

Anogenital skin necrosis with fibrin thrombosis induced by crotamiton

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Crotamiton (CAS no. 483-63-6) is widely used to treat pruritus and scabies. We report two peculiar cases of severe anogenital skin necrosis with fibrin thrombosis caused by a crotamiton-containing cream.

CASE REPORTS

A 72-year-old Japanese man (Patient 1) was prescribed a topical crotamiton-hydrocortisone cream (Eurax H Cream; Nissin Pharmaceutical, Yamagata, Japan) to soothe perianal slight pruritic erythema. Despite 1 month of this topical treatment, the perianal skin became severely inflamed and formed an ulcer with purpura (Figure 1A,C). Biopsy specimens of the perianal purpura revealed partial epidermal necrosis, multiple fibrin thrombi with blood cell extravasation, and perivascular infiltration of inflammatory cells in the upper dermis (Figure 1B). The skin ulcer recovered 1 month later with moist wound-care dressing. He had been treated for hypertension and hyperlipidaemia but had no medical history suggesting coagulation defects. Protein C, protein S, anti-cardiolipin, and anti- β 2GPI antibodies were negative.



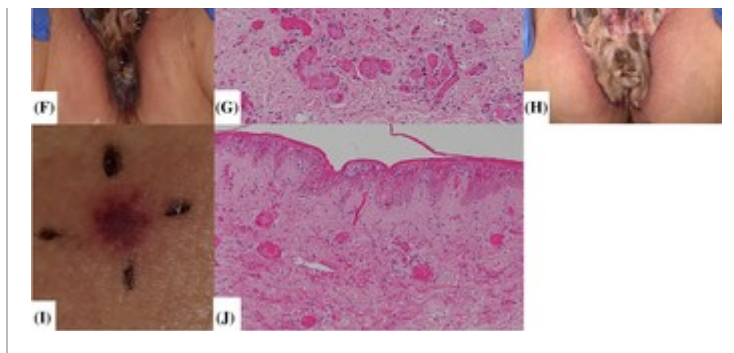


FIGURE 1

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Patient 1: **(A)** Clinical finding at the first visit. Purpura and ulcer in the perianal area. **(B)** Skin biopsy (haematoxylin and eosin [H&E] stain). Microvenous thrombosis in the dermal papillae and extravasation of blood cells and perivascular inflammatory cells in the dermis. **(C)** Clinical finding 7 days after the first visit. Ulcer and yellowish necrosis in the perianal area. **(D)** Patch test with the Eurax H Cream at D2 revealed purpura, mimicking the perianal area. **(E)** Skin biopsy at D2 from the patch test area (H&E stain). Microvenous thrombosis in the dermal papillae and extravasation of blood cells. Patient 2: **(F)** Clinical finding at the first visit. Purpura and ulcer in the genital and perianal areas. **(G)** Skin biopsy taken from genital purpura (H&E stain). Microvenous thrombosis in the dermal papillae and extravasation of blood cells and perivascular inflammatory cells in the dermis. **(H)** Clinical findings 7 days after the first visit. Brownish and yellowish necrosis with ulcer in the genital and perianal areas. **(I)** Patch test with the Eurax Cream 10% at D2 revealed purpura. **(J)** Skin biopsy at D2 from the patch test area (H&E stain). Microvenous thrombosis in the dermal papillae and extravasation of blood cells

A 90-year-old Japanese woman (Patient 2) with a 2-week history of a genital ulcer had used a crotamiton-containing cream (Eurax Cream 10%; Nissin Pharmaceutical) for genital pruritus without eruption for an unknown period before ulceration. Severe necrosis with ulcer and purpura were observed in the genitals (Figure 1F,H). The histological findings from the purpura biopsy specimens were similar to those of Patient 1 (Figure 1G). She had been treated for high blood pressure, type 2 diabetes, and hyperuricemia. Blood tests showed no coagulation defects. The skin ulcer recovered 4 months later with moist wound-care dressing. Both patients had no medical history of atopic dermatitis or allergy to specific agents.

We performed closed-patch tests for the creams “as is” and their ingredients for both patients, using patch testers (Torii Pharmaceuticals, Tokyo, Japan). Patch testers were removed at day (D) 2, and the reaction was evaluated at D2, 3, and 7 (Table 1). The patch testing result from the Eurax H Cream “as is” for Patient 1 and Eurax Cream 10% “as is” for Patient 2 revealed purpura at D2 (Figure 1D,I). The histopathological findings of the patch test areas were identical to those of anogenital purpura (Figure 1E,J). Fibrin thrombi were confirmed by phosphotungstic acid–haematoxylin staining. In the patch tests of the ingredients, results of both patients revealed purpura at D2 with crotamiton (5% pet.), whereas the other tested ingredients of the Eurax Cream 10% and Eurax H Cream showed

no reaction at D2, 3, or 7. Patient 1's patch test area subsequently developed an ulcer at D7 and re-epithelized within a week.

TABLE 1. Results of the patch testing for the creams and their ingredients

Patient 1	Name	Test site	D2	D3	D7
Causative cream	Eurax H Cream “as is”	Buttock; intact nonlesional skin	Purpura	Purpura	Ulcer
Tested ingredients contained in the causative cream ^a	Crotamiton (5% pet.)	Upper arm	Purpura	Purpura	Purpura
	Perfume PCV45		—	—	—
	Methyl parahydroxybenzoate		—	—	—
	Propyl parahydroxybenzoate		—	—	—
	Stearyl alcohol		—	—	—
	Polyoxyl 40 stearate		—	—	—
	Propylene glycol		—	—	—
	Hydrocortisone		—	—	—
Patient 2	Name	Test site	D2	D3	D7
Causative cream	Eurax Cream 10% “as is”	Upper back	Purpura	Purpura	Purpura
Tested ingredients contained in the causative cream	Crotamiton (5% pet.)	Upper back	Purpura	Purpura	Purpura
	Perfume PCV45 (0.1% aq.)		—	—	—

^a Information on test concentrations and test vehicles of the ingredients other than crotamiton was not retrievable from the medical records.

DISCUSSION

Crotamiton is a very-low toxic and rarely sensitizing drug and has thus been used to treat scabies and various pruritic disease.^{1, 2} The characteristic finding of our patients was severe skin ulcer with fibrin thrombosis in the anogenital area. Their patch test results confirmed that crotamiton was the causal factor. The patients' clinicopathological findings and patch test results are inconsistent with those of allergic contact dermatitis and typical irritant dermatitis.³ The unique histological changes may indicate that the initial formation of fibrin

thrombi by crotamiton causes severe ischemic change and subsequent epidermal damage.

We applied patch tests for crotamiton in three healthy volunteers; however, no reaction was observed. Our patients' results suggest that fibrin thrombosis induced by crotamiton depends on the patient's personal constitution.

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AUTHOR CONTRIBUTIONS

Yuji Kan: Supervision (equal). **Tokimasa Hida:** Supervision (equal). **Tomoyuki Minowa:** Supervision (equal). **Yasuyuki Sumikawa:** Supervision (equal). **Hisashi Uhara:** Supervision (equal); writing – review and editing (equal).

CONFLICTS OF INTEREST

There are no conflicts of interest.

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