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1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

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Epidermolysis bullosa dystrophica pretibialis – Clinical snapshot and management of a rare orphan disease

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Summary

If blistering occurs in childhood, the possibility of hereditary epidermolysis bullosa should be considered even if the symptoms are mild. Besides clinical and histological examination, molecular genetic screening is diagnostically relevant. For localized forms, symptomatic, topical therapy options are currently still the primary choice. Of particular interest is the new option of topical therapy with diacerein 1 % cream. In the case of a pronounced clinical picture with extracutaneous organ involvement, multidisciplinary management is required.

In the future, new forms of therapy such as autologous epidermal stem cell transplantation and gene therapeutic procedures may be applied. Human genetic counselling is indispensable.

Case report

A foster mother presented her three-year-old boy in our dermatology department for examination of a solitary blister forming recurrently on the left knee every 2–3 weeks. She claimed that the blister always appeared without additional symptoms at the exact same location. On several occasions, this was temporally linked to drug intake or vaccination; currently, for example, the boy had been vaccinated against influenza. Shortly after his birth, during perinatal hospitalization, several blisters had developed once on hands and feet. At that time, this had not been investigated further. The boy had no other known diseases or allergies. The foster mother was not able to give any information about the family history.

Provided photographs showed a pronounced bulla below the left knee. In clinical examination, an erythematous macule with post-bullous milia measuring approximately 2 × 1 cm was found at exactly this location (Figures 1, 2). The remaining integumentary system, especially nails and oral mucosa, were inconspicuous.

In view of the clinical findings and history, we made the tentative diagnosis of epidermolysis bullosa dystrophica pretibialis. Given the temporal connection with drug intake in the medical history, a bullous fixed toxic drug reaction had to be considered as potential differential diagnosis. After comprehensive consultation with the foster mother and with her consent, EDTA blood was sent for further diagnostic workup by molecular genetic analysis to the Diagnostic Laboratory for Cytogenetics and Molecular Genetics at the Institute of Human Genetics of the University Hospital of Freiburg. The relevant genes in epidermolysis bullosa were to be analyzed by multigene panel analysis with *next-generation sequencing* (NGS). This included desmoplakin (*DSP*), dystonin (*DST*), exophilin 5 (*EXPH5*), junction plakoglobin (*JUP*), Kelch-like protein 24 (*KLHL24*), keratin 5 (*KRT5*), keratin 14 (*KRT14*), collagen VII (*COL7A1*), plakophilin 1 (*PKP1*), plectin (*PLEC*), transglutaminase 5 (*TGM5*), laminin subunit alpha 3 (*LAMA3*), laminin subunit beta 3 (*LAMB3*), laminin subunit gamma 2 (*LAMC2*), integrin subunit alpha 6 (*ITGA6*), integrin subunit beta 4 (*ITGB4*), integrin subunit alpha 3 (*ITGA3*), fermitin family homolog 1 (*FERMT1*). Given that no fresh blister was available, we did not obtain tissue for histopathological/immunohistological examinations.

In the molecular analysis, a heterozygous pathogenic variant (class 5) in the collagen VII gene (*COL7A1*) was identified. Accordingly, in view of the history and together with clinical and molecular findings we diagnosed a pretibial variant of autosomal dominant, hereditary epidermolysis bullosa dystrophica.

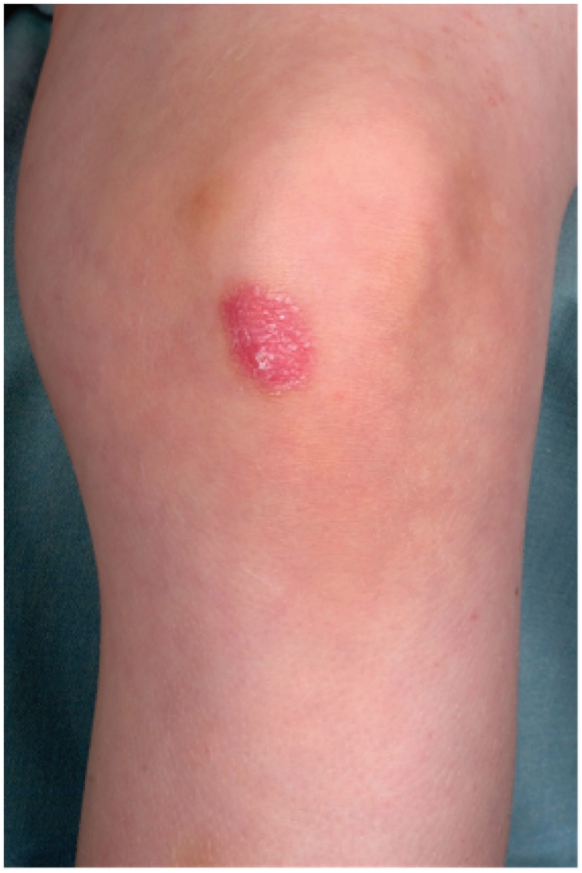

Figure 1 Left knee, pretibial: erythematous macula with postbullous milia, measuring approximately 2 × 1 cm.

Discussion

Epidermolysis bullosa dystrophica belongs to the rare disease group of hereditary epidermolyses/blistering genodermatoses that has an estimated incidence of one per 50,000 births [1, 2]. The underlying cause is a mutation in the gene encoding for collagen VII, *COL7A1*. Collagen VII is a major component of anchoring fibrils in the papillary dermis beneath the basement membrane. A mutation in this gene may result in separation below the lamina densa of the basement membrane with subsequent blister formation [1, 3].

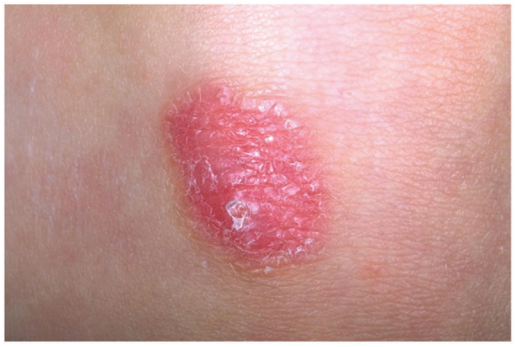

Figure 2 Image detail from Figure 1.

Numerous clinical subtypes of epidermolysis bullosa dystrophica with varying clinical manifestation have been described. Based on their inheritance, these can be divided into dominant and recessive forms [3, 4]. Dominant epidermolysis bullosa dystrophica usually starts during infancy and often presents, similar to our patient, with mild skin fragility restricted to the acra or isolated dystrophic nail modifications [5]. In contrast, the recessive forms often have a severe course with generalized epidermolysis. In addition to nail dystrophy, alopecia, skin and tooth involvement, as well as contractures of hand and feet, oral, laryngeal, pharyngeal, and esophageal mucosal membranes may be affected causing difficulties in swallowing and esophageal strictures. This may result in malnutrition and growth impairment. Furthermore, secondary occurrence of hydronephrosis in case of urethral strictures with subsequent renal insufficiency, cardiomyopathy, and an increased risk of cutaneous squamous cell carcinoma from as early as 10–20 years of age (which is why close skin cancer screening should be performed) have been described in connection with this pathology [1, 3, 6]. Apart from a reduced life expectancy, this will often result in invalidity, as well.

Besides clinical and molecular genetic analysis, histological/immunohistological (immunofluorescence mapping) and/or electron microscopic examinations are diagnostically relevant [5, 6].

The therapy of epidermolysis bullosa is based on the severity of the disease. Currently, there is no cure. For mild skin lesions, local treatment according to the principle "as simple as possible and as much as necessary" as recommended by a panel of international experts [7] is usually sufficient. It is crucial to avoid mechanical stress (including shear forces and friction) and iatrogenic pain [7]. Following disinfection, fresh blisters should be lanced and, dependent on the local finding, cleansed, treated with wound ointments, micro or non-adherent foam dressings, non-adhesive wound dressings that are covered by padding with soft fleece dressings and fixed with soft gauze bandages, tube bandages, or cohesive, conforming bandages [7]. A promising new option is the topical treatment with diacerein 1 % cream [8]. Diacerein is a compound derived from the rhubarb root (Rhei radix) and belongs to the group of anthraquinone derivatives. As a prodrug, it is converted in the body to its active metabolite rhein. It has anti-inflammatory and analgesic effects based in part on the inhibition of cytokines (such as interleukin-1) and proteolytic enzymes, and on a reduction in collagen destruction [8, 9].

In a randomized, placebo-controlled, double-blind clinical study with 15 epidermolysis bullosa simplex patients,

four-week treatment with diacerein 1 % cream resulted in a reduction of blister formation by 40 % in 86 % of the patients compared to only 14 % in the placebo group. Patients treated with diacerein 1% cream also reported reduced pruritus and pain [8]. Moreover, treatment resulted in improved wound healing without scarring combined with good tolerability [8]. In Austria, diacerein is available in the form of capsules. Currently, neither Austria nor Germany have approved a topical formulation. It remains, therefore, an experimental therapeutic approach.

In severe cases and/or upon extracutaneous organ involvement, an individualized, interdisciplinary management is usually required. In subtypes of epidermolysis bullosa with pronounced clinical findings, such as blistering in oral and pharyngeal areas with subsequent difficulties in swallowing, systemic therapeutic options should be integrated into the local therapy. This includes pain therapy as well as infection prophylaxis and therapy, and an optimized, mucosa-sparing diet [6, 10].

In recent years, major progress in basic research has revealed interesting perspectives for new therapeutic options for severe forms of epidermolysis bullosa. Examples include autologous epidermal stem cell transplantation, intraepidermal injection of allogeneic fibroblasts, protein therapies (intradermal or intravenous administration of recombinant collagen VII), and potentially curative gene therapeutic procedures [6, 11]. In the meantime, several patients with severe variants of epidermolysis bullosa, including a seven-year-old boy with potentially lethal junctional epidermolysis bullosa [11], have been treated successfully with gene therapy. Prior to the first transplantation of autologous transgenic keratinocytes, this patient presented with a detachment of 80 % of the total integumentary system; after a follow-up of 21 months, the skin condition was stable. In this therapeutic procedure, epidermal stem cells were initially taken from the patient after clinical, molecular genetic and biochemical characterization [11]. After insertion of the correct gene segment into isolated stem cells genetically corrected keratinocytes were cultivated *in vitro*. Following safety testing, the autologous transgenic keratinocytes were re-transplanted on three occasions and the patient was monitored.

Fortunately, our patient does not suffer from a severe variant of epidermolysis bullosa. We diagnosed epidermolysis bullosa dystrophica pretibialis, with, at present, only minor skin lesions in the left pretibial region. Epidermolysis bullosa dystrophica pretibialis is a very rare pathology, and accurate data on its incidence are not available. (A Medline search with the search terms "epidermolysis bullosa dystrophica simplex pretibialis", "epidermolysis bullosa simplex pretibialis", "epidermolysis bullosa dystrophica pretibialis", "epidermolysis bullosa pretibialis", or "epidermolysis bullosa acral" on 04/14/2020 yielded 61 hits for "epidermolysis bullosa acral" only). The pathogenesis of this disease, with recurrent appearance of lesions in a circumscribed skin area, is only poorly understood. Our case demonstrates that drugs and vaccinations should also be discussed as potential trigger factors. In addition to a strict local therapy conforming to the recommendations mentioned above [7], we also recommended genetic consultation for our patient. This is essential for optimal assessment of important issues, including ethical questions. Additional aspects of family planning need to be considered in addition to risk assessment, in case of a later wish to have children. For example, prenatal diagnosis and preimplantation genetic diagnosis (PIGD) are generally possible. The required examinations for prenatal diagnosis (chorionic villus sampling) are accompanied with a slightly increased rate of miscarriage (maximum 1 %). Therefore, in localized forms of epidermolysis bullosa, the consequence of such examinations must be well considered beforehand.

In addition, we informed our patient's foster mother about consultation opportunities in self-help organizations (*Interessengemeinschaft Epidermolysis Bullosa e. V. DEBRA Deutschland*, Schulstraße 23, 35216 Biedenkopf, Germany; *Angeborene Bindegewebserkrankungen e. V.*, Falkenstraße 74, 33758 Schloss Holte-Stukenbrock, Germany).

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JA, ICH HABE MEINE VITILIGO AKZEPTIERT. SCHLIESSLICH HABE ICH KEINE WAHL.

65 % aller Menschen mit Vitiligo wird gesagt, ihre Erkrankung sei nicht behandelbar.[1] Noch gravierender ist, dass nahezu die Hälfte aller Betroffenen eine Behandlung überhaupt nicht mehr in Betracht zieht.[1] Wie Sie wissen, tritt Vitiligo meist im Teenageralter auf – und ohne zugelassene Therapie fühlen sich viele Betroffene in einem Zustand der Ungewissheit gefangen. Deshalb forschen wir an neuen wissenschaftlichen Ansätzen. Denn wenn wir uns alle mehr mit der Erkrankung Vitiligo befassen, haben Ihre Patientinnen und Patienten eines Tages vielleicht wieder eine Wahl.

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1. Bibeau K, et al. Diagnosis and Management of Vitiligo From the Perspectives of Patients and Healthcare Professionals: Findings From the Global VALIANT Study. Maui Derm for Dermatologists. Maui, HI. January 24th–28th 2022.