Dominant Dystrophic Epidermolysis Bullosa Pruriginosa Responding to Naltrexone Treatment

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Dominant dystrophic epidermolysis bullosa pruriginosa (DDEB-Pr) is a rare subtype of dystrophic epidermolysis bullosa (DEB). The disease was first proposed by McGrath in 1994 and is caused by mutations in the *COL7A1* gene, which encodes type VII collagen (1, 2). The skin is characterized by bullae and erosions located on the extensor sites of the extremities from early childhood. Patients experience intense pruritus and other manifestations, such as papules, nodules, scarring and nail dystrophy in adulthood (3).

We report here a case of DDEB-Pr with a clinical response to naltrexone treatment.

CASE REPORTS

Case 1

A 40-year-old man presented with a history of pruritic skin lesions on the extensor sides of the lower extremities since his teenage years. Multiple, excoriated, infiltrated, hypertrophic linear and nodular elements were seen symmetrically on the forearms, shins and feet. Other findings included scars and toenail dystrophy. No skin blistering was observed during childhood or in adult life, and the patient was not able to cause blisters by rubbing. His mucosa, teeth and hair were normal.

A punch skin biopsy was performed in 1988 and was originally described as a folliculitis. The HE-stained slide was found in our archive and reviewed retrospectively in December 2018. Standard histology showed a slightly acanthotic multi-layer squamous epithelium with a cell-poor subepidermal blister and hyperkeratosis. There was sparse fibrosis in the underlying papillary dermis. No inflammatory cells were found in the blister and only a few lymphocytes in the papillary dermis. No milia were present. No specific signs of folliculitis could be found. Collagen IV staining was performed and collagen IV was found in the roof of the blister. The changes were consistent with the expected findings in DEB. Further subdivision of the clinical subtypes was not possible based on routine histology specimens.

In adulthood a genetic investigation revealed a mutation in the *COL7A1* gene: c.6846G>C (p.(Leu2282=)).

Local treatment with potent topical corticosteroid and potassium permanganate were tried without convincing effect. Naltrexone treatment was started at a dose of 50 mg once daily since pruritus was the main complaint. The itch was reduced and the patient showed marked clinical improvement in the lesions located on the lower legs after 3 months treatment with naltrexone and use of bandages (**Fig. 1**). The treatment was continued for a total of 11 months and no side-effects occurred.

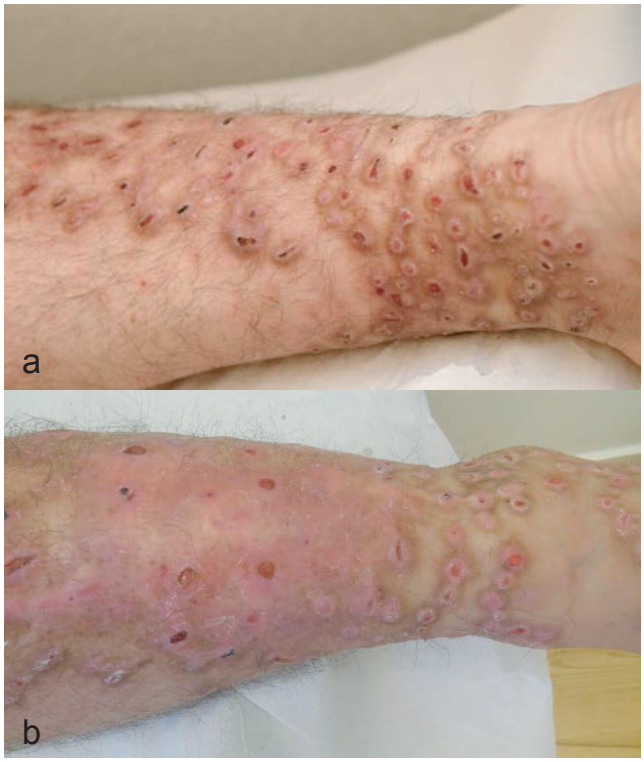

Fig. 1. Skin manifestations in Case 1. (a) Before naltrexone treatment and (b) during treatment.

Case 2

The father of the index case was also known with clinical signs of DDEB-Pr since the age of 10 years. He showed multiple, hypertrophic linear and nodular lesions on the extensor surfaces of the extremities. The intense pruritus was reduced by a daily bath in the sea. He had toenail dystrophy (**Fig. 2**, right).

Case 3

The 10-year-old son of the index case was suspected to have DDEB-Pr due to a newly developed tendency of trauma-induced ulcerations on his legs. The genetic investigation revealed the same mutation in the *COL7A1* gene: c.6846G>C (p.(Leu2282=)). He had no pruritus or toenail dystrophy (Fig. 2).

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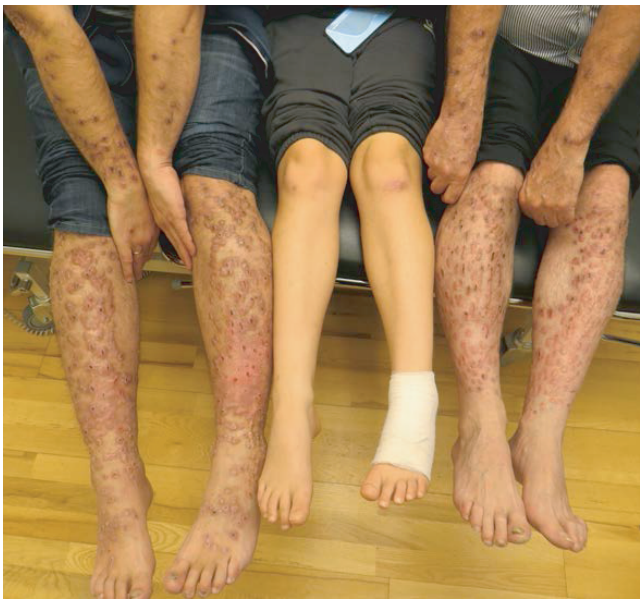

Fig. 2. Left to right: 40-year-old proband (Case 1) with his son (Case 3) (middle) and father of proband (Case 2) (right). The proband and his father present multiple, hypertrophic linear and nodular elements on the extensor side of the arms and legs. The son of the proband has a few trauma-induced ulcerations on the knees.

DISCUSSION

Epidermolysis bullosa is a genetic mechanobullous skin disorder characterized by skin fragility and blister formation from mechanical trauma. DEB is one of the 4 major subtypes of EB (4) and is caused by a mutation in *COL7A1* gene, which encodes type VII collagen. The mutation leads to subepidermal blistering at the sub-lamina densa level. Inheritance of DEB can be autosomal dominant or autosomal recessive (5, 6). DDEB-Pr is a rare clinical subtype of DEB. The onset of DDEB-Pr typically appears in childhood with mild acral blistering and erosions. Later in life the disease is characterized by intense pruritus and other symptoms, such as multiple nodular and infiltrated lesions, skin fragility, blistering, scars and milia. The skin manifestations are mostly seen on the shins and forearms. The nails, especially toenails, can be dystrophic (3).

The genetic investigation in the first case revealed a mutation in the *COL7A1* gene: c.6846G>C (p.(Leu2282=)). This variant was detected in a heterozygous form and is associated with autosomal dominant inheritance. The same mutation in *COL7A1* has been reported in another Danish family (7).

Clinically, differential diagnoses from DDEB-Pr are prurigo nodularis, hypertrophic lichen planus and lichen simplex chronicus when pruritus is a prominent symptom.

No definitive treatments have been established for DDEB-Pr. One case report has described the effect of ketamine 0.5% and amitriptyline 2% topical gel together with oral sertraline (8). Other reports have documented effect of tacrolimus, ciclosporin, mizoribine, corticosteroids, antihistamines, thalidomide and cryotherapy (9, 10).

Naltrexone is an opioid antagonist that inhibits the morphine-induced itch via μ-opioid receptor and can be used to treat burdensome symptoms such as pruritus. The pathomechanism of itch in DDEB-Pr is unknown.

To our knowledge, this is the first case report of DDEB-Pr with a treatment response to naltrexone.

In conclusion, the approach to patients with DDEB-Pr could include the use of naltrexone as a therapeutic option for the management of associated pruritus.

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