European Journal of Dermatology
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Successful treatment of a cutaneous ulcer due to cholesterol crystal embolization with topical basic fibroblast growth factor

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Short title: Cutaneous CCE treated with bFGF
Abbreviations: Cholesterol crystal embolization (CCE), basic fibroblast growth factor (bFGF)
KEY WORDS: Cholesterol crystal embolization, foot ulcer, basic fibroblast growth factor

Funding statement: No funding

The authors have no conflicts of interest to declare.

Word count: 693/700 words in the main text, 8/10 references, 1 figure

Cholesterol crystal embolization (CCE) refers to the embolization of the contents of an atherosclerotic plaque from a proximal large-caliber artery to distal small to medium arteries, causing end-organ damage by mechanical plugging and an inflammatory response [1]. The three organ systems most commonly affected by cholesterol emboli are the kidneys, the gastrointestinal system and the skin [2]. Cutaneous CCE can occur sporadically, but is more commonly associated with iatrogenic events via invasive vascular procedures or therapies [2]. Livedo reticularis and acrocyanosis are the most frequently described cutaneous findings. Falanga *et al.* reported that ulceration is seen in 17% of cutaneous CCEs [3]. To date, there are still no specific therapies for this disorder, including for the ulceration.

In 1984, Bohlen *et al.* characterized basic fibroblast growth factor (bFGF) for the first time [4]. bFGF plays an important role in tissue repair through its *in vivo* angiogenic activity. bFGF also enhances tube formation by endothelial cells. Clinically, topical bFGF is an effective treatment, especially for decubitus and refractory leg ulcers resulting from burns [5]. In this report, we describe the successful use of topical bFGF to treat ulceration from CCE.

A man in his 70s was referred with atrial flutter to the department of internal

medicine. He received catheter ablation and coronary angiography. Approximately 24 hours later, he had continuous pain in the hip and legs. Physical examination revealed livedo reticularis on the legs and several blue toes. He did not have diabetes mellitus, trauma or any prior diseases. The laboratory test results were as follows: WBC count of 6,200/mm^3 (normal: 3,800-8,500) with 9% eosinophils (normal: 1-6%), BUN of 44.6 mg/dL (normal: 8-22), creatinine of 2.83 mg/dL (normal: 0.6-1.1) and CRP of 0.16 mg/dL (normal: 0-0.3). Histologically, cholesterol clefts within the lumen of blood vessels in the lower dermis (Fig. 1a). We diagnosed the condition as CCE and started oral prednisolone (0.5 mg/kg/day). Although the patient gradually recovered from the renal failure, he noted a painful ulcer with yellow necrosis on the left heel (Fig. 1b). It had been treated with topical antibiotic ointments that had only minimally improved the lesion. We switched to topical bFGF as a once-daily spray with a product-to-target distance of 5 cm, leading to rapid improvement (Fig. 1c) within 4 weeks, without any adverse effects. <u>According to the manufacturer, the bFGF product used here contains 250 μg bFGF in 2.5 mL solvent. (Approximately 30 μg of bFGF was sprayed per day.)</u>

Systemic therapies aim to achieve an anti-inflammatory effect, immunosuppression, improvement of the bloodstream by vasodilatation, and the stabilization of the plaque. Thus far, several reports have suggested that oral

corticosteroid treatment might be useful. In addition, there is some evidence that statin therapy decreases the risk of cholesterol embolization syndrome [1]. Recently, low-density lipoprotein apheresis with or without systemic corticosteroid has been reported as a possible treatment for skin manifestations of CCE [6]. However, we sometimes hesitate to use systemic treatments because they have several adverse effects [7]. With respect to topical therapies for cutaneous CCE, Avci *et al.* reported not being able to find widely accepted standard surgical treatments for these skin lesions [2].

In recent years, immunological factors have been considered to be involved in the progression of CCE, similar to skin manifestations in vasculitis [6]. Local inflammation and microcirculation defects caused by cholesterin crystals have been considered as a core pathogenic factor for CCE. Akita *et al.* described that local bFGF might alter the TGF-β expression pattern and thus might inhibit excessive collagen deposition as observed in hypertrophic scars or keloids under certain conditions [5]. During wound healing, TGF-β regulates not only re-epithelialization, but also inflammation, angiogenesis, and granulation tissue formation [8]. Taken together, we speculate that bFGF might exert anti-inflammatory effects by changing the TGF-β expression pattern and that bFGF promotes epithelization of cutaneous ulcers due to

CCE.

In conclusion, this is the first report of topical bFGF treatment for a cutaneous ulcer caused by CCE. Although it is difficult to evaluate its efficacy from only the present case, our finding suggests that topical bFGF might be a useful and powerful tool to accelerate epithelization and to improve quality of life for CCE patients.

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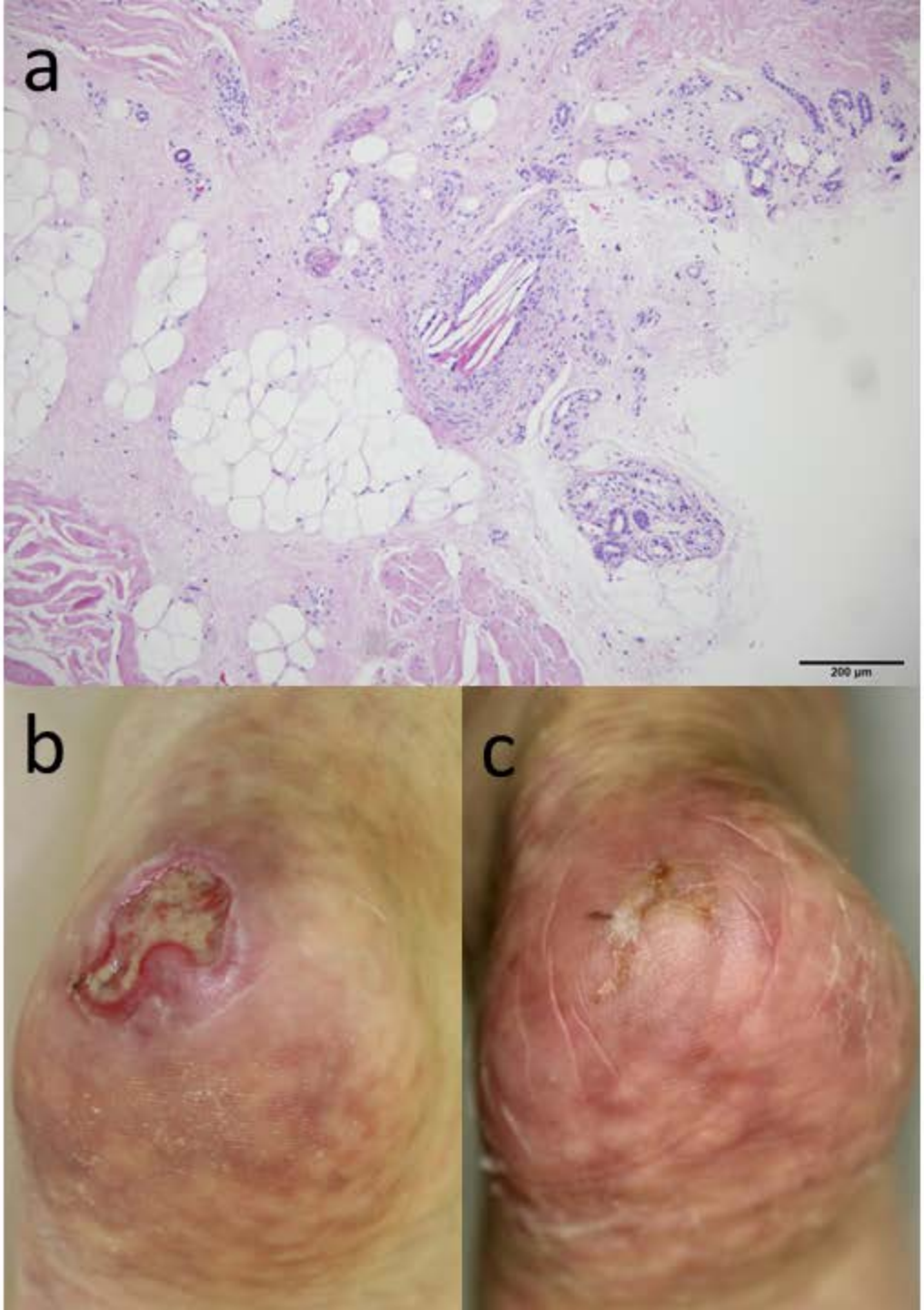
Figure legends

Figure 1. Clinical features of the patient

(a) Light microscopy of cyanotic skin from the left toe biopsy reveals cholesterol clefts within the lumen of blood vessels in the lower dermis. Scale bar: 200μm. (b) Before topical treatment with bFGF. Livedo reticularis and ulcer accompanied by yellowish necrotic tissue on the heel. (c) After 4 weeks of topical treatment with bFGF. Complete epithelization is seen.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