Letter to the Editor Calcinosis cutis in epidermal necrolysis: role of caspofungin?

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Letter to the Editor
Calcinosis cutis in epidermal necrolysis: role of caspofungin?

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Toxic epidermal necrolysis (TEN) is a rare life-threatening condition, usually drug-induced, characterised by a diffuse epidermal and mucosal detachment. Skin histology reveals pan epidermal necrolysis. Mucocutaneous healing usually lasts 2 to 3 weeks.[1] Calcinosis cutis is reported in various skin diseases, with dystrophic calcification following tissue damage being its most common cause.[2] We describe four patients who presented TEN and atypical healing retardation due to calcinosis cutis.

Between 2015 and September 2021, four patients, three males and one female, aged from 40 to 59 years-old, were diagnosed with TEN, idiopathic or following intake of ibuprofen, pantoprazole, and allopurinol respectively. Three to 22 days following the beginning of cutaneous healing, they presented a secondary cutaneous detachment with atone fibrinous plaques (Fig. 1). A new biopsy revealed in the four cases calcium deposition in the superficial dermis and in the epidermis (Fig. 2A). Ionized serum calcium and phosphate levels were normal. One patient died without healing, whereas complete healing was slowly obtained within 5.5 and 11 months for two patients, and is still ongoing for one.

To investigate the origin of these cutaneous calcifications, osteogenic markers, assessed by immunohistochemistry were performed in three patients. Results were negative on keratinocytes and fibroblasts, making unlikely trans-differentiation of these cells to an osteochondrogenic phenotype, a mechanism frequently suspected in calciphylaxis.[3] µFourier transform infra-red spectroscopy revealed that calcifications consisted of apatite, a classic component of dystrophic skin calcifications observed in other diseases.[2,4] Field emission scanning electron microscopy revealed that the ultrastructure of these skin calcifications consisted of small spherical entities of 500 nm aggregating into voluminous plaques (Fig. 2B, 2C and 2D), as previously described in other ectopic calcifications.[5] These spherical entities were also identified within the papillary dermis (Fig. 2E and 2F). Calcium-phosphate nature of these entities was confirmed by energy dispersive x-ray spectroscopy.

Reviewing the medical chart, we found that the four patients were treated with caspofungin for invasive fungal infection to *Candida parapsilosis*, *Candida lusitaniae*, *Candida albicans* or non-documented septic shock one to eight days before the secondary epidermal detachment. Among the 130 patients with Stevens-Johnson syndrome or TEN referred in our center between 2015 and 2021, four other patients with TEN received caspofungin: three died in the following days without any dermatological examination. In the fourth case, new fibrinous plaques were described in the medical chart 4 days later, without imaging or histology performed.

We report herein four patients with TEN exhibiting calcinosis cutis after caspofungin administration. Caspofungin is an agonist of ryanodine receptor (RyR).[6,7] RyR is strongly expressed in keratinocytes and application of RyR's agonist induced intracellular calcium flux, leading to delayed cutaneous healing in a mouse model.[8] By modifying keratinocytes' calcium intracellular concentration, caspofungin might have altered the new keratinocytes at the very initial stage of cutaneous healing, explaining the presence of upper dermis and epidermal calcifications and the relapse of epidermal detachment followed by a major healing retardation. Calcifications were small spherical entities aggregated into voluminous plaques contiguous to the epidermal necrosis, made of apatite, and were not caused by trans-differentiation of the skin cells into an osteochondrogenic phenotype. Presence of calcified entities within the upper but not the deeper dermis suggests a link between local inflammation induced by TEN and calcifications, as observed in other dystrophic calcified skin diseases. Skin calcifications have also been described in other diseases associated with diffuse epidermal detachment, such as porphyria cutanea tarda and dystrophic epidermolysis bullosa.[9,10]

Liposomal amphotericin B or fluconazole might therefore be preferred for these patients in case of invasive fungal infection. Further studies regarding dermatological adverse events induced by caspofungin, especially on mucocutaneous healing, should be performed.

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Figure legends:

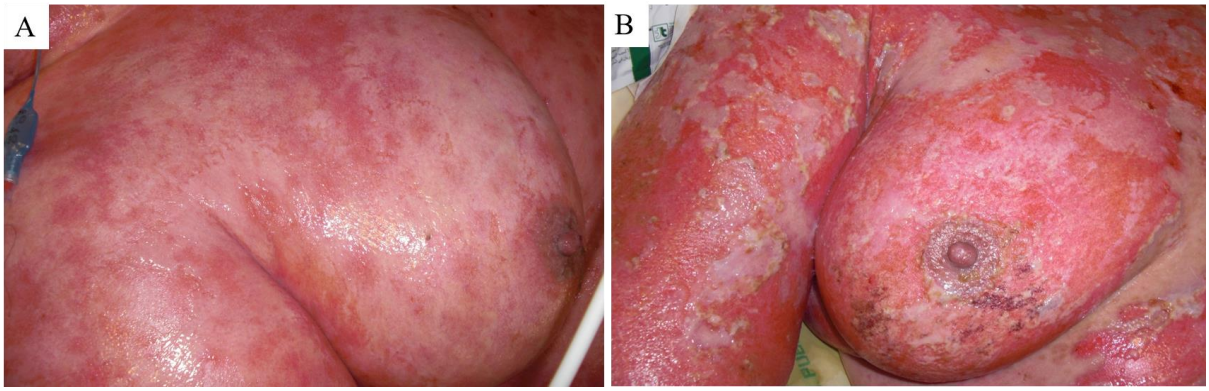

Fig. 1: Clinical presentation of one patient. A, Dermatological examination on day 12, revealing almost complete mucocutaneous healing. B, Dermatological examination on day 29, 11 days after the introduction of caspofungin, revealing diffuse epidermal detachment associated with the presence of fibrinous plaques.

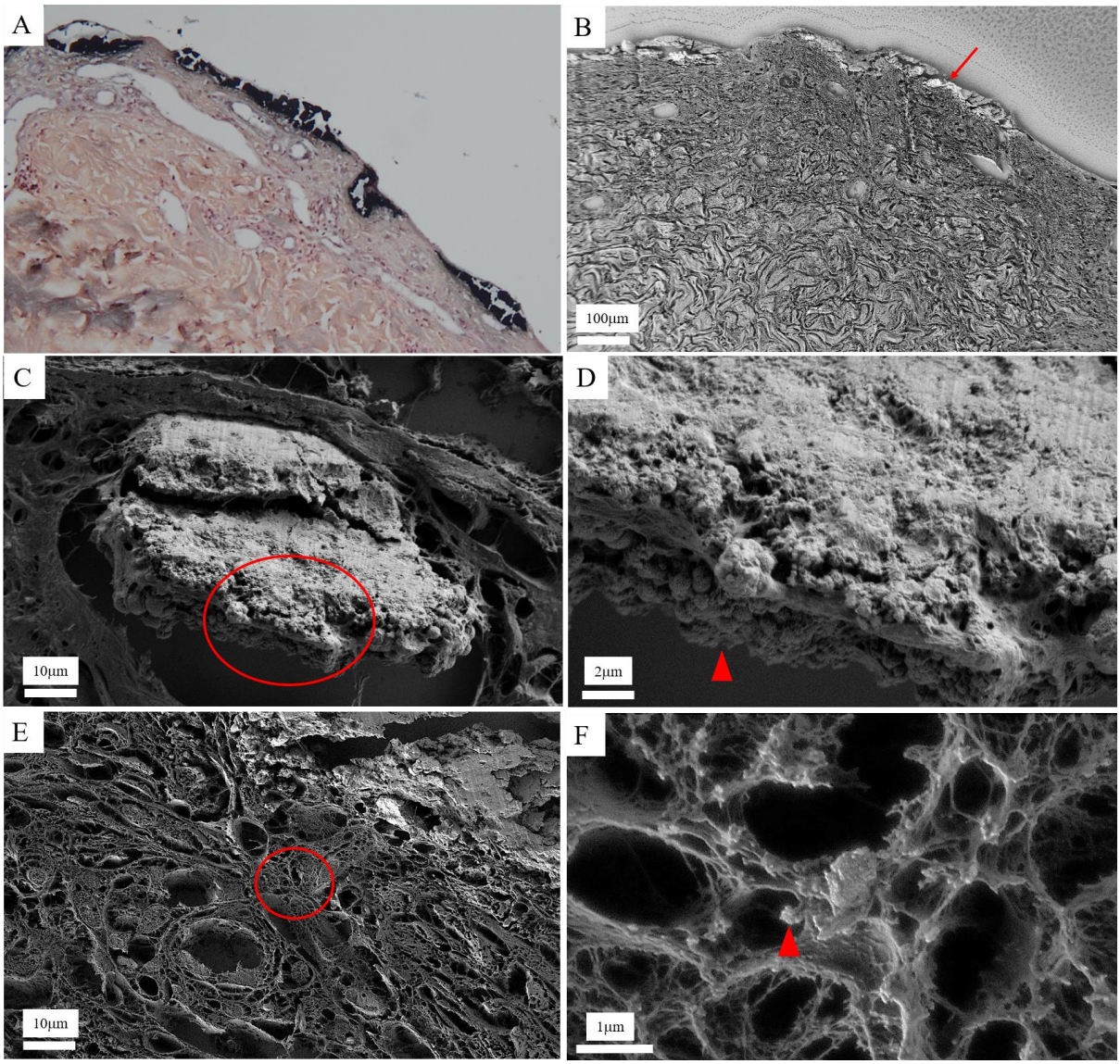

Fig. 2: Skin biopsy sections. Diffuse necrosis of the corneal layer associated with calcium deposition in the superficial dermis. A, Von Kossa staining (× 100). B, Field emission scanning electron microscopy. Arrow indicates the voluminous calcifications. C-F: Field emission scanning electron microscopy. C, The lower part of the voluminous calcification (circle) consists of many small aggregated spherical entities. D, High magnification of panel C circled area. E, Papillary dermis below voluminous calcification. F, High magnification of panel E circled area, showing many spherical calcifications within the papillary dermis.