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Leukocytoclastic Vasculitis: Another Coumarin-induced Hemorrhagic Reaction

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A 67-year-old male developed a hemorrhagic eruption 4 weeks after initiation of coumarin therapy. Examination revealed a well-demarcated, purple patch with a central hemorrhagic bulla on the anterior aspect of the leg, surrounded by small petechiae. Histological examination of the purple plaque revealed leukocytoclastic vasculitis. It is suggested that leukocytoclastic vasculitis be considered in the differential diagnosis of coumarin-induced hemorrhagic reactions. ***Key words: Purpuric eruption; Coumarin-induced necrosis.***

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Purpuric eruptions attributed to coumarin therapy include petechiae and ecchymoses due to prolonged prothrombin time, coumarin necrosis (1–3), the purple toe syndrome (4–6) and acral purpura (7). We present a case of coumarin-induced hemorrhagic eruption resulting from cutaneous vasculitis. To the best of our knowledge there has been no previous mention of this association in the literature.

CASE REPORT

A 67-year-old man was admitted to our department in July 1992 because of a painful purple rash of 3 days' duration on the anterior aspect of the left leg and foot. Metastatic adenocarcinoma of the rectum had been diagnosed one year earlier, for which the patient underwent an anterior resection in July 1991, followed by 5 months of chemotherapy. A large intestinal anastomosis with transverse loop colostomy was performed in June 1992 because of a large bowel obstruction. Neoplastic dissemination of the tumour was noted throughout the abdominal cavity and perineum. A few days after the operation, the patient's left calf became swollen and tender. Deep vein thrombosis was suspected and coumarin (warfarin sodium) therapy was initiated. Four to 5 weeks later a 15 × 10 cm painful purple patch surrounded by ecchymoses developed on the anterior aspect of the leg, and a purpuric rash appeared on the dorsum of both feet and toes.

Remarkable findings on physical examination at admission included pitting edema on both lower extremities, more pronounced on the left side, and 7 cm greater diameter of the left than the right calf. Laboratory results showed hemoglobin 9.2 g/dl, hematocrit 28%, and white blood count 15,000/mm^3. Other blood chemistry values, including platelet count, prothrombin time and partial thromboplastin time, were within normal limits.

A day later after admission a few hemorrhagic vesicles developed on the purple patch of the leg (Fig. 1). Venous doppler revealed bilateral deep femoropopliteal vein thrombosis. Coumarin was discontinued and IV heparin was given, resulting within 4 days in fading of the purple plaque and disappearance of the ecchymoses and purple discoloration of the foot and toes. None of the bullae progressed to skin necrosis. A biopsy specimen taken from the purple plaque adjacent to a hemorrhagic bulla showed leukocytoclastic vasculitis with nuclear dust (Fig. 2). There was no evidence of capillary plugging with fibrin thrombi.

DISCUSSION

Cutaneous complications associated with warfarin-related agents include hemorrhagic complications, macular, papular, purpuric or vesicular eruptions (8–10), urticaria (11) and the purple toe syndrome (4–6). Warfarin-induced necrosis was first reported in 1943 (1), and since then numerous reports have been published (2, 3).

Our patient showed some of the clinical and morphological features of coumarin-induced necrosis, namely, a patchy, bright erythematous lesion that quickly expanded and evolved into a purple plaque with a central hemorrhagic bulla (1–3). However, our case differed from coumarin-induced necrosis in many aspects. It developed 4–5 weeks after coumarin administration, while previously reported cases invariably developed between the 2nd and 10th day following initiation of anticoagulant

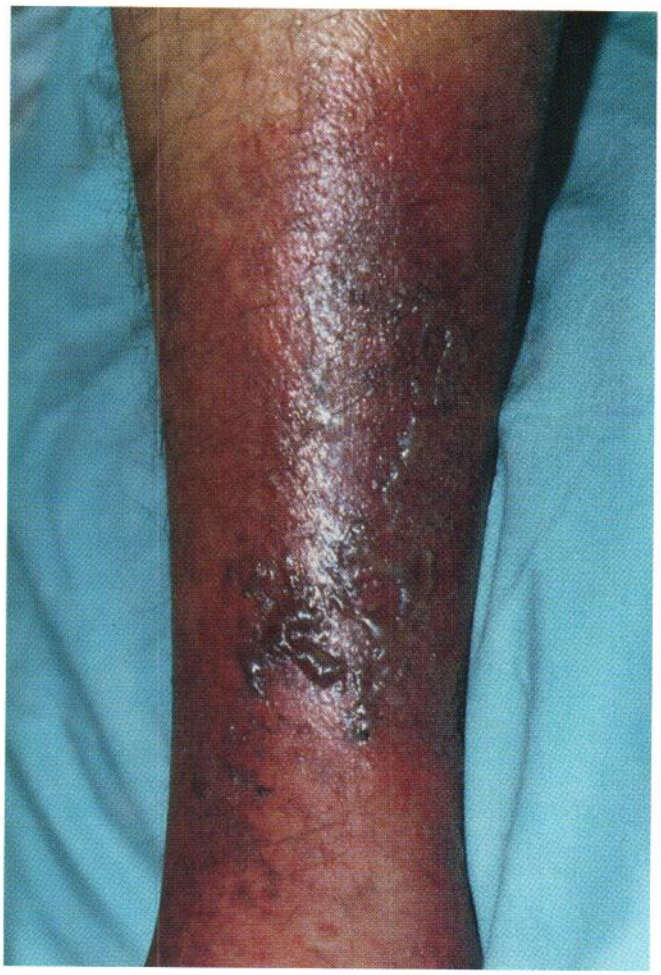

Fig. 1. Purpuric eruption on the anterior aspect of the leg and foot, with central hemorrhagic bullae.

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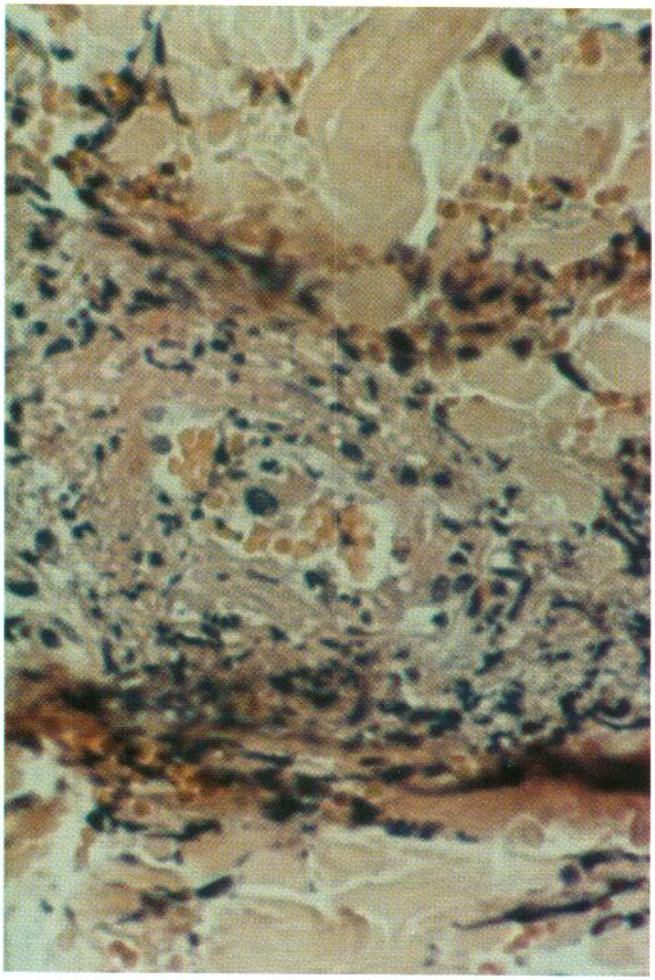

Fig. 2. Fibrinoid necrosis of dermal blood vessels, surrounded by acute inflammatory infiltrate composed mainly of neutrophils and nuclear dust.

therapy, with more than 90% of the lesions appearing on the 3rd to 5th day. Until now, only one case with a longer incubation period has been reported (12). The lesion appeared on the shin and foot in our patient, while coumarin-induced necrotic skin lesions are bilateral and occur in areas of abundant subcutaneous fat, such as on the breasts, buttocks and abdomen. The disease lasted only a few days in our patient, in contrast to the prolonged healing time of several months in coumarin-necrosis. The discrepancy in healing time might be due to the lack of deep subcutaneous fat necrosis in our patient.

Histologically, our patient showed leukocytoclastic vasculitis without any evidence of fibrin thrombi. The lesions of coumarin-induced necrosis, on the other hand, are characterized by extensive occlusion of dermal and subcutaneous vessels with fibrin and platelets forming thrombi (3). This dermovasculature occlusion with secondary distal hemorrhage and infarct is the most widely accepted theory for the pathogenesis of warfarin necrosis. The fundamental differences between our patient and coumarin-induced skin necrosis led us to speculate that our patient represents a form of coumarin-induced cutaneous vasculitis. It is noteworthy that several days after the appearance of the hemorrhagic lesion, more purpuric lesions characteristic of cutaneous vasculitis appeared on the patient's leg. The differential diagnosis between this entity and coumarin-induced necrosis is of theoretical and practical importance.

Another adverse cutaneous reaction to coumarin that should be considered in the differential diagnosis is the purple toe syndrome (4–6), first described by Feder & Auerbach in 1961 (4). The 3- to 8th-week onset following the initiation of oral anticoagulant therapy resembles our case, but the clinical and histological pictures of these two conditions are entirely different. Purple toe syndrome consists of bilateral, tender, purple discoloration on the plantar surfaces and sides of the toes which, unlike in our patient, blanches on moderate pressure and partially fades upon elevation of the feet. Biopsy examination of this syndrome is usually unremarkable in contrast to the vasculitis observed in our case.

To the best of our knowledge, leukocytoclastic cutaneous vasculitis has never been reported as an adverse reaction to coumarin and should be considered in the differential diagnosis of any coumarin-induced purpuric eruption.

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