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## Tache and talon noir in patient with mycosis fungoides on acitretin

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To the Editor:

Acitretin, an oral synthetic retinoid, is commonly used for systemic therapy of mycosis fungoides (MF). It can cause a variety of cutaneous adverse reactions including but not limited to xerosis, nail dystrophy, and alopecia. Acitretin-induced hemorrhage is a rare, newly reported adverse effect and has been seen in patients with psoriasis, Darier disease, and MF [1-4]. Herein, we report a case of tache and talon noir in a patient with MF treated with acitretin.

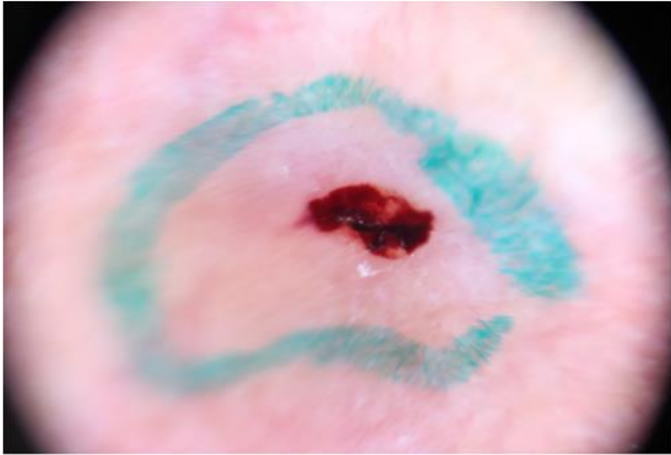
A 93-year-old man with longstanding plaque-stage MF on 50mg of acitretin daily for 2.5 years presented for evaluation of a new-onset rash on the extremities. This was noted 6 weeks after re-initiation of narrowband UVB treatment, which had been held due to the COVID-19 pandemic. On examination, many dark red and black macules were noted on the dorsal and volar hands and the dorsal and plantar feet (**Figure 1**). Similar macules were also present on the forearms, shins, and subungual toes. A punch biopsy of the right dorsal hand revealed

subepidermal fibrin and hemorrhagic scale in the cornified layer of the epidermis in the setting of perivascular and interstitial inflammation with eosinophils in the dermis (**Figures 2, 3**). No evidence of vasculitis or thrombosis was noted. Given previous reports of acral hemorrhage in those treated with acitretin, the dosage of acitretin was decreased to 35mg daily with interval improvement of hemorrhagic macules.

Cutaneous hemorrhage in the setting of acitretin use is a rare phenomenon [1-4]. Six cases of acitretin-induced hemorrhage have been reported, all of which involved acral sites (**Table 1**), [1-4]. In one patient with psoriasis, subungual hemorrhagic macules were seen. In those with Darier disease, hemorrhagic vesicles, bullae, and macules were observed. The relationship between acitretin and acral hemorrhage was supported by lesion regression with cessation of acitretin treatment and in some cases by recurrence following rechallenge



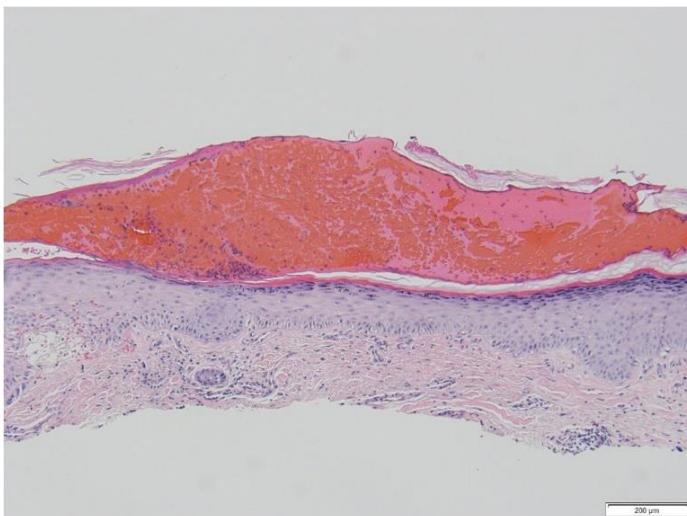
**Figure 1.** Dark red and black macules on **A)** dorsal foot, **B)** dorsal hand, and **C)** volar hand.



**Figure 2.** Punch biopsy site on right dorsal hand.

[1,3,4]. In patients with MF, hemorrhagic macules were also seen distributed along acral areas. One patient also developed hemorrhagic macules on the breast [2]. These lesions are asymptomatic and can be treated through dose reduction or cessation of acitretin [1,2].

The acral hemorrhage seen in our patient is most likely tache and talon noir given the punctate brown-black macules and petechiae on the patient's hands and feet [5,6]. This diagnosis is further supported by well-established histologic features of focal and pooling hemorrhage within the stratum corneum. Tache and talon noir typically occurs due to repeated trauma and shearing forces on palmar and plantar



**Figure 3.** Punch biopsy of the right dorsal hand showing subepidermal fibrin and hemorrhagic scale in the cornified layer of the epidermis in the setting of perivascular and interstitial inflammation with eosinophils in the dermis. H&E, 20x.

surfaces respectively [6]. Superficial desquamation from acitretin can cause skin fragility, which in the setting of microtrauma, can produce the seen tache and talon noir [2]. Since this skin fragility is not limited to palmar and plantar surfaces, it accounts for the involvement of dorsal surfaces in our patient. Another important diagnosis to consider are pyogenic granulomas, a rare side effect reported with acitretin use [7]. These benign vascular proliferations on cutaneous tissues can bleed due to trauma; however, the ulcerated lobules of capillaries and inflammatory cells commonly seen on histology do not fit the pathologic findings of this case.

Although acitretin-induced skin fragility is one possible explanation for the exhibited sub-corneal hemorrhage, the pathogenesis of acitretin-induced hemorrhage remains unclear. Trans-retinoic acids are known to promote gene transcription of vascular endothelial growth factor which consequently modifies permeability of endothelial cells [8]. In Darier disease, empty intraepidermal lacunae form due to loss of adhesion between epidermal cells in the setting of abnormal keratinization [4]. Zavattaro et al. suggested that increased endothelial permeability induced by oral retinoids aids in the accumulation of serum and erythrocytes in the formed lacunae, producing the seen hemorrhagic vesicles and macules [4]. It is important to note that patients with MF were often concomitantly treated with phototherapy (psoralen ultraviolet A or narrowband UVB during the course of acitretin administration. However, phototherapy is unlikely to be implicated in the pathogenesis since it is usually not associated with skin hemorrhage (apart from severe photodamage and solar purpura), and cessation of acitretin produced lesion regression despite continuation of phototherapy [2].

We report a patient with acitretin-associated tache and talon noir occurring in the treatment of a patient with MF. Clinicians should be aware of this rare side effect of treatment which may necessitate modulation of therapy.

### Potential conflicts of interest

The authors declare no conflicts of interest.

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**Table 1.** Clinical features of acitretin-induced acral hemorrhage.

Source	No. of patients	Age/Sex	Diagnosis	Therapy-Duration	Site of acral hemorrhage	Histopathology	Regression after cessation of acitretin
Presented patient	1	93/M	Mycosis Fungoides (plaque stage)	Acitretin (50mg/day) 2.5 years, NB-UVB 1.5 months	Dorsal volar hands, dorsal plantar feet, subungual toes, forearms, shins	Extravasated erythrocytes in the papillary dermis, subepidermal fibrin, hemorrhagic scale in the stratum corneum, perivascular and interstitial inflammation with eosinophils in the dermis	+ <sup>a</sup>
Baykal et al. 2017 [2].	3	75/M	Mycosis Fungoides (folliculotropic)	Acitretin (35mg/day) 7 months, PUVA 9 months	Palms, heels	Extravasated erythrocytes in the stratum corneum, mild spongiosis, nonspecific superficial inflammation	? <sup>b</sup>
		48/F	Mycosis Fungoides (plaque stage)	Acitretin (25mg/day) 3 months, PUVA 4 months	Heel, breast	N/A	+
		69/F	Mycosis Fungoides (tumor stage)	Acitretin (25mg/day) 2 weeks, PUVA 3 months, Systemic interferon-alpha 2 months	Palm	N/A	+
Aydogan et al. 2007 [1].	1	20/F	Psoriasis	Acitretin (35mg/day) 1 month	Subungual fingers	N/A	+ <sup>c</sup>
Zavatarro et al. 2014 [4].	1	84/F	Darier disease	Acitretin (25mg/day) 4 months, (12.5mg/day) 3 months	Palmoplantar dorsal aspect of fingers	Subcorneal hemorrhagic vesicles, hyperkeratosis, acanthosis, papillomatosis, hypergranulosis, and dyskeratosis	+ <sup>c</sup>
Nguyen et al. 2018 [3].	1	40/M	Darier disease	Acitretin (30mg/week) 1 month, triamcinolone 0.02% cream (PRN)	Palmoplantar dorsal aspect of hands and feet	Suprabasal bullae with erythrocytes and neutrophils, no acantholysis, mild spongiotic dermatitis with an intraepidermal bullae, extravasated erythrocytes in superficial keratotic debris	+

+, regression occurred; ?, unclear if regression occurred; F, female; M, male; N/A, not applicable; NB-UVB, narrowband ultraviolet B; No., number; PRN, pro re nata, medication taken as needed; PUVA, psoralen ultraviolet A.

<sup>a</sup>Acitretin therapy was not ceased but dose decrease to 35mg/day improved hemorrhagic macules.

<sup>b</sup>Patient was lost to follow up. Baykal et al. noted that dose decrease to 25mg/day produced lesion regression but new ones formed, leading to cessation of therapy [2].

<sup>c</sup>Rechallenge with acitretin reproduced lesions.