

Bullous Congenital Ichthyosiform Erythroderma: Safe and Effective Topical Treatment with Calcipotriol Ointment in a Child

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Sir,

Bullous congenital ichthyosiform erythroderma (BCIE), or epidermolytic hyperkeratosis (MIM# 113.800), is a rare disorder of keratinization associated with blistering in its early phase. It was first described by Jean-Louis Brocq in 1902 as *érythrodermie congénitale ichthyosiforme avec hyperépidermotrophie*. Although most cases are sporadic, familial cases show an autosomal dominant pattern of inheritance. The disorder is linked to keratin clusters on chromosome 12q and 17q (1). Several researchers have described mutations in the highly conserved regions of keratins K1 and K10 (2, 3). Moreover, transgenic mice carrying mutant K10 have developed skin abnormalities similar to BCIE (4).

Emollients are of only limited value in the treatment of BCIE, as the scales are often waxy and macerated (5). Retinoids, such as acitretin or etretinate administered systemically, are the treatment of choice in disorders of keratinization (6). However, they should be viewed with caution owing to their skeletal toxicity, especially in children and adolescents (7, 8). Effective therapies lacking significant adverse effects are therefore needed for these patients. Topical calcipotriol has been shown to be safe and effective in treating adolescent and adult patients with congenital ichthyoses (5) and other disorders of keratinization, including one

case of BCIE (5). Here, we report the safe and successful long-term (>3 years) topical therapy with calcipotriol ointment in a 9-year-old boy with BCIE.

CASE REPORT

A 9-year-old boy was first seen in September 1998 with a keratinization disorder. Immediately after birth he was diagnosed with BCIE by histology and electron microscopy at the University of Heidelberg, Germany. There was no family history of keratinization disorders. The erythroderma faded in infancy, but the scaling progressed.

On clinical examination at our clinic, the patient showed yellow-brown waxy scales with a cobblestone appearance, predominantly on the trunk and joint flexures (Figs. 1a and 2a). There were flaccid blisters and superficial erosions in the groin. The central face and scalp were only mildly affected, without alopecia. Body odour was occasionally noted by the patient's mother.

Emollients, including ointments with glycerol and urea, failed to improve the condition. Since the patient suffered considerable psychological distress and did not improve with standard topical treatment, he was offered an experimental approach. His parents consented

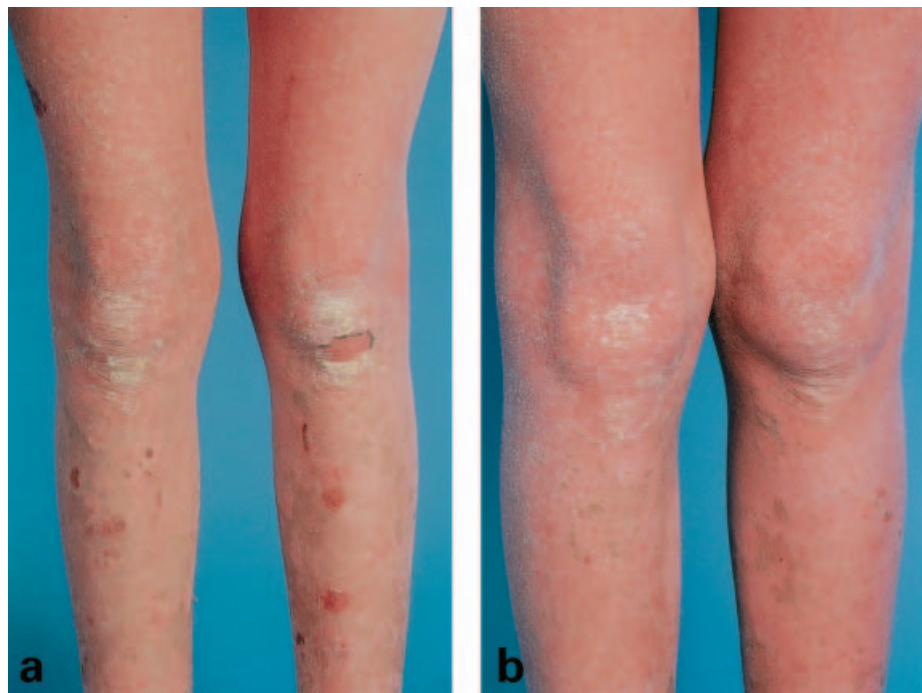


Fig. 1. Patient with verrucous plaques and tender erosions over bony prominences before topical treatment (a) and after 3 weeks of topical treatment with calcipotriol ointment (left leg) and tretinoin ointment (right leg) (b). Substantial improvement of scaling and erosions was observed on both legs, but more marked on the calcipotriol-treated left leg.

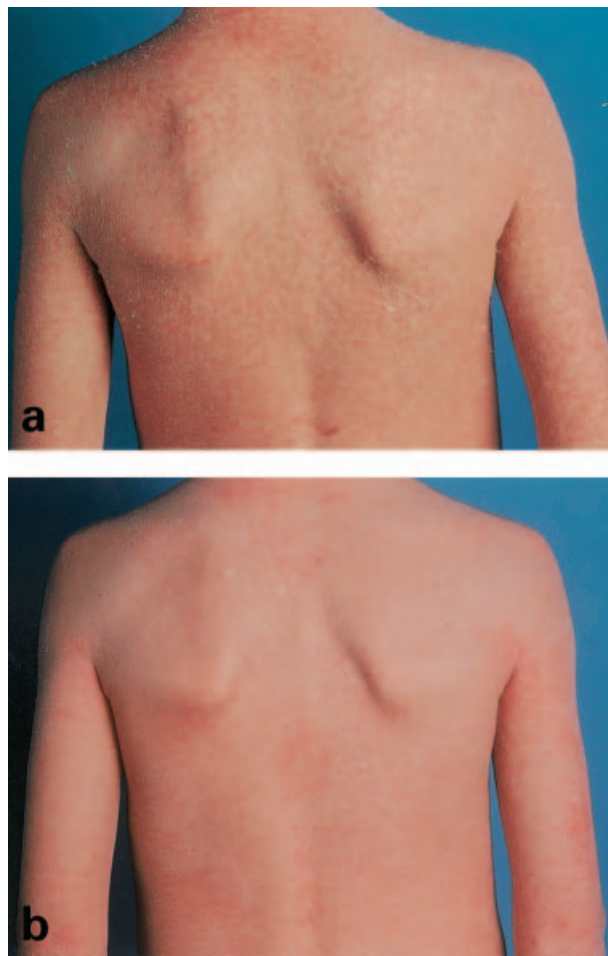


Fig. 2. Extensive hyperkeratosis on the trunk before topical treatment (a) and after 3 weeks of treatment with topical calcipotriol ointment (b).

to a trial employing four different topical treatments. Each extremity first received a different topical preparation in an observer-blind pilot study: (1) calcipotriol (50 µg/g) on the left leg; (2) ointment containing vitamin A acid (tretinoin 30 mg/100 g) on the right leg; (3) ointment containing urea (10%), lactic acid (5%) and glycerol (5%) on the right arm; (4) ointment containing urea (10%) and sodium chloride (10%) on the left arm. Prior to the start of treatment, the serum calcium level was measured and found to be within the normal range (2.47 mmol/l).

Of all four preparations, topical calcipotriol administered twice daily (cumulative dose 60 g ointment per week) produced the most pronounced reduction of both scaling and itching without skin irritation already after 3 weeks (Fig. 1b, left leg). Moreover, skin tenderness improved. A marked improvement was also achieved by topical application of the tretinoin containing ointment (Fig. 1b, right leg). In contrast, the other ointments applied to the arms did not produce a noticeable reduction in skin keratosis. Subsequently, therapy was continued with calcipotriol ointment alone and including the trunk (Fig. 2b). The patient has

continued this treatment for over 3 years with sustained benefit and no adverse effects. Serum calcium levels as well as urinary calcium excretion were monitored monthly and have remained normal throughout his therapy.

DISCUSSION

Calcipotriol is a vitamin D3 analogue with a high binding affinity to the cellular receptor for the biologically active form of vitamin D3, 1,25 dihydroxy-vitamin D3 (calcitriol). Calcipotriol and calcitriol produce an equivalent dose-dependent inhibition of proliferation as well as stimulation of terminal differentiation in cultured human keratinocytes (9). Clinical investigations have not revealed a significant rise in serum calcium levels, or increase in urine calcium excretion, in patients using less than 100 g and 120 g per week, respectively (5). Other investigators, however, have reported hypercalcaemia (10) or even hypercalcaemic crisis (11) after treatment with topical calcipotriol.

In our child, a continuous topical therapy with calcipotriol ointment twice daily led to a lasting substantial improvement in keratosis, pruritus and skin tenderness. In addition, the social well-being of our patient improved considerably already after 3 weeks. No clinically adverse effects or rise in serum calcium levels or urinary calcium excretion have been detected up to the present. Likewise, Lucker et al. (12) reported the safe use and substantial clinical effect of calcipotriol in the topical treatment of congenital ichthyoses, including one adult patient with BCIE. However, the treatment of extensive areas of ichthyotic skin will usually require large amounts of calcipotriol ointment, and this may constitute a limiting factor in this therapeutic modality, because it impinges on calcium resorption (12). It is therefore essential to monitor serum calcium levels or 24-h urinary calcium excretion. The latter has been suggested to be a more sensitive parameter than serum level (13). The potential biochemical side effects can be mitigated by reducing the cumulative dose, i.e. the application frequency.

In some disorders of keratinization, topically administered retinoids are also effective (14), as in our patient (see Fig. 2b, right leg). Interestingly, recent molecular evidence indicates a synergistic effect of the vitamin D receptor and the retinoid-X receptor- α at a nuclear (transcriptional) level, but only in the presence of both ligands, i.e. 1,25-dihydroxy-vitamin D3 and 9-*cis*-retinoic acid (15). These data imply the attractive but yet speculative possibility that a combination therapy of systemically or even topically applied retinoids and calcipotriol may mutually increase or potentiate their therapeutic effects, thus allowing low maintenance dose levels of retinoids. This is of special interest in the case of children, in whom retinoid side effects could thus be minimized.

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