

Case report



EPIDERMOLYSIS BULLOSA PRURIGINOSA, A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Purpose: Epidermolysis bullosa pruriginosa (EBP) is a rare clinical subtype of inherited Epidermolysis bullosa dystrophica (EBD). It is characterized by severe itching and hypertrophic papules affecting the extensor surfaces of the extremities.

Materials and methods: We present a 48 years old woman complaining about intense itching and plaques on the shins, started after mosquito bites. The patient was diagnosed with EBD, by electronic microscopy at the age of 32, because of blisters and painful erosions of the skin, appearing after trauma since birth. She has a daughter with the same skin disease.

Results: Pathological skin changes were presented by excoriated erythematous papules and plaques on the lower 2/3 part of the shins. Erythematocrustous lesions, atrophic scars, hypopigmented macules and milia in the elbows and knees were revealed. Severe toenail dystrophy was found. The mucous membrane found no pathological changes. The complete blood count and biochemistry were in normal ranges. The microbiological examination found *Staphylococcus aureus*. The genealogical analysis revealed autosomal-dominant inheritance of the disease. The histopathological examination revealed a large subepidermal blister. On the basis of medical history, status and the results of histopathological and electronic microscopy examinations, the diagnosis EBP was confirmed. Treatment with desloratadine, emollients and topical corticosteroids was started. The patient is being followed up.

Conclusion: We presented a rare case of EBP with autosomal-dominant inheritance in a 48 years old woman with the beginning of the pruritus and aggravation of clinical manifestation of the disease after mosquito bites.

Keywords: epidermolysis bullosa pruriginosa, autosomal-dominant inheritance, mosquito bite

BACKGROUND

Epidermolysis bullosa pruriginosa (EBP) is a rare clinical subtype of inherited Epidermolysis bullosa dystrophica (EBD). It is characterized by severe itching and hypertrophic papules, plaques and nodules, mainly affecting the extensor surfaces of the extremities. [1, 2] The disease often presents differential diagnosis difficulties, because at first sight it can be mistaken with a series of different dermatoses. In most of the cases, a lot of time passes from the beginning of the symptoms to the establishing of the correct diagnosis. According to Cha et al. (2015), the period of time for diagnosis varies from 1 to 46 years, average 13.2. [3]

CASE DESCRIPTION

We present a 48 years old female patient who was admitted for the second time in our Clinic of Dermatology and Venereology. She has been complaining about intense itching accompanied by the appearance of elevated plaques on the skin of the shins for 3 years. The patient connects the onset of the rash with previous multiple mosquito bites. From the beginning of its appearance, the itching is constant throughout the years, and the plaques gradually confluent and grow in size. The disease worsens during the warm summer months. The first hospitalization of the patient was at the age of 32, due to a congenital skin disease that began 9 days after birth, with the recurrent occurrence of painful blisters and erosions appearing especially after rubbing and trauma. The blisters were localized predominantly on the skin of the elbows and knees, healing with atrophy. Severe deformity of the fingernails and toenails with age developed. In connection with these complaints and on the basis of an electronic microscopy examination of the lesional skin, the diagnosis EBD subtype Cockayne-Touraine in the patient has been made. She suffers from hypertonic heart disease from 3 years, also. The latter was treated irregularly with

Bisoprololfumarate, a medicine from a group of β -blockers. The patient has a 17 years old daughter suffering from the same hereditary skin disease. *Physical examination:* The respiratory and cardiovascular systems were without significant abnormalities. Blood pressure was measured 150/90mm Hg, and the pulse rate was 72 per minute. Extremities were without swelling. An overweight of 89 kg and body mass index 37 were found.

DERMATOLOGICAL STATUS

The pathological skin changes affect the anterolateral and posterior surfaces of the lower 2/3 part of the shins bilaterally. They were presented by erythematous and violaceous polygonal papules and plaques with whitish surfaces and soft-elastic consistency. (fig. 1, 2.) The plaques were covered with excoriations. In the dorsal surfaces of the palms and soles, elbows and knees, erythematocrustous lesions, atrophic scars, hypo- and hyperpigmented macules and milia were presented. (fig. 3. fig. 4.) The mucose membrane of the mouth found without pathological changes. Severe nail dystrophy of the fingers and toes revealed. (fig. 5.) The following differential diagnoses in the patient were conducted: Lichen planus hypertrophicus, Lichen simplex chronicus, Amyloidosis cutis, Dermatitis arteficialis, Keratosis lichenoides chronica in the background of inherited skin disease DEB. In connection with the latter, the following paraclinical studies were performed. The complete blood count and biochemistry were in normal ranges. Microbiological examination of wound exudate found *Staphylococcus aureus*. Electrocardiography revealed ischemic changes in V2-V3. The genealogical analysis revealed autosomal-dominant inheritance of the inherited disease in the family of the patient. The histopathological examination of a lichenified plaque from the left lower extremity revealed a large subepidermal blister full of fibrine and erythrocytes, epidermis with mild atrophy, vacuole degeneration of keratinocytes, fibrosis with a proliferation of thin blood vessels in the dermis, without inflammation infiltrates. (fig. 6.) Previous skin biopsies of the patient, examined by the electronic microscope, were revised and rupture of the dermo-epidermal basement membrane below the level of lamina densa and rudimentary anchoring fibrils in sublamina densa were revealed. (fig. 7.) On the basis of medical history, dermatological status and the results of histopathological and electronic microscopy examinations, the diagnosis Epidermolysis bullosa dystrophicapuriginosa (EBP) was confirmed. Systemic treatment with Desloratidine tabl. 5 mg/ daily and local therapy with non-adherent dressings and emollients for erosive lesions of the extensor surfaces of the extremities were started. Methylprednisolone aceponate 0,1% cream for the itching plaques of the shanks for 3 months, were prescribed. Because of the absence of clinical improvement after the third month, treatment with Tacrolimus 0,1% ointment was prescribed. The patient is being followed up.

Fig. 1, 2. Erythematous and violaceous lichenification polygonal papules and plaques with whitish surfaces covered with excoriations on the left and right shins.



Fig. 3. Erosive-crustous lesions, atrophic scars and milia on the right elbow.



Fig. 4. Postlesional hypo- and hyperpigmented macules with mild skin atrophy on the left knee.



Fig. 5. Severe dystrophy of the toenails.



Fig. 6. Histopathological examination of a lichenified plaque on the shin (H&E x 100)- epidermis with mild atrophy, a large subepidermal blister full of fibrine and erythrocytes, fibrosis with proliferation of blood vessels without inflammation infiltrates in the dermis.

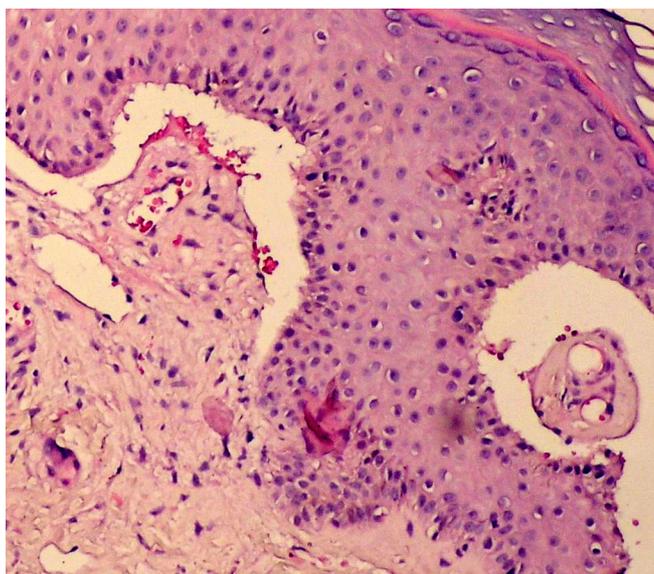
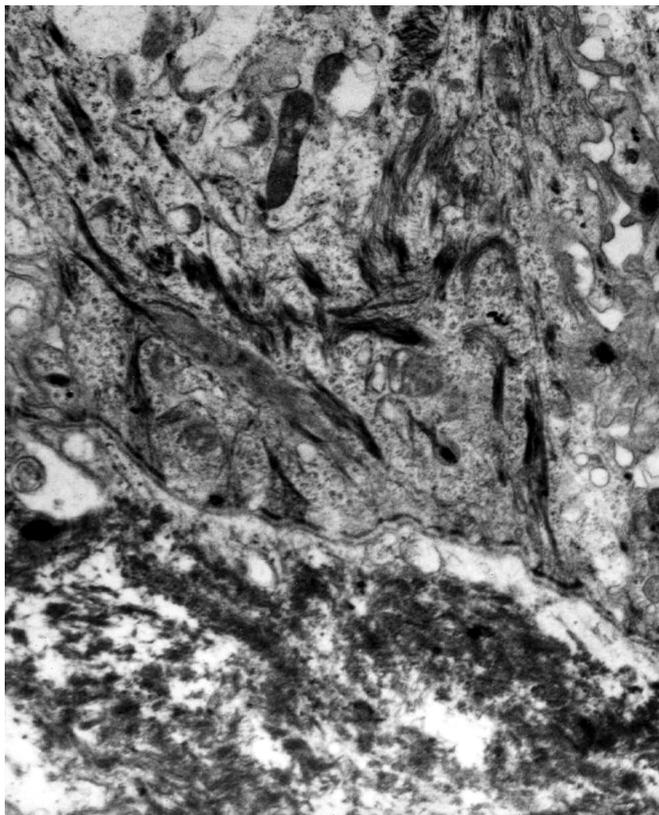


Fig. 7. Electronic microscopy examination (magn. x4600)-rupture of the dermo-epidermal basement membrane below the level of lamina densa.



DISCUSSION

Epidermolysis bullosa pruriginosa (EBP) also known as pretibial epidermolysis bullosa, is a rare clinical subtype of EBD, first described by McGrath in 1994. Epidermolysis bullosa dystrophica is caused by mutations of the gene COL7A1 coding the synthesis of collagen type VII, which leads to blisters formation under the level of lamina densa. [1, 2] Collagen type VII constructs anchoring fibrils in the dermo-epidermal basement membrane zone. The disease can appear immediately after birth, but also in adolescent or middle-aged years, up to 50 years old [4]. Both sexes are equally affected. In many of the cases described in the literature, there is a family inheritance, and in some affected families consanguinity between the parents is established. Most of the cases of EBP are sporadic, but there is autosomal-dominant and autosomal-recessive mode of inheritance also. [2, 5] Pathogenesis of itching in the disease is not established yet. It can be localized, but can also affect the whole body. The disturbed configuration of Collagen type VII, most commonly due to mutations associated with glycine substitution in the structure of COL7A1 gene, could activate kinin-cascade, leading to the interaction of bradykinin with other mediators, leading to intense itching. [6, 7] In the literature many trigger associations with EBP are described, such as filaggrin gene mutations, elevated levels of IgE, iron deficiency, matrix metalloproteinase 1 gene polymorphisms, interleukin 31 gene haplotype, kidney,

liver and thyroid gland dysfunction and scabies infestation. [8, 9] Usually, dominant EBP often shows a typical mild phenotype, until the onset of pruritus, like in the case described by us. Interestingly in our case is the beginning of uncontrolled pruritus after multiple mosquito bites, leading to aggravation of the disease after the years 45 of age. Such a trigger factor for EBP has not been described in the literature. The cases of EBP described in the literature are not more than one hundred. Clinical presentation of the pruriginous subtype of EBD is often introduced by excoriations and pretibially located hypertrophic lichenoid, violaceous prurigo-like papules and plaques, resembling lichen planus and prurigo nodularis. Morimoto et al. described flagellate scarring lesions in patients with EBP. Rarely, intact blisters are seen, usually due to repeated scratching. Postlesional skin atrophy, milia, ablopapuloid lesions and severe nail atrophy to totalanonychia are observed. Mucous membranes are rarely affected. [10] Light microscopic findings include hyperkeratosis, mild acanthosis, subepidermal blister or cleft, fibrosis, vascular proliferation, and lymphocytic infiltrates. Such histologic findings may be used to exclude other skin diseases of close resemblance, such as hypertrophic lichen planus and nodular prurigo and entertain a possible diagnosis of EBP with late onset, respectively. Direct immunofluorescence of the lesional skin in EBP is always negative. Electronic microscopy examination of lesional skin confirms the diagnosis EBD, as it establishes rupture of the dermo-epidermal basement membrane below the level of lamina densa and reduced count of rudimentary anchoring fibrils in sublamina densa. [1] In the case described by us, we found the same changes. Because of the rareness of the disease, most of the patients are wrongly diagnosed with psychogenic pruritus, lichen simplex chronicus, nodular pemphigoid, hypertrophic lichen planus, amyloidosis cutis, dermatitis artefacta etc. [11, 12] In none of these diagnoses the routine histopathological examination finds a subepidermal blister. [13] The differential diagnosis also consists of autoimmune bullous dermatoses Epidermolysis bullosa aquisita and localized Bullous pemphigoid. Both of them are confirmed by positive direct immunofluorescence of the lesional skin. The combination of hyperkeratotic papules, milia and trauma-induced blisters are clinical signs suggestive of the diagnosis of EBP. Clinical data, together with the results from the histopathological examination and electron microscopy of lesional skin, lead to the correct diagnose. Mutation analysis may also be used to confirm the diagnosis. [1, 13] The chronic pruritus in patients with EBP negatively affects their psychiatric health and social adaptation. The role of inflammation in the pathogenesis of EBP has been highlighted by several studies in which anti-inflammatory drugs have led to a rapid improvement in pruritus. The main purpose of the treatment of patients with EBP is to control the itching and excoriations, which lead to the formation of new blisters and hyperkeratotic lesions. [14] The local treatment is presented by topical corticosteroids with or without occlusion, tacrolimus 0.03% ointment and intralesional application of triamci-

nolone acetone. In some cases, cryotherapy was used successfully. There is data for clinical improvement after systemically used antihistamines and corticosteroids. Satisfactory results are described from low dosage Thalidomide and Cyclosporine (2mg/kg/day). During this treatment it is necessary to weekly monitor the renal function, haematological and liver parameters and daily monitoring of blood pressure, also [8, 15, 16] More treatment options are described for patients suffering from EBP with Dapsone, Etretinate and UV-B irradiation. These anti-inflammatory agents may reduce pruritus by modulating healing and scarring processes of skin lesions. [12] Shehadehet al. presented a case of successful treatment with Dupilumab of pruritus in a 52 years old woman without a personal or family history of atopy, suffered from EBP with elevated IgE levels. The authors suggest that the severe pruritus associated with EBP has been connected to immune dysregulation, and the fast and success-

ful clinical response in EBP is regulated by Th2-immune mechanisms. [17] Not only treatment with medicines, but the good skincare with emollients, has a successful antipruritic effect, also. [14]

In conclusion, we presented a rare case of EBP with autosomal-dominant inheritance in a 48 years old woman, treated with system antihistamines and local corticosteroids without success. The disease EBP is a diagnostic and therapeutic challenge for the physician. In many of the described cases, the diagnosis is delayed, which leads to inadequate treatment. Interesting in our case is the beginning of pruritus and aggravation of the disease with the appearance of lichenified and hypertrophic plaques, after mosquito bites. More observations are needed in order to provide better, evidence-based care and control of pruritus in patients with EBP and to improve their quality of life.

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