Case Report

Recessive dystrophic epidermolysis bullosa mitis - Case report*

*Epidermólise bolhosa distrófica recessiva mitis - Relato de caso clínico**

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Abstract: Epidermolysis bullosa are congenital bullous dermatoses that lead to spontaneous or post-traumatic formation of blisters. There are three recognized disease groups, according to the second international consensus: simplex, junctional and dystrophic. The genetic defect of the dystrophic forms is due to a mutation in the COL7A1 gene, which is responsible for codifying collagen VII, the main representative of anchoring fibrils, which participate in the adherence of the "lamina densa" to the dermis. The authors describe a case of a 15 year-old female patient who presented ulcers on her legs, serous blisters and atrophic scars on her arms and body. Dystrophic ungual and dental abnormalities had also been observed since her birth. Blister histopathological examination was compatible with epidermolysis bullosa, which, in association with clinical data, allowed the classification of recessive distrophic epidermolysis bullosa.

Keywords: Collagen type VII; Epidermolysis bullosa; Epidermolysis bullosa dystrophica

Resumo: ***As epidermólises bolhosas são dermatoses bolhosas congênitas que levam à formação de bolhas espontaneamente ou após trauma. São reconhecidos três grupos de da doença, de acordo com o segundo consenso internacional: simples, juncional e distrófica. Nas formas distróficas, o defeito genético deve-se à mutação no gene COL7A1, responsável pela codificação do colágeno VII, principal constituinte das fibrilas de ancoragem, que participam na aderência da lâmina densa à derme. Os autores relatam o caso de paciente do sexo feminino, de 15 anos, apresentando ulcerações nas pernas, bolhas serosas e lesões atrófico-acastanhadas nos braços e tronco. Foram observadas distrofias ungueais e alterações dentárias, iniciadas a partir do nascimento. O exame histopatológico da bolha revelou quadro compatível com epidermólise bolhosa, que, associado aos dados clínicos, permitiram a classificação do caso na forma distrófica recessiva mitis.***

Palavras-chave: Colágeno tipo VII; Epidermólise bolhosa; Epidermólise bolhosa distrófica

INTRODUCTION

Epidermolysis bullosa (EB) forms a group of hereditary bullous disorders in which blisters form either spontaneously or they are triggered by trauma, having this denomination been suggested by Köebner in 1886.[1,2]

Basal keratinocytes connect to the dermis through the basal membrane area (dermoepidermical junction), as evidenced by SPA (Schiff's periodic acid) under optic microscopy as a fine, homogenous linear region. Under electron microscopy, two regions are observed: lamina lucida, which is electron-sparse, below basal keratinocytes, and another, lamina densa or basalis, above the dermal area that binds to the

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upper portion of the latter by anchoring fibrils, which are electron dense filaments.[1]

Under optical microscopy, EBs present with blisters in the sudepidermal region and, observing this region under electron microscopy, over 16 subtypes were observed and gathered in three main groups.[1,3]

1. Epidermolysis bullosa simplex - there is an intraepidermal cleavage at the lower portion, owing to cytolytic alterations of basal keratinocytes with defects in cytokeratines 5 (KRT5 gene) and 14 (KRT14 gene).[4] Subtypes: Köebner, Weber-Cockaine, Dowling-Meara and Ogna's variant.

2. Epidermolysis bullosa junctionalis - cleavage occurs at lamina lucida or at the central region of the basal membrane area, the ceiling being represented by epidermis and the floor by lamina densa. It is owed to alterations in laminin-5 (LAMA3, LAMB3, LAMC2 genes), integrin-$\alpha 6\beta 4$ (ITGA6 and ITGB4 genes) and transmembrane collagen XVII (COL17A1 gene), being the same as bullous pemphigoid antigen.[4] Subtypes: Herlitz, non-Herlitz e benign generalized atrophic.

3. Epidermolysis bullosa dystrophica - cleavage ocurrs at sublamina densa. Epidermis and lamina lucida represent the ceiling of the blister and dermis represents the floor. Alteration is exclusively in COL7A1 gene.[4] Subtypes: Cockaine-Touraine, Pasini, Hallopeau- Siemens and the recessive mitis dystrophic form.[5-7]

Acquired epidermolysis bullosa is na auto-antibody-mediated disease, in which these antibodies deposit on lamina and sublamina densa, emerge in adulthood, with formation of blisters in areas submitted to trauma, which heal with atrophic scars and milium. In this type of EB there is no mutation, however, immunogenetic studies have demonstrated a connection with HLA DR2.

Chart 1 describes in detail clinical differences, inheritance pattern and prognosis of the subtypes of epidermolysis bullosa.

Hallopeau-Siemens' dystrophic epidermolysis bullosa corresponds to a severe form, usually lethal in childhood. It presents with hands and feet synechia, esophageal stenosis, anemia, growth retardation, dysplastic teeth and atrophic scars on the scalp. Mitis subtype is characterized by more discrete alterations, which may vary according to genetic inheritance.[4-7]

In EB, both dominant and recessive inheritance patterns are found, up to this date with no association with histocompatibility antigens (HLA).[5-7]

According to epidemiological data from the United States of America, epidermolysis bullosa occurs in 50 cases out of 1,000,000 born alive, 92% of them with simple EB, 5% with dystrophic EB, 1% with junctional EB and 2% non-classified.[8] Data from North Ireland have shown that during a period of 23 years (1962-1984), 48 cases of EB were identified, with the following distribution: 31 cases of simple EB (65%), one case of junctional EB (2%), 12 cases of dystrophic EB (25%) and four cases of the acquired form (8%).[9] In Brazil, there are no epidemiological data.

CASE REPORT

White, female, 15 year-old patient, student and residing in the rural area of Afonso Cláudio, ES. Sought medical assistance due to the presence of well-outlined, extense and confluent exulcerations in the leg, covered by an exuberant granulation tissue, without exudation or inflammatory signs (Figure 1), some serous blisters and brown atrophic lesions in the extensor surface of upper limbs, back and abdomen, denouncing preexisting blisters.

Upon dermatological examination, no epidermal cysts, white papulloid lesions, milia and palmary-plantar hyperkeratosis were observed. Hair and body hair were normal, and nails presented the following alterations (Figure 2):

- Anonychia in the first and fifth left toes and ungueal hypekeratosis in the third left toe;
- Hyponychia of the right toes;
- Finger hyponichia.

A total prosthesis of the upper dental arcade was also observed, and had been used since 12 years of age, and lower teeth were irregularly implanted, fractured and brown-yellowish colored.

Previous history indicated that the patient had been born with serous blisters on the scalp and fingers, due to delivery trauma. Blisters would burst, leaving superficial ulcerations and later atrophic hyperchromic lesions. Nails were fragile, brownish and easily detached by trauma, teeth erupted normally, yet, developed with darkening, cavities and fragility (Figure 3).

No similar cases were observed in the family.

After the elaboration of the diagnostic hypothesis of epidermolysis bullosa, biopsies of two leg blisters were carried out. Histopathological examination revealed a low cleavage area, in the dermoepidermal junction, along with vascular congestion, diffuse edema and slight perivascular infiltration of lymphocytes and mononuclear cells in the dermis (Figure 4).

All other laboratory tests - complete blood count, clotting tests, biochemistry, seric proteins and stool for parasites - were normal.

Initial therapy consisted on systemic steroid therapy with prednisone 40 mg/day, systemic antibio-

CHART 1: Features of epidermolysis bullosa subtypes according to the international consensus on diagnosis and classification of epidermolysis bullosa

	Inheritance	Architectural alt	Cleavage	Location	Onset	Nails	Oral cavity	Scars	Progn.	Comments
Simple generalized EB (Koebner)	Dominant	Chrom.17 Kerat.14	Basal cell cytolysis	Pressure areas	Birth or infancy	Ungueal thickening	Few blisters or erosions in the oral mucosa	Plamary-plantar hyperkeratosis	Good	Increased alpha fetal protein Decreased LAgalactosil-hydroxilysil glucosil transferase
Simple localized EB (Weber-Cockaine)	Dominant	Chrom.12 Kerat.5	Intraepi-dermal, spares basal cells	Hands and feet	Two first years of life, adoles-cence up to 18	None	None	None	Plamary-plantar hyperhydrosis	
Simple EB (Ogna's variant)	Dominant	*Locus* TGP erythrocyte	Intra-epi-dermal basal cell cytolysis	Hands and feet	Birth	None	None	Echimoses	Good	———
Simple Herpes-like EB (Dowling-Meara)	Dominant	Chrom.17	Intra-epi-dermal	Trunk and limb roots	First years of life	Punctuated hyperkeratosis and dystrophies	Very com-promised	Milia and anonychia	Good	Plamary-plantar hyperkeratosis in third infancya
Junctional EB (Herlitz)	Recesive	Alteration in the expression of laminin 5 and integrin	Lamina lucida	Disseminated (perioral, nasal, trunck, neckline area)	Birth	Absent or thickened	Blisters and erosions, dysplastic teeth	Absent, Axillary synechia	Severe	Scalp lesions, ane-mia, hypopro-teinemia, growth retardation
Non-Herlitz benign atrophic generalized junctional EB	Recesive	Laminin-5 and collagen XVII	Lamina lucida	Extremities, trunck and scalp	Birth	Intense dystrophies - anonychia	Moderate mucosal lesions Alt. enamel	Skin atrophy. Scaring alopecia	Good	Plamary-plantar hyperkeratosis without anemia
Dominant dystrophic EB (Cockaine-Touraine)	Dominant	Mutation of type VII collagen and metab. alteration GAG	Lamina densa	Extremities; Acral distribution	Early or late	Normal, absent or thickened	Minimal with normal teeth	Hypo or hyperpig-mented hypertrophic scars, Milia	Good	Normal scalp
Dominant dystrophic EB (Pasini)	Dominant	Anchoring fibrils	Lamina densa	Hands, feet, knees, elbows, trunck	Adolescence (without previous blisters)	Dystrophic or absent	Blisters and mucosal erosions	Perifollicular white elevated plaques (white papulloid)	Good	Condroitin Sulfato and GAG in fybroblasts
Recessive dystrophic EB (Hallopeau-Siemens)	Recesive	Coll.VII (increase in collagenase)	Lamina densa	Disseminated	Birth	Ungueal hypoplasia	Chronic erosion - synechia and dyplastic teeth	Cysts Atrophy on the scalp	Severe	Hands and feet synechia: functional inutility. Growth retardation, symblepharus

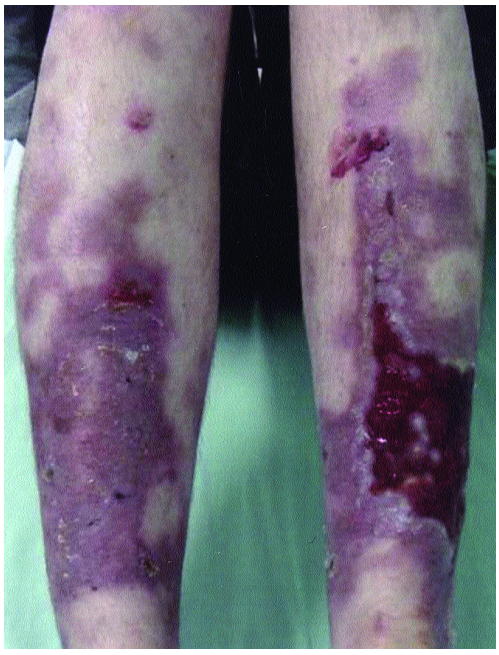

FIGURE 1: Extense, ulcerated and confluent lesions in the leg, covered by granulation tissue - posterior and anterior lesions

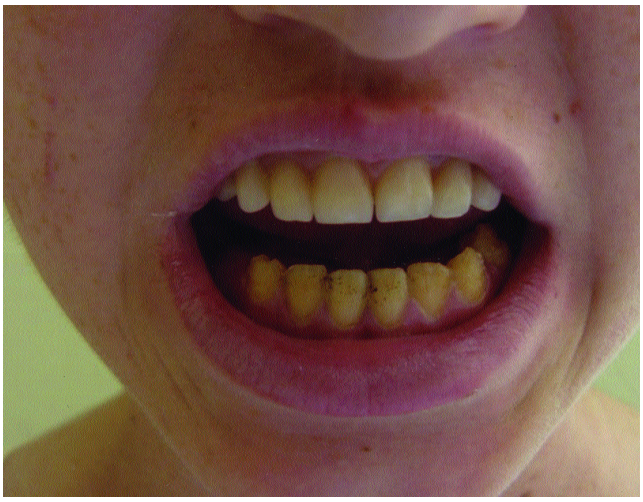

FIGURE 3: Irregularly implanted, fractured and Brown-yellowish lower teeth, and total prosthesis in upper dental arcade

tic (erythromycin 2 g/day) and bandages with neomycin cream on exulcerated lesions for 10 days. Steroid therapy was maintained up to this period, with a graded dose reduction until complete suspension (Figure 5).

DISCUSSION

EB diagnosis relies on history, physical examination and blister biopsy, which allows differentiation, under optic microscopy, from other bulloses, such as phemphigi. Electron microscopy or direct immunofluorescence evidenced blister cleavage level in the subepidermal region, thus allowing differential diagnosis among EB subtypes.[10]

As shown in chart 1, clinical distinction among EB subtypes is also possible. In the case here described, the patient presents features of the recessive dystrophic form, albeit with more discrete alterations: lesions located in areas more often submitted to trauma, such as knees and extremities, hypertrophic granulation tissue in the ulcerations, dental and nail abnormalities, leading to classification as mitis form.

Due to the patient's financial difficulties, elec-

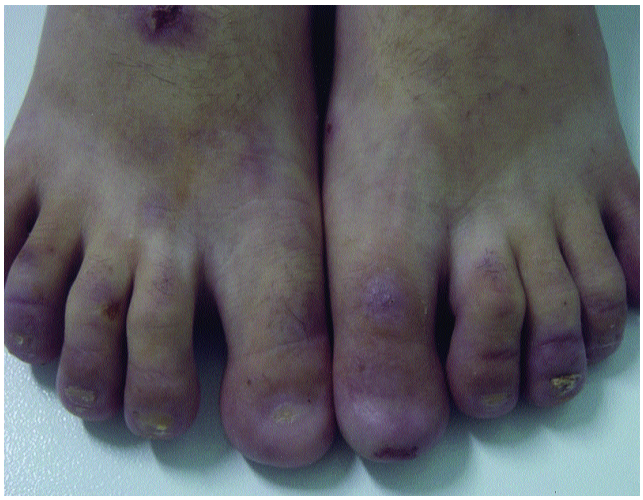

FIGURE 2: Right toes hyponychia. Anonychia in the first and fifth left toes and ungueal hypekeratosis in the third left toe

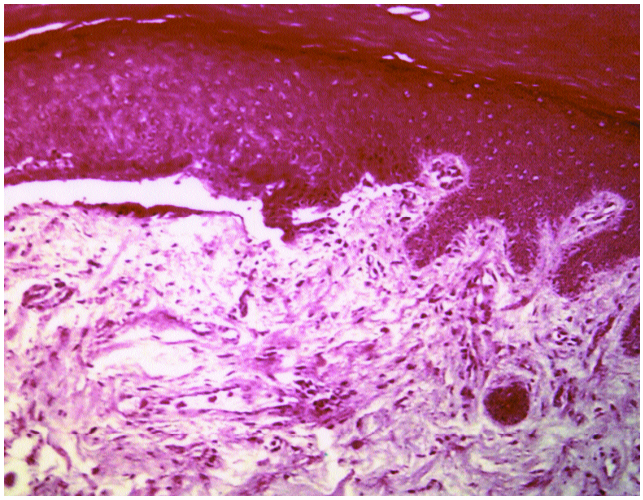

FIGURE 4: Histopathological examination: (HEx40) blister in the dermoepidermal junction, vascular congestion and diffuse dermal edema

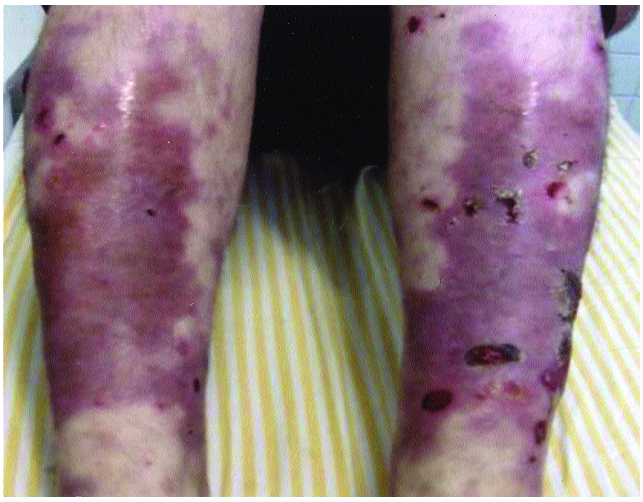

FIGURE 5: After 40 days, a great improvement is observed in the cutaneous picture, due to general hygiene care and local protection

tron microscopy and immunofluorescence were not performed, since they are not available in our service.

Other forms of EB were excluded due to clinical signs which were present:

Simple EB: there are no scars, neither ungueal or dental alterations;

Junctional EB: it is usually fatal, anemia, synechiae, growth retardation, disproteinemia, scaring alopecia, palmary-plantar hyperkeratosis also occur;

Dominant dystrophic EB: presence of white papulloid lesions, milia, hypertrophic scars and normal teeth;

Hallopeau-Siemens' recessive dystrophic EB: severe form in which the child usually does not reach adulthood. Presents with hands and feet synechia with functional inutility, esophageal stenosis, anemia, growth retardation, dysplastic teeth and atrophic scars on the scalp. Mitis form is characterized by more discrete alterations.[4-7]

In dystrophic EB, the degree of genetic defect varies from a subtle alteration to a complete absence of type VII collagen. In recessive forms, mutation of COL7A1 gene causes an early interruption of codons, thereby resulting in an absence of collagen VII in the tissues. Mutations that do not cause such early interruption produce less severe forms, such as mitis.[3]

Mitis form is referred to as being of moderate severity, and is a consequence of a mutation on COL7A1 gene, due to a replacement of glycine (most frequent mutation),[5] leading to alterations of type VII collagen,[3] which is the major component of anchoring fibrils. These collagen alterations can be either quantitative or qualitative, hence the phenotype variation.[5,11]

EB annual incidence in the United States of America is of 50 cases/1,000,000 born alive, 5% of them being dystrophic,[6] and moderate severity forms are admitted to be undernotified. Among these is the mitis form, which is why only few publications about it were found in the litearture.[5]

Steroid therapy is controversial for epidermolysis bullosa: Sampaio & Rivitti suggest the systemic use of corticosteroids, hydantoin (which has an inhibitory action on collagenase) and vitamin complementation, whereas Marinkovich et al.[3] refer that, because these are genetic disorders, no drug is capable of correcting the molecular defect, which would thus contraindicate prolonged steroid use, mainly because of side effects.

Treatment generally consists of local care (ulcerations, infections, surgical management) and of other organs (support with mushy diet, laxatives, vitamin E) and screening for Spinocellular Carcinoma (SCC), in the dystrophic forms.[12]

Recent studies have identified specific proteins and genetic abnormalities for the majority of EB subtypes, advances that have been contributing, in molecular research, for the development of novel gene and protein therapies.[12]

Ortiz-Urda et al. (2003) have published a study with intradermal fybroblast injection, expressing type VII collagen in integer skin of patients with recessive dystrophic EB and observed that these cells locally restored the expression of type VII collagen *in vivo* and normalized clinical aspects of the disease, including subepidermal blisters and anchoring fibril defects.[13]

The patient was being treated with prednisone 40 mg/day with improvement of the cutaneous picture. A graded reduction of the steroid was employed until total suspension, and general measures, such as trauma prevention and local antibiotic drugs, were adopted, resulting in good clinical control.

The patient is currently being followed up, with visits every 6 months, due to the risk of carcinomatous transformation of skin lesions. Incidence of these tumors has been increasing as a consequence of better management and increased survival rates of these patients.[14]

Unlike ultra violet radiation-induced SCCs, these develop in extremities, sites of chronic blister formation, and have been reported as complication of chronic infection, since the latter, along with tissue repairing, is responsible for tissue alterations that allow tumor formation. Moreover, exposure to repetitive trauma can lead to a rapid uncontrolled epidermal growth, with consequent differentiation and transformation of keratinocytes.[14] SCCs are well differentiated, and yet have worse prognosis and high

mortality rate.[15] Treatment for such cases is surgical, which reinforces the importance of early dignosis and intervention.[14]

The authors emphasize referral to a medical genetics service, for orientation about inheritance patterns and probability of transmission to descendants.[8] ❑

REFERENCES

1. Fonseca JCM, Obadia I. Epidermólise bolhosa: Recentes avanços. An Bras Dermatol. 1990; 66: 171-4.
2. Silva F. Epidermólise bolhosa distrófica: Epidermólise bolhosa de tendência cicatricial com cistos epidérmicos e formações albo-papulóides. An Bras Dermatol. 1941; 16: 5-11.
3. Marinkovich P. Epidermolysis bullosa. [serial on the Internet]. 2001 [cited 2003 Apr 3];11:[about 9p.]. Available from: www.emedicine.com/Derm/Topic124.htm
4. Almeida Jr HL. Genética Molecular das Epidermólises Bolhosas. An Bras Dermatol. 2002; 77: 519-32.
5. Ryoo YW, Kim BC, Lee KS. Characterization of mutations of the type VII colagen gene (COL7A1) in recessive dystrophic epidermolysis bullosa mitis (M-RDEB) from three Korean patients. J Dermatol Sci. 2001; 26: 125-32.
6. Vaccaro M, Moretti G, Guarneri F, Cannavò S, Magaudda L. "Sporadic" dystrophic epidermolysis bullosa: a new dominant or mitis recessive mutation? Eur J Dermatol. 2000; 10: 436-8.
7. Hashimoto I, Kon A, Tamai K, Uitto J. Diagnostic dilemma of "sporadic" cases of dystrophic epidermolysis bullosa: a new dominant or mitis recessive mutation? Exp Dermatol. 1999; 8: 140-2.
8. Horn HM, Tidman MJ. The clinical spectrum of dystrophic epidermolysis bullosa. Br J Dermatol. 2002; 146: 267-74.
9. McKenna KE, Walsh MY, Bingham EA. Epidermolysis bullosa in Northern Ireland. Br J Dermatol.1992; 127: 318-21.
10. Alves ACF, Cymbalista NC, Oliveira ZNP, Machado MCRM, Sotto MN, Prianti MG, et al. Imunomapeamento no diagnóstico das epidermólises bolhosas hereditárias distróficas. An Bras Dermatol. 2001; 76: 551-60.
11. Betts CM, Posteraro P, Costa AM, Varotti C, Schubert M, Bruckner-Tuderman L, et al. Pretibial dystrophic epidermolysis bullosa: a recessively inherited COL7A1 } splice site mutation affecting procolagen VII processing. Br J Dermatol. 1999; 141: 833-9.
12. Marinkovich MP, Pai S. Epidermolysis bullosa: new and emerging trends. Am J Clin Dermatol. 2002; 3: 371-80.
13. Ortiz-Urda S, Lin Q, Green CL, Keene DR, Marinkovich MP, Khavari PA. Injection of genetically engineered fibroblasts corrects regenerated human epidermolysis bullosa skin tissue. J Clin Invest. 2003; 111: 251-5.
14. Bosch RJ, Gallardo MA, Ruiz del Portal G, Sanchez P, Arce MF, Herrera E. Squamous cell carcinoma secondary to recessive dystrophic epidermolysis bullosa: report of eight tumours in four patients. J Eur Acad Dermatol Venereol. 1999; 13: 198-204.
15. Webr F, Bauer JW, Sepp N, Högler W, Salmhofer W, Hintner H, et al. Squamous cell carcinoma in junctional and dystrophic epidermolysis bullosa. Acta Derm Venereol. 2001; 81: 189-92.

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