellow, Riverside Hospital, Trenton, Mich; and Dr Blais is an associate professor, Medicine Department, Texas College of Osteopathic Medicine, Fort Worth. Dr Brooks is currently in private practice of cardiology, Fort Worth.

Reprint requests to Lloyd W. Brooks, Jr, DO, PO Box 470097, Fort Worth, TX 76147-0097.

tin time. The patient's initial course was uncomplicated. On the seventh hospital day, heparin therapy was discontinued; 10 mg of sodium warfarin was given orally, followed thereafter with 2.5 mg daily, maintaining the prothrombin time at 27.8 seconds (control, 12.5 seconds). On the ninth day of hospitalization, the patient was discharged on a daily regimen of warfarin (2.5 mg orally).

Two days after discharge, the patient was readmitted when nursing home personnel noticed a bright erythematous spot on the lateral aspect of the patient's right hip early in the morning, which enlarged, turned purple, and began to spread down the leg. A second area of erythema was noticed on the patient's left shoulder. The patient denied having suffered any trauma. Prothrombin time on admission was 22.8 seconds (control, 11.2 seconds; normal, < 14 seconds), partial thromboplastin time was 30 seconds (normal, < 40 seconds), and thrombocytopenia was now present (platelet count, $50 \times 10^9/L$; normal, 150 to $400 \times 10^9/L$). Findings were consistent with coumarin-induced skin necrosis.

Warfarin therapy was stopped and heparin therapy was initiated after a bone marrow aspirate was obtained from the posterior iliac crest, and a biopsy specimen was obtained from the margin of the lesion on the thigh. Results of a bone marrow and peripheral smear were normal, and the thrombocytopenia was considered consumptive. Histologic study of the lesional biopsy specimen showed a scattering of mononuclear inflammatory cells and extravasation of erythrocytes in the papillary dermis. A large number of vessels within the subcutis showed evidence of thrombosis, with focal areas of hemorrhagic fat necrosis.

The patient continued to deteriorate and died of cardiac arrest on the ninth hospital day. No postmortem examination was obtained.

Discussion

Coumarin-congener-associated skin necrosis was first reported by Flood and coworkers³ in 1943 as thrombophlebitis migrans disseminata with breast involvement. Verhagen⁴ more accurately described the entity in 1954. In a series of 13 patients with diagnoses including

Table 1
Coumarin Congeners Implicated in Production of Hemorrhagic Skin Lesions as a Complication of Anticoagulant Therapy¹

Agent	No. of reported cases
Bishydroxycoumarin (Dicoumarol)	27
Phenprocoumon (Marcumar, foreign trade name; Liquamar, United States)	20
Phenindoione (Danilone, Hedulin)	3
Acenocoumarol (Sintrom)	8
Ethyl biscoumacetate (Tromexan ethyl acetate, Dicoumacyl [available outside United States])	7
3,3-Ethyl-bis-(4-oxycoumarin) (Pertromben and Thromboton [available outside United States])	1
Sodium warfarin (Coumadin sodium)	3

fractures, postpartum state, thyroidectomy, and thrombosis, he concluded that "any disease, when complicated by a thrombosis and treated with dicoumarol . . . can lead to the discussed haemorrhagic complications." Kipen⁵ was the first to properly ascribe the gangrenous changes to anticoagulant therapy. Since Kipen's description in 1961, approximately 200 cases have been reported in the literature.

Skin necrosis occurs in approximately 0.1% of patients receiving anticoagulant therapy with a coumarin derivative.⁶ Most patients (90%) are middle-aged, obese women¹ who are being treated for thrombophlebitis of the lower extremities, pulmonary embolus, or cerebrovascular or coronary thrombosis. The onset and course of skin necrosis occur in a consistent pattern.⁷ Onset is between the third and sixth day of coumarin therapy, with the patient complaining of pain in a region of abundant subcutaneous fat. Sites of involvement are most commonly the buttocks, breasts, thighs, anterior aspect of the calves, and dorsum of the feet.

The patch is typically erythematous, with poor demarcation and often edema. Petechiae develop, followed within a few hours by ecchy-

motoc discoloration surrounded by an erythematous halo. Bullae may occur that contain sterile serosanguineous fluid, and are often followed by hemorrhagic infarcts and gangrenous necrosis that involve deeper tissues, producing sloughing that may require acute surgical debridement, skin grafting, or amputation. Usually, no extension of the lesion occurs.^{1,8,9}

Numerous cases of full recovery without sequelae have been reported.⁶ Clinical differentiation between subcutaneous hemorrhage and skin necrosis is paramount, because the treatment and prognosis are different. Nudelman and Kempson⁹ have summarized the differences (Table 3).

Histologically, the lesions demonstrate occlusion of dermal and subcutaneous veins, with fibrin thrombi and, occasionally, with neutrophilic vasculitis¹⁰; arteries appear to be spared while thrombosis is the inciting factor. Hypersensitivity vasculitis is unlikely because the lesion appears too late to be an immediate-type reaction and too soon to be an allergic-mediated reaction.⁴ Skin tests for allergic vasculitis have been negative,⁸ as have histologic studies.¹¹

Table 2
Some Uncommon Adverse Reactions to Coumarin Drugs²

Hemorrhagic reactions	Other reactions
Central nervous system hemorrhage Bleeding from eardrum Hemarthrosis Carpal tunnel syndrome Intramuscular hematoma Hemopericardium Hemorrhagic pancreatitis Hemorrhage from surreptitious self-administration Adrenal hemorrhage Hemorrhage into pituitary adenoma Retroperitoneal and intramural intestinal bleeding	Urticaria Extensive dermatitis "Purple toes" Drug interactions Intestinal necrosis Alopecia Orange-red staining of hands and urine Intestinal obstruction Maculopapular, purpuric, or vesicular skin lesions

Table 3
**Comparison of Hemorrhage and Necrosis in Patients
Receiving Coumarin Therapy¹**

Hemorrhage	Necrosis
Affects men and women equally Onset unrelated to initiation of therapy Corrected with administration of vitamin K Continuance of coumarin worsens complication Heparin worsens complication Necrosis absent Surgery not indicated	Female predominance Onset 3 to 6 days after initiation of therapy Progresses despite administration of vitamin K Continuance of coumarin has no effect on degree of complication Heparin may be beneficial Necrosis present Surgery often necessary

In their pathogenic explanation, based on serial biopsy specimens, Nalbandian and co-workers¹ proposed two stages to the disorder. The first stage occurs at the junction of the capillary and precapillary arteriole in the dermovascular loop. The clinical changes can be correlated with this localization, such as the initial erythematous flush with capillary dilation in the loop, followed by petechial formation when the capillary walls rupture. Ecchymoses represent coalescence of hemorrhage from the petechiae secondary to the previously administered anticoagulant.

The second stage—hemorrhagic infarct or gangrenous necrosis—correlates with stasis and subsequent thrombosis in the venules immediately distal to the dermovascular loop, where thrombotic occlusion of the larger veins of the dermis and subcutaneous tissue causes

extensive necrosis and sloughing of the subcutaneous adipose tissue.

The coumarin congeners alter the hepatic synthesis of coagulation factors II, VII, IX, and X by interference with vitamin K utilization in the carboxylation of the glutamic acid residues of the precursors of these coagulation factors, resulting in dysfunctional factors. Because coumarin derivatives alter only the production of the vitamin K-dependent factors, not preformed factors or their catabolism, depletion of the preformed factors must occur before full anticoagulation occurs.

The concentration of functional factor VII (plasma half-life, 5 to 6 hours) first decreases, then factor IX (half-life, 20 to 24 hours), X (half-life, 40 hours), and II (half-life, 60 hours). Antithrombogenic effects occur only after functional concentrations of factors IX and X are

sufficiently diminished, usually in 2 to 7 days.¹²

Recent biochemical studies have defined a correlation between protein C deficiency and coumarin-induced skin necrosis. Protein C is a vitamin K-dependent protein that, along with protein S and factors II, VII, IX, and X, is a γ -carboxyglutamic acid protein.¹³ In contrast with the vitamin K-dependent coagulation factors, protein C, with the aid of protein S, induces a fibrinolytic state, with a decrease in whole blood clot lysis time but without systemic plasminogen activation.¹⁴ Activated protein C (protein C_a) selectively inactivates active cofactors V_a and VIII_a, while inhibiting platelet coagulant activity by inactivation of platelet factor X and V_a.⁸

Absence or deficiency of proteins C and S is strongly associated with congenital thrombotic disease¹⁵ and recurrent venous thromboembolism.¹⁶ The ability of protein C_a to promote clot lysis by enzymatically binding to, or degrading, an inhibitor of tissue plasminogen activator (TPA) may herald a synergistic use of protein C_a in TPA-induced thrombolysis.¹⁷

Functionally, when coumarin therapy is initiated, protein C levels drop rapidly, paralleling factor VII levels; however, factor X and prothrombin are not depleted for 3 to 9 days. Therefore, with decreased protein C levels, the risk of thrombosis or extension of existing clots may increase until factor X and prothrombin are sufficiently depleted to achieve anticoagulation. Concurrent administration of heparin and warfarin during initial anticoagulation may prevent this clotting process. At the onset of coumarin therapy, however, large doses of coumarin should be avoided. Measurement of proteins C and S functional levels prior to initiation of coumarin therapy is ideal but impractical and not cost-efficient.³

Numerous regimens have been used to treat coumarin-induced skin necrosis, including local hypothermia, lumbar sympathectomy, vasodilators, vitamin K, and vitamin C, all without success. Nalbandian and associates¹⁸ report a successful regimen of heparin and vitamin K₁, but only if initiated before the occurrence of infarcts. They also state that heparin

will not prevent the occurrence of the necrosis.

Zauber and Stark¹⁹ report that they prevented skin necrosis in a patient who had previously had coumarin necrosis and who required reinitiation of coumarin anticoagulation by the infusion of fresh frozen plasma (which is rich in protein C) along with heparin for 3 to 5 days to maintain protein C levels until all vitamin K-dependent factors were depleted. Continuation of coumarin therapy during the episode did not appear to hamper recovery or to cause further morbidity. Recurrence of skin necrosis on rechallenge, however, appears to be the exception rather than the rule.

Summary

Coumarin-congener necrosis may be precipitated by decreased levels of protein C, either inherently or iatrogenically, allowing formation or extension of clots by other remaining clotting factors. This clotting leads to infarction and necrosis of the dermis and subcutaneous adipose tissue.

Concomitant heparin therapy during initiation of low-dose coumarin therapy or therapy with coumarin congeners on day 1 of heparin administration may prevent the occurrence of the associated skin necrosis. The necrosis may also be prevented if the early signs (erythema, pain, and edema) are recognized and heparin therapy is initiated. Once infarction has occurred, surgical management may be the only available treatment.

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