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Dystrophic Epidermolysis Bullosa Inversa – Case Report and Review of the Literature

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ABSTRACT Dystrophic epidermolysis bullosa inversa is a very rare subtype of inherited dystrophic epidermolysis bullosa with a unique clinical manifestation. Generalized blistering in the neonatal period and in early infancy improves with age, with lesions becoming restricted to intertriginous areas, axial parts of the trunk, and mucous membranes. In contrast to other variants of dystrophic epidermolysis bullosa, the inverse type has a more favorable prognosis. We present a case of a 45-year-old female patient with dystrophic epidermolysis bullosa inversa, diagnosed in adulthood based on typical clinical presentation, transmission electron microscopic findings, and genetic analysis. Additionally, genetic analysis revealed that the patient also suffered from Charcot-Marie-Tooth disease, a hereditary motor and sensory neuropathy. To our knowledge, the coexistence of these two genetic diseases has not been reported so far. We describe clinical and genetic findings in the patient and review previous reports on dystrophic epidermolysis bullosa inversa. A possible temperature-related pathophysiology for the peculiar clinical manifestation is discussed.

KEY WORDS: dystrophic epidermolysis bullosa inversa, COL7A1 gene mutation, Charcot-Marie-Tooth disease, MFN2 gene mutation

INTRODUCTION

Hereditary epidermolysis bullosa (EB) is an orphan disease, comprising a group of clinically and genetically heterogeneous skin and mucous membranes fragility disorders. It is characterized by the formation of blisters and wounds in response to minor mechanical trauma due to impaired dermo-epidermal integrity (1).

Based on the level of blister formation, four major types of EB can be distinguished: EB simplex, junctional EB, dystrophic EB (DEB) and Kindler syndrome (2). DEB is the most severe type of EB, affecting the skin with subepidermal blistering, which leads to scarring and mutilations accompanied by severe mucosal involvement and extracutaneous manifestations (1). According to the USA National EB Registry (data collected from 1986 to 2002), the estimated incidence of dominant DEB is 2.12 per million live births and a prevalence of 1.49 per million. The estimated incidence of recessive DEB is of 3.05 per million live births and a prevalence of 1.35 per million (3).

The inversa type of recessive dystrophic epidermolysis bullosa (RDEB-I) is a rare variant of DEB. The estimated prevalence is 0.1 per million live births (3). The inheritance of RDEB-I is autosomal recessive (4).

Acta Dermatovenerol Croat
2022;30(3):151-156

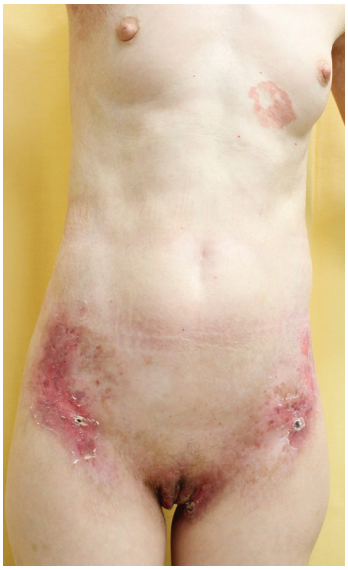

Figure 1. Residual erythema with peripheral scaling and scarring with postinflammatory hyper- and hypopigmentation in the inguinal area. Residual erythema of labia majora.

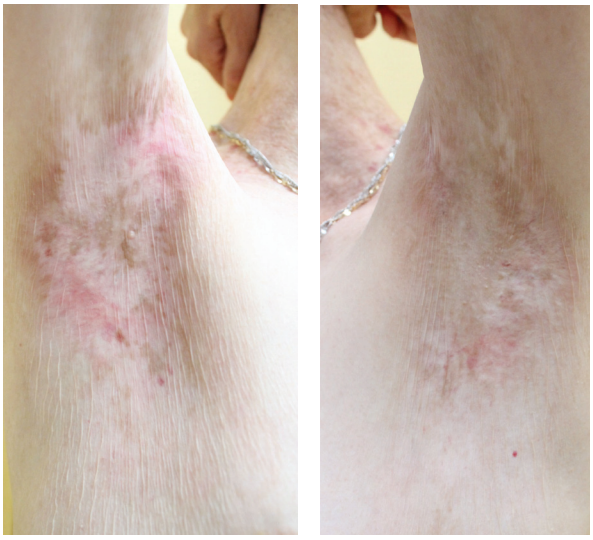

Figure 2, 3. Postinflammatory hyperpigmentation, hypopigmentation with mild erythema (poikiloderma), and scarring. Also note similar changes on the lateral portions of the patient's neck.

Like other DEB variants, it is caused by a mutation in the *COL7A1* gene that encodes the type VII collagen protein, the major constituent of anchoring fibrils (5). Dystrophic epidermolysis bullosa inversa was first described in 1971 by Gedde-Dahl (6), while its dystrophic nature was first established with ultrastructural studies by Hashimoto *et al.* in 1976 (7). According to a PubMed search, only 28 cases had been reported in the literature up to January 2022.

The diagnosis of RDEB-I in early childhood cannot be established clinically, since the localization of skin lesions is very similar to other EB types. However, in adulthood, diagnosis can be based on its unique clinical presentation.

Charcot-Marie-Tooth (CMT) disease is one of the most common inherited neuromuscular disorders, with a prevalence of 1 in 2.500 people (8). It is also referred to as hereditary motor and sensory neuropathy and is characterized by muscle wasting, weakness, and sensory loss, which is more severe distally. The feet and legs are usually affected first and, after a few years, similar symptoms and signs can also be experienced in the hands (8).

We present the case of a female patient with two genetic disorders, RDEB-I and CMT disease, affecting the skin and the neural system. To the best of our knowledge, the co-existence of DEB-I and CMT in the same patient has not previously been reported.

CASE REPORT

A 45-year-old female patient was admitted to the Department of Dermatovenereology at University Medical Centre Ljubljana due to blistering, painful erosions, and residual scarring in the scalp, occipital area of the neck, and axillary, lumbosacral, and inguinal area (Figures 1-5). Post-inflammatory hypopigmentations, hyperpigmentations, and atrophic scars in both axillary and inguinal regions, scarring alopecia (Figure 4) and anonychia of all fingers and toes were observed. On examination, there were no erosions in the oral or genital mucosa, although the patient reported frequent development of erosions in the oral, anal, and genital areas. She had lost all her teeth due to dental caries at the age of 20 and had worn dentures since then. The patient denied

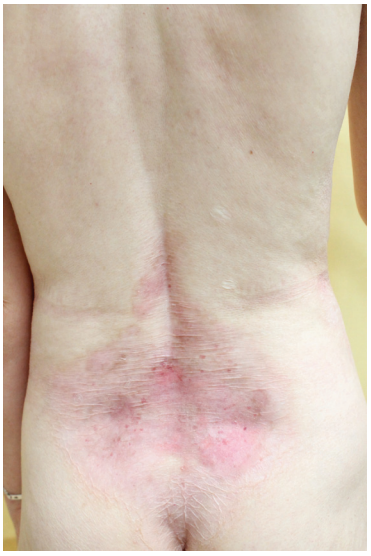

Figure 4. Residual scarring with mild erythema on the lumbosacral region.

Acta Dermatovenerol Croat
2022;30(3):151-156

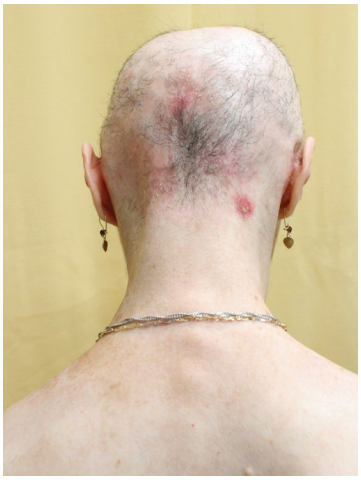

Figure 5. Erosion on the right occipital area of the scalp, erythema, and diffuse scarring alopecia.

having problems with either vision or hearing. She reported an aggravation of the disease during summer or when in a warmer environment. The patient had mild difficulties with swallowing food and difficulties in walking.

Blistering and erosions had been present since birth, although they began to localize in the flexural regions in early adulthood. The diagnostic procedure of skin lesions began at the age of 45 years, since at that time she moved to Slovenia from Bosnia and Herzegovina. We did not have any information on previously performed diagnostic procedures or treatment. The family history revealed that she had one brother with similar skin lesions and that another brother had died at birth from an unknown cause.

We performed a punch biopsy from the skin of the left axillary area. The histopathological examination revealed a subepidermal blister formation (Figure 6). Transmission electron microscopy revealed dissociation of the epidermis immediately below the lamina

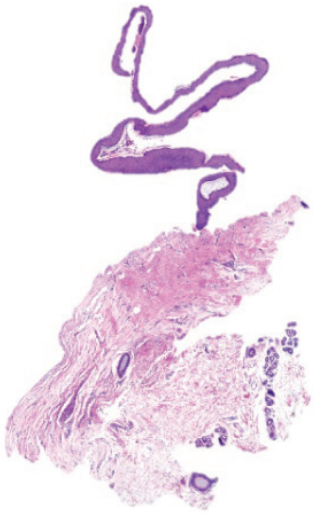

Figure 6. Low power magnification reveals the presence of a subepidermal blister. Note the absence of inflammation in the dermis. Hematoxylin and eosin, original magnification ×20.

densa, and anchoring fibrils were absent (Figure 7). A genetic analysis was performed from the peripheral blood, which revealed two mutations – mutation of the *COL7A1* gene, which was consistent with RDEB, and a mutation of the *MFN2* gene, which causes the autosomal dominant axonal type of Charcot-Marie-Tooth disease type 2A2. A diagnosis of two inherited disorders was therefore established, namely RDEB-I and CMT disease.

Comprehensive assessment of extracutaneous manifestations of EB was performed. Complete blood cell count showed anemia (hemoglobin 118 g/L). General biochemistry was normal, except for a low level of creatinine (32). Serum protein electrophoresis showed mild elevation of beta 2 globulins. Urinalysis was normal. Fecal occult blood test was negative. Otolaryngological examination revealed erosions of

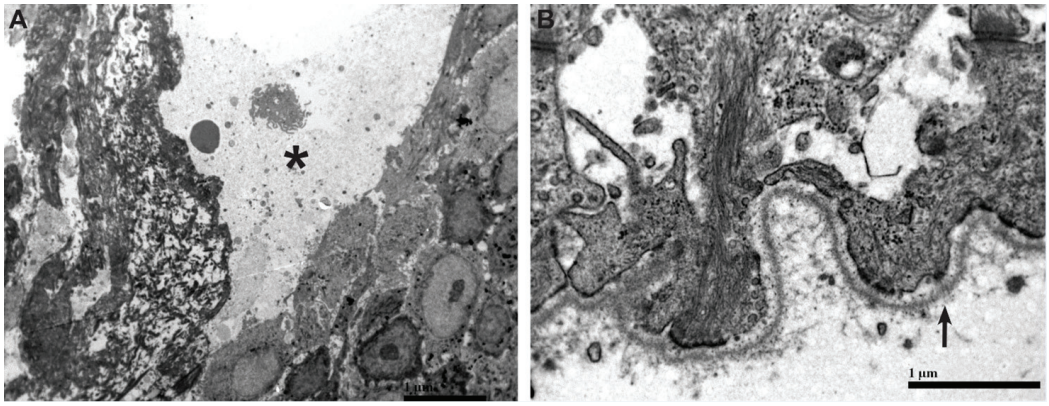

Figure 7. (A) Transmission electron microscopy micrograph showing dissociation (asterisk) of epidermis below the lamina densa. Scale bar: 1 µm. (B) Higher magnification of the micrograph showing absence of anchoring fibrils (arrow). Scale bar: 1 µm.

Acta Dermatovenerol Croat
2022;30(3):151-156

Table 1. Proposed evaluation of patients with RDEB-I

Part of multidisciplinary team	Screening for
Dermatologist	- Cutaneous involvement - Mucosal involvement (oral, esophageal, genital and anal mucosa) - Nail involvement - Alopecia
Pediatrician	- Growth and development
Dentist	- Dental hygiene - Dental caries
Gastroenterologist	Esophageal stricture Constipation
Otolaryngologist	Conductive hearing loss
Physiotherapist	
Psychologist	Depression
Physiotherapist and/or occupational therapist	Flexion contractures Daily limitations due to contractures and/or pseudosyndactyly
Endocrinologist	Osteoporosis
Hematologist	Anemia

the oral mucosa, tongue, and pharynx. The patient refused examination of the esophagus. Bone densitometry revealed osteoporosis.

Treatment of skin lesions was symptomatic, with antiseptic cream and hydrocolloid dressings for erosions. Anemia was treated with iron supplementation, and osteoporosis was treated with peroral drops of vitamin D3 and ibandronate. The patient was referred to a neurologist for further management of CMT disease.

DISCUSSION

RDEB-I is a very rare autosomal recessive disease. It is caused by a mutation in the *COL7A1* gene encoding the type VII collagen protein (9). Mutations in this gene can alter the structure and function of collagen VII. In contrast to RDEB, collagen type VII in RDEB-I is normally present or slightly reduced with immunofluorescence (9). However, with electron microscopy, anchoring fibers are absent or immature in the lesional skin as opposed to non-lesional skin (10), suggesting a structural abnormality of collagen VII that impairs its assembly into anchoring fibrils (11). Immunofluorescence of the skin was not performed in our patient; however, the absence of anchoring fibrils was clearly shown by transmission electron microscopy.

RDEB-I is associated with specific glycine and arginine substitutions in the triple-helix domain of type VII collagen, while other RDEB subtypes lack this abnormality (12). The arginine and glycine substitution leads to synthesis of thermo-labile collagen type VII, which is less stable in the warmest areas of the patient's body (13). This might explain the unique distribution of skin lesions in RDEB-I, which are limited to flexural areas, where the temperature is higher than in other areas of the body. Similarly, exposure to sun, high outside temperature, and mechanical friction of flexural areas might worsen the disease (12,14), as was also observed in our patient. Although the aggravation of RDEB-I during the summer is mentioned in some cases (13), more severe blistering during warmer months was not reported in 20 patients with RDEB-I in a study by van den Akker (12). A temperature-related pathophysiology for an intertriginous location pattern is suspected, but the exact mechanisms are not yet understood.

The clinical presentation of RDEB-I changes with age. In the neonatal period and early infancy, the lesions are more generalized and difficult to differentiate from other types of inherited DEB (9). The age of transition of blistering to flexural involvement can range from 1 to 18 years but is mainly observed before the age of 4 (4,9,10,12). A late onset of RDEB-I has also been described at the age of 30 years (14). In such cases, the differential diagnosis should also include EB aquisita and Hailey-Hailley disease (14).

There is a wide spectrum of clinical presentation in patients with RDEB-I. Patients differ in the extent and severity of mucosal and/or cutaneous involvement. Mucosal involvement predominates in some patients, while in others the skin is more severely affected. Changing of the involved sites to flexural areas is often accompanied by improvement of skin involvement and worsening of mucosal symptoms (9).

The hands and feet may be involved in infancy, but are rarely affected in later life (9). However, in more severe forms, a significant acral involvement can be observed in adults (9). This can lead to flexion contractures and pseudosyndactyly (12). In most patients, a moderate to severe involvement of oral, esophageal, anal, and/or genital mucosa is observed (12,14). This can result in oral scarring, microstomia, ankyloglossia, and esophageal stricture. Esophageal involvement can require repeated mechanical dilatation (15). Due to mucosal involvement, patients are more prone to decreased food intake, poor dental

hygiene, oral infections, dental caries, constipation, and limited sexual function (12). Blistering can be also present in the external auditory canal, leading to conductive hearing loss (12). Anemia was diagnosed in some patients, and was occasionally treated with blood transfusions (12). Osteoporosis was not reported in previously published cases but is a well-known comorbidity in patients with DEB. In our opinion, osteoporosis in our patients could also be attributed to CMT disease, due to difficulties in walking and impaired mobility.

Diagnosis of RDEB-I is based on the typical clinical presentation, along with other diagnostic criteria for DEB, such as histopathological examination, electron microscopy, and genetic analysis. In our case, the diagnosis was based on several criteria: i) clinical presentation with a flexural distribution of skin lesions, ii) histopathological skin examinations with subepidermal cleavage and transmission electron microscopy findings with an absence of anchoring fibrils, iii) genetic analysis, which revealed mutation of the *COL7A1* gene, and iv) positive family history.

According to the patient's history, her brother also had similar skin lesions. RDEB-I in siblings has also been reported in previous cases (9,12,15-17). A positive family history can be considered an additional facilitating factor for diagnosis.

The prognosis of patients with RDEB-I is more favorable than in other RDEB subtypes for several reasons. Firstly, the condition improves with age (14). Secondly, despite the skin involvement in the neonatal period being generalized, the growth and development of patients are not retarded. Finally, the course of the disease is milder compared with other types of DEB, with presumably no risk of squamous cell carcinoma development (12). The development of squamous cell carcinoma has not been observed in previous cases (12).

Evaluation of patients with RDEB-I should include all aspects of the skin and mucosal as well as extracutaneous manifestations of the disease. A multidisciplinary treatment approach is needed, including a dermatologist, pediatrician, dentist, gastroenterologist, otolaryngologist, and psychologist (Table 1). Dermatologists should evaluate the patient for the extent and severity of cutaneous and mucosal involvement. Careful follow-up of growth and weight, as well as intensive dental care, is necessary during childhood (12). Audiological evaluation is recommended at later ages. In the case of flexion contractures and/or pseudosyndactyly, a physiotherapist should also be part of the team. The patient should be evaluated for clinical findings and individual needs.

Patients should be informed about the potentially thermo-sensitivity nature of the disease to avoid aggravation of the disease with increased skin temperature. They should be advised to keep the temperature of the involved sites as low as possible, to avoid sun exposure, to minimize mechanical friction of intertriginous areas, and to consume cold food and beverages (13). These simple recommendations can reduce the severity of the disease and improve patient quality of life.

Treatment of all types of inherited EB is currently unfortunately only supportive, comprising appropriate wound care, minimizing the risk of blister formation, and targeting specific complications (1,18). However, new possible therapeutic options for EB are emerging, including protein replacement, gene editing, and gene therapy (19,20), with promising results.

In conclusion, the clinical presentation and course of the disease were typical for RDEB-I in our patient, with inverse skin distribution, nails dystrophy without pseudosyndactyly, with scarring alopecia and mucosal involvement. Our case also adds a new observation of two concomitant genetic diseases, affecting the skin and the neural system. CMT disease is relatively common, while RDEB-I is extremely rare. To the best of our knowledge, a similar coincidence of genetic diseases has not been previously reported in the literature.

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