Necrosis and Gangrene as a Complication of Coumarin Therapy

A Case Report

BY RONALD CAMPBELL, M.D.*, THOMAS O. CLANTON, M.D.†, AND JAMES D. HECKMAN, M.D.†, SAN ANTONIO, TEXAS

From the Section of Orthopaedic Surgery, Audie Murphy Veterans Administration Hospital, and the Division of Orthopaedic Surgery, University of Texas Medical School at San Antonio, San Antonio

Necrosis of the skin and soft tissues — an unusual albeit well documented[1-8] complication of therapy with coumarin and coumarin congeners — rarely comes to the attention of orthopaedic surgeons. It typically affects obese, middle-aged women on the third to fifth day of coumarin therapy. But, as in the case report presented here, it may also affect men. The lesion ranges in severity from pain, erythema, and ecchymoses of the skin to the formation of large hemorrhagic bullae with frank necrosis. Depending on the severity of the initial lesion, the necrotic tissue may regress totally or may progress to sloughing or even gangrene.

Case Report

A previously healthy, fifty-six-year-old white man was admitted to the Audie Murphy Veterans Administration Hospital on July 7, 1978, because of chest pain on the left side and a six-week history of migratory pain and swelling in the limbs. The diagnosis was migratory thrombophlebitis and possible pulmonary embolus. Heparin treatment was begun and was continued until July 12, 1978, when all evidence of pulmonary embolus had subsided. Examination of brushings from a brochoscopic examination showed malignant cells. The heparin therapy was discontinued and the patient was prepared for thoracotomy, but on July 30 bilateral thrombophlebitis of the lower extremities required that heparin therapy be reinstituted. Despite adequate heparin treatment, recurrent pulmonary embolus was diagnosed. The patient underwent ligation of the inferior vena cava on September 11, 1978. On September 15, a thoracotomy and left lower lobectomy were done and a large-cell poorly differentiated carcinoma with involvement of multiple nodes was diagnosed.

On September 18, the patient was begun on coumarin therapy, five milligrams per day for three days. The daily dose was decreased to 2.5 milligrams on September 21. On that day the patient's prothrombin time was three times the control value and heparin therapy was discontinued. On September 22, ecchymosis of the right great, second, and third toes developed. During the next twenty-four hours, the ecchymosis spread to all of the toes and to the mid-metatarsal level of the dorsal and plantar surfaces of the foot. The following day a similar spreading lesion developed in the first three toes of the left foot. There was pain in both feet which gradually became severe. On the third day after the onset of the lesions, the toes became cold and purple, with erythema and swelling of the entire right foot to the level of the ankle joint. The dorsalis pedis and posterior tibial pulses remained strong and palpable in both feet. There was decreased sensitivity to light touch and pinprick in the involved toes, but deep pain and proprioception were intact.

* 4830 "P" Street, Sacramento, California 95819.

† Division of Orthopaedic Surgery, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78284.

By September 25, large hemorrhagic bullae had developed over the toes of both feet extending onto the dorsum of the right foot. Roentgenograms on this date did not demonstrate signs of subcutaneous emphysema or bone changes. Because of the diagnosis of coumarin necrosis, the coumarin therapy was discontinued on September 28. Heparin therapy was reinstituted, resulting in gradual resolution of the erythema and ecchymosis. Doppler ultrasound tests showed that the pulsations of the dorsalis pedis, posterior tibial, and digital arteries of the great toe were normal in both feet. There was frank necrosis of the skin of the toes with demarcation at their bases. The pain in the feet had decreased and the patient was able to walk comfortably. The patient was treated with cyclophosphamide and local irradiation for the lung carcinoma.

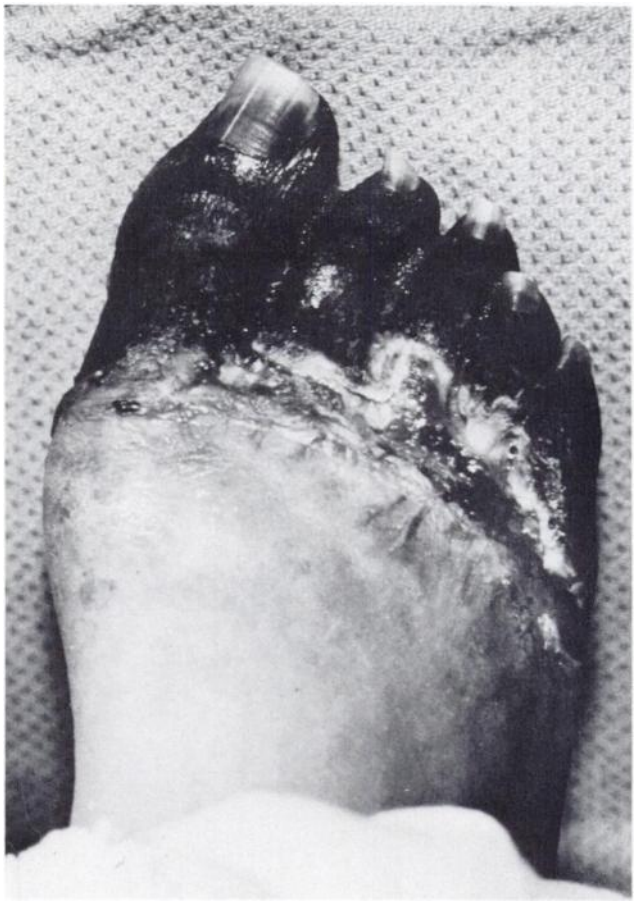

FIG. 1

The right foot of our patient, two months after the onset of coumarin necrosis. Well demarcated necrosis of the skin and soft tissues is present.

In February 1979 the patient had a successful transmetatarsal amputation of the right foot which healed without difficulty. An eschar of the left great toe was debrided at the same time. However, despite treatment, the patient's respiratory status deteriorated and he died of metastatic carcinoma on April 2, 1979.

Discussion

Twenty-five cases of this entity have been reported in the English literature to date, and in 1968 a review of the world literature showed 150 reported cases[4].

The lesion is usually seen three to ten days after beginning therapy with coumarin derivatives. Ninety-three per cent of the cases were manifest three to five days following the institution of coumarin therapy. Ninety per cent of the patients reported with this lesion were women. The average age of the patients was approximately fifty years, with a range of eighteen to ninety-three years. The lower half of the body was affected 80 per cent of the time and approximately one-fourth of the patients had lesions at multiple sites. Twenty per cent of the cases were bilateral and moderately symmetrical. Only one other case in the English literature, reported by Bahadir et al. in 1977, resulted in amputation.

The most widely held theory of pathogenesis is that a chemical toxicity directly affects the endothelial cells, initially at the dermovascular loop at the junction of the precapillary arteriole and the capillary[2]. A resulting vasodilation produces erythematous flushing, with subsequent rupture of the capillary walls producing a petechial rash. The anticoagulant then acts systemically so that the bleeding is protracted and the ecchymosis and bullae develop. Infarction and necrosis follow due to thrombosis of the venules, secondary to the stasis distal to the capillary loop[2].

Other causal mechanisms have been suggested[2], chief among which are hypoprothrombinemia and a hypersensitivity reaction. Hypoprothrombinemia is unlikely because no generalized hemorrhagic lesions are present, and the prothrombin time is typically in the therapeutic range.

The postulated hypersensitivity is supported by several findings[6]. The lesions seem to occur more commonly after the second course of coumarin therapy rather than after the first. Also, there is a histological as well as a clinical resemblance between these lesions and the lesions of the Schwartzmann phenomenon. Some findings do not support the hypersensitivity explanation[2]. Subcutaneous injections of coumarin derivatives in affected patients have revealed negative results and there have not been any consistent findings of an allergic vasculitis.

The currently accepted treatment of the lesions is immediate discontinuation of the coumarin therapy and the initiation of intravenous administration of heparin in high doses[5]. This treatment may or may not be effective in stopping the progression of the lesion, depending on the stage at which the lesion is diagnosed. Unless the treatment is begun early, the lesions will follow their natural course, as was evident in our patient. With progression to gangrene, escharectomy and skin-grafting should be considered rather than amputation, as the necrosis usually is superficial and the deeper tissues remain viable.

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