Skin Necrosis Induced by Coumarin Congeners

Skin necrosis resulting from use of oral anticoagulants is well documented but not necessarily well known. I present here the salient features of this potentially devastating and sometimes fatal drug reaction and show images of representative lesions in 2 women under my care.

Some authors refer to this condition as “coumarin-induced skin necrosis.” \(^1\) - \(^8\) The term is inappropriate because coumarin itself has no anticoagulant properties, even when given in large doses over prolonged periods. \(^2\) Coumarin, however, is the parent compound of congeners that are responsible for skin necrosis: bishydroxycoumarin (dicumarol), phenprocoumon, acenocoumarol (nicoumalone), fluindione, and warfarin sodium (Coumadin\(^\text{®}\)). \(^10\) - \(^14\) Of these, warfarin is the one most widely used. Hence, most of the reports on anticoagulant-induced skin necrosis involve warfarin. \(^10\) - \(^15\) - \(^20\) In this editorial, we will refer to skin necrosis induced by coumarin congeners as SNICC.

Salient Features

Incidence
This reaction reportedly affects 0.01% to 0.1% of patients who are taking warfarin or some other coumarin congener. \(^4\) - \(^11\) - \(^14\) - \(^18\) By 2000, more than 300 cases had been identified worldwide. \(^20\)

Demographics
Victims of SNICC have ranged in age from 16 years to 93 years \(^13\) and are chiefly women (75% of the cases). \(^14\) Deep vein thrombosis, pulmonary embolism, and various types of heart disease are the reasons for anticoagulation. There is no relation to race, ethnicity, or comorbid disease. \(^15\)

Presentation
Skin necrosis induced by coumarin congeners is unpredictable, begins suddenly, and almost always occurs within the first 10 days of therapy, especially on days 3 to 6. \(^1\) - \(^4\) - \(^11\) - \(^14\) - \(^18\) - \(^21\) - \(^22\) It has occurred, however, after only 4 hours \(^4\) or after 15 years \(^8\) of warfarin administration. One patient had 5 separate episodes over a 6-month period. \(^5\)

Pain and redness herald the characteristic lesion. The redness quickly spreads, petechiae emerge, and a dark-reddish plaque develops, surrounded at times by a reddish halo. \(^4\) - \(^15\) - \(^29\) The lesion might stabilize at this point and heal completely with conservative care, or it might progress within hours to necrosis with bullous formation (Fig. 1). An eschar then forms and ultimately sloughs, leaving a soft-tissue defect. Healing with scarring might take place on its own or need surgical intervention. \(^4\) - \(^15\) - \(^18\)

Sites are random but usually involve areas with abundant subcutaneous tissue, such as the breast, abdomen, buttocks, and thighs. \(^3\) - \(^4\) - \(^11\) - \(^15\) - \(^13\) Other sites include the arms, \(^15\) - \(^25\) hands, \(^15\) - \(^25\) - \(^27\) feet, \(^1\) - \(^4\) - \(^13\) - \(^15\) - \(^18\) - \(^26\) - \(^22\) extremities, \(^3\) - \(^6\) - \(^13\) - \(^15\) nose, \(^15\) and penis. \(^16\) Single lesions are most prevalent. In approximately one third of the cases, however, lesions are multiple and asymmetric. \(^4\) - \(^11\) Occasionally, they are symmetric. \(^4\) - \(^11\) - \(^24\)

Histopathology
Little is known about the changes that take place before necrosis develops. In one case, however, biopsy of an early, nonnecrotic, purpuric lesion showed evidence consistent with leukocytoclastic vasculitis. \(^11\) Almost all other biopsy specimens have been taken later from distinctly necrotic areas. Those specimens have shown infarction of the
skin and subcutaneous tissue with thrombi in the capillaries, venules, and small veins.\textsuperscript{11,15} Vascular inflammation and arterial involvement are routinely absent.\textsuperscript{11,15,20} Curiously, some of these specimens have shown islands of normal tissue within zones of frank gangrene.\textsuperscript{4,13,20}

**Diagnosis**

During the first 10 days of therapy with a coumarin congener, the abrupt onset of a painful red skin lesion that becomes necrotic within hours is essentially pathognomonic of SNICC.

Conditions that might mimic SNICC include calciphylaxis, septic and cholesterol emboli, heparin-induced skin necrosis, disseminated intravascular coagulation, purpura fulminans, necrotizing fasciitis, cryoglobulinemia, decubitus ulcer, snake venom–induced skin necrosis, inflammatory breast cancer, and antiphospholipid antibody syndrome.\textsuperscript{11}

**Pathogenesis**

In spite of numerous theories and decades of investigation, the exact cause of SNICC is still a mystery. Clearly, however, it is not dose-dependent, has no allergic basis, does not result from trauma, and bears no link to the Arthus phenomenon or Shwartzman reaction.\textsuperscript{1,13} The popular hypothesis that coumarin congeners are themselves toxic to the vascular endothelium of the skin lacks convincing proof.\textsuperscript{1,2,4,13,20}

Probable contributory factors (whose precise roles remain ill-defined) include congenital or acquired deficiencies of protein C, protein S, and antithrombin III,\textsuperscript{3,6,8,10,14,21} G20210A mutation of the prothrombin gene,\textsuperscript{19} and heparin-induced thrombocytopenia.\textsuperscript{11,23,24}

**Treatment**

Ordinarily, the first step in the management of an adverse drug reaction is to withdraw the offending agent. But SNICC is far from ordinary, and there is little evidence that withdrawing the drug alters the clinical course.\textsuperscript{18} In fact, continuing this therapy without interruption, or stopping it and then starting it again with the same or different congener, does not necessarily affect established lesions or cause new ones to form.\textsuperscript{2,4,10-12}

Nevertheless, when long-term anticoagulation is essential for a victim of SNICC, using one of the new oral anticoagulants might be advisable.\textsuperscript{27,28}

Some authors have recommended stopping the oral anticoagulant, replacing it with intravenous or subcutaneous heparin, and reversing the effects of the congener by administering vitamin K, fresh-frozen plasma, or both.\textsuperscript{4,11,16,18,21,23,24,26} In addition, if the original anticoagulant is to be restarted, it should be given without a loading dose and in small, incremental amounts until a therapeutic international normalized ratio has been reached. At that point, the heparin can be discontinued.\textsuperscript{10,21,22}
Other treatment options depend on the specific aspects of the individual case. For example, if the lesion does not become necrotic, or if the necrotic process naturally stops at an early stage, conservative care and diligent monitoring will suffice. But if the necrosis becomes fully developed, it might need debridement, resection (breast), skin grafting, or amputation of affected extremities. Use of fibrinolytic agents, corticosteroids, and sympathetic nerve block has not shown benefit.4,13

Sites.11,21,23 Use of fibrinolytic agents, corticosteroids, is indicated to control or eradicate infection of involved lesions when multiple courses of therapy with coumarin congeners continue without interruption; and (5) unpredictability of a victim’s susceptibility to new SNICC remains poorly understood. Some of its features continue to baffle investigators and defy explanation:1) unpredictable sites of skin involvement; 2) sporadic presence of normal skin within zones of gangrenous necrosis; 3) occasional occurrence of symmetric lesions and a more frequent occurrence of multiple asymmetric lesions; 4) no exacerbation or impaired healing of established lesions when therapy with coumarin congeners continues without interruption; and 5) unpredictability of a victim’s susceptibility to new lesions when multiple courses of therapy with coumarin congeners are given. These enigmas exemplify the longstanding inability to decode the precise mechanism of SNICC.

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References

