Chronic leg ulcers as a rare cause for the first diagnosis of epidermolysis bullosa dystrophica

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Key words
Chronic wound; Epidermolysis bullosa; Genetic disorder; Leg ulcer

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Abstract
Chronic leg ulcers occur most frequently in the elderly population as a result of an underlying vascular disease especially chronic venous insufficiency. But it also occurs less commonly in younger people due to other aetiologies, for example, infections, vasculitis, neoplasia or genetic diseases. The following case report presents chronic leg ulcers as a rare cause for the first diagnosis of dystrophic epidermolysis bullosa. We report about a 21-year-old man with painful chronic leg ulcers resistant to different wound treatments for 4 months. After exclusion of the more common vascular aetiologies and reviewing the patient’s family history, we considered an epidermolysis bullosa dystrophica which could be confirmed by genetic analyses. We treated the patient with debridement, modified negative pressure therapy with non-adhesive foil and skin grafting. The chronic leg ulcers healed completely. This case report demonstrates that the family history and genetic diseases should be considered as rare causes for therapy-refractory chronic leg ulcers, especially in young patients.

Key Messages
• chronic leg ulcers are a common in patients with vascular diseases
• other etiologies are vasculitis, pyoderma gangrenosum, infections, neoplasia, calciphylaxis, drug-induced or genetic diseases
• epidermolysis bullosa dystrophica as a very rare described cause for chronic leg ulcers
• histological examination revealed in our patient dermatolytic bullae, type VII collagen lightly stained at the roof of the blister, a6, b4 integrins discrete reduced, type IV, type XVII collagen, plectin, laminin 332, cytokeratine, cytokeratine 14, plakophilin and pankeratinmarker
• treatment started with mechanical debridement with Debrisoft™
• antiseptic polihexanide hydrogel was initially used for wound therapy
• a modified non-adhesive negative pressure therapy using a non-adhesive foil to avoid irritating the skin, blistering or formation of new ulcers was used for wound bed preparation

Introduction
Chronic leg ulcers are a common symptom in patients with vascular diseases. According to current data in central Europe, the most common aetiology for chronic leg ulcers is chronic venous insufficiency which is the dominating causative factor in 47.6% of the patients with chronic leg ulcers. Altogether, 17.6% of ulcers are due to combined arterial and venous diseases, whereas arterial occlusive diseases are the underlying cause in 14.5%. Rarer causes included vasculitis (5.1%), exogenous factors (3.8%), pyoderma gangrenosum (3.0%), infections (1.4%), neoplasia (1.1%) and calciphylaxis (1.1%). This can be completely different in other parts of the world. For example, ulcerating infectious diseases like leishmanioses or buruli ulcers are common causes for chronic ulcers even in younger people in Africa. Moreover, there are other very rare causes like the genetic diseases described mostly in younger patients which should be considered when other more common aetiologies are excluded (1,2).

We report the case of a young man with chronic leg ulcers that did not improve by conventional therapy. We considered epidermolysis bullosa dystrophica as a rare cause of his chronic leg ulcers.
finaly the wounds were grafted with meshed split-skin
80% of all chronic leg ulcers are caused by venous or arterial diseases
epidermolysis bullosa represent a group of inherited skin disorders
four main types of epidermolysis bullosa can be classified
clinical diagnosis of epidermolysis bullosa based on skin findings
confirmation of the diagnosis require a genetic testing
most effective treatment is skin grafting after adequate wound bed preparation

Case presentation

A 21-year-old man was admitted to our department with painful leg ulcers for at least 4 months. Upon examination, multiple ulcerations ranging from 1 to 3 cm² over erythematous plaques distributed over the bilateral pretibial area were observed. Ulcers were shallow with undefined edges, some were partially crusted with necrotic tissue (Figures 1 and 2). The surrounding skin shows violaceous, firm, lichenoid papules that coalesced into large plaques.

Although the patient showed some excoriation signs on the forearms and partially dystrophic fingernails and toenails, there were no other dermatological findings on the rest of his body. The family history indicated that the patient has a positive history of epidermolysis bullosa, in the father and the grandmother, but the type of their epidermolysis bullosa was not specified and they did not experience similar ulcers.

Until the patient arrived to our hospital, a specific diagnosis for the ulcers was not carried out and no association between the family history and the leg ulcers was discussed. The patient’s ulcers were treated with different wound dressings, but there was no healing in any of the ulcers. However, the pain worsened and the wound size increased. Our laboratory data showed increased white blood cell count and C-reactive protein. The patient showed no clinical signs for an infection. The bacteriology swap and culture from the surface of the ulcers showed *Staphylococcus aureus*. Arterial and venous diseases were excluded by ultrasonographic examinations.

The histological examination with immunofluorescence mapping of a skin biopsy showed dermatolytic bullae, type VII collagen lightly stained at the roof of the blister, α6β4 integrins discrete reduced, type IV collagen, type XVII collagen, pietkin, laminin 332, cytokeratine, cytokeratine 14, plakophilin and pankeratin marker were unremarkable. These results and the clinical findings are compatible with those of patients suffering from epidermolysis bullosa dystrophica.

We started the treatment with a mechanical debridement with Debrisoft™ (Lohmann & Rauscher, Neuwied, Germany). After cleaning the wound surfaces, an antiseptic polihexanide hydrogel was applied once daily. The inflamed surrounding skin was treated with a glucocorticoid ointment twice daily. In the second step, a modified non-adhesive negative pressure therapy using a non-adhesive foil to avoid skin irritation, blistering or formation of new ulcers was used for wound bed preparation (3). After two cycles of negative pressure therapy, we grafted the ulcers with meshed split-thickness grafts (4–6). During the regular follow-up at our outpatient wound’s clinic for 8 months, the patient showed progressive improvement and almost complete healing of the grafted ulcers. The treated areas remained free of any new lesions.

Discussion

The most common aetiologies for chronic leg wounds are vascular diseases especially chronic venous insufficiency (CVI) and/or peripheral arterial occlusive disease (PAOD), which are responsible for at least 80% of all chronic leg ulcers (2). Hereditary bullous dermatoses like diseases from the epidermolysis bullosa group are very rare cause for leg ulcers.

Epidermolysis bullosa represent a group of inherited disorders in which skin blisters and ulcers develop in response to minor trauma. Four main types of epidermolysis bullosa can be classified as: dystrophic epidermolysis bullosa, epidermolysis bullosa simplex, junctional epidermolysis bullosa and Kindler syndrome (7). Even within the main types listed
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Figure 2 Ulcer on the left lower leg in detail.

above, there are many subtypes. There exist some inherited/genetic and acquired forms of epidermolysis bullosa. Mild cases of epidermolysis bullosa may not be diagnosed until adulthood. Having a family history of the disease, and especially having a parent with it, is one main risk factor. The clinical suspicion of epidermolysis bullosa is based on the clinical appearance of the skin findings. Identifying the exact type of epidermolysis bullosa is complicated. The tests that are used to confirm the diagnosis are genetic testing, skin biopsy usually with immunofluorescent tests or electron microscopy and special microscopic tests of skin samples (7,8). According to these clinical features, our patient presented with painful ulcerations, but did not report the typical ischaemic rest pain characteristic of ischaemic ulcers. The patient was not elevating or lowering the leg for pain relief.

The location and morphology of his leg ulcers was not characteristic for venous, vasculitis or neurotrophic ulcers. Our patient was treated with wound dressings but there was no healing in any of the ulcers, however, the pain worsened and the wound size increased. One key to the correct diagnosis was the evaluation of the patient’s family history. The patient informed that he has a family history of epidermolysis bullosa, in the father and the grandmother, but the type of their epidermolysis bullosa was not specified and they did not experience similar ulcers.

Ulcerated epidermolysis bullosa at the lower legs is a rare manifestation of dominant dystrophic epidermolysis bullosa and is distinguished from the other forms by its delayed onset and its localisation. Kuske was the first to recognise pretibial epidermolysis bullosa as a distinct clinical picture characterised by a later age of onset, nail dystrophy and predominantly pretibial, lichenoid skin lesions, which were the same in our patient (9,10). Type VII collagen plays a major role in the pathogenesis of most forms of dystrophic epidermolysis bullosa. Genetic linkage studies have solidly confirmed the linkage with the gene for type VII collagen (11,12). Therefore, histological examination shows diagnostic value, as demonstrated in this case. No clear explanation has been offered to account for the lesions in pretibial dystrophic epidermolysis bullosa remaining localised principally in the pretibial area. Tidman and Eady showed that anchoring fibrils were structurally normal but significantly reduced in both dominant and localised recessive dystrophic epidermolysis bullosa, compared with site-matched samples taken from healthy adults. They discerned no difference in the characteristics of the anchoring fibrils in sites that are and are not susceptible to blistering (13). In the Cockayne–Touraine type of dominant dystrophic epidermolysis bullosa, Hashimoto reported a significantly lower number of anchoring fibrils in the sites predisposed for this type of dominant dystrophic epidermolysis bullosa compared with those not so predisposed (14). Furue found a decreased number of anchoring fibrils, which were qualitatively defective, in the normal-appearing skin of the pretibial region. This fact may explain the therapeutic successes by skin grafting (4–6).

Conclusion

Diagnosis of leg ulcers caused by a type of epidermolysis bullosa is often difficult because of its rare presentation. The ulcers are associated with pain and often resistant to conventional wound care treatment. Beside the family history and the typical clinical findings, the histological and genetic examination is necessary to objectify the correct diagnosis. The most effective treatment for non healing ulcers in patients with dystrophic epidermolysis bullosa is skin grafting after adequate wound bed preparation(3–6).

Our case report indicates that other factors, apart from vascular disorders or infections, may induce chronic leg ulcerations. Therefore, we suggest that clinicians should be aware of genetic diseases as a rare cause for a chronic leg ulcer especially in young patients.

References


