AUTOSOMAL RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA (DEB-AR) AND SQUAMOUS CELL CARCINOMA (SCC)

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Abstract: *Introduction: Congenital epidermolysis bullosae is a genodermatosis characterized by the appearance of bullae and ulcers after minor trauma due to defect of collagen VII. Autosomal recessive dystrophic epidermolysis bullosa (DEB) is the most severe and is associated with increased risk of aggressive squamous cell carcinoma (SCC). Case report: We report a case of a 17 year-old patient, diagnosed with DEB since the age of 3, with sporadic presentation to dermatologist, who developed several months ago ulcers on the lips, mainly on the lower one. There was raised the suspicion of lip SCC due to increased incidence of SCC among these patients, clinical aspect and long evolution, but the diagnosis was excluded after lip biopsy. Conclusions: DEB is a condition with severe psychosocial impact because of evolution and complications, and by associating aggressive skin carcinomas with a poor prognosis. Strict monitoring of these patients is required for early detection of the neoplastic processes and rapid initiation of specific therapy.*

INTRODUCTION

Congenital epidermolysis bullosa represents a family of genodermatosis characterized by the appearance of blisters and ulcerations after minor injury. Since 2008, epidermolysis bullosa is classified into 4 groups: simple or intraepidermal epidermolysis bullosa, junctional, and dystrophic epidermolysis bullosa and mixed or Kindler syndrome.(1) In dystrophic form, the most disabling form of epidermolysis bullosa, the cleavage is below the lamina densa. In this form of the disease, the immunofluorescence mapping shows the reduction or absence of skin collagen VII, the main component of anchoring fibers. You can also highlight the fault of anchoring fibers by electronic microscopy (ME).

In patients with dystrophic epidermolysis bullosa (DEB), there has been reported an increased risk of developing squamous cell carcinomas (SCC), up to 50-80%, especially on chronic ulcers or dystrophic scars, frequent mucosal and semimucosal localization and extremely aggressive evolution to metastasis, especially in the severe Hallopeau-Siemens type.(2)

CLINICAL CASE

We present the case of a 17-year-old male patient, from rural environment, diagnosed with congenital epidermolysis bullosa, dystrophic form, at age 3, when he was first presented at a dermatological examination. In his family history, there are no other members with DEB signs or other forms of epidermolysis bullosa. Over the years, the patient came in sporadic visits to the dermatologist, when he suffered aggravation of lesions. As a result, chronic ulcers occurred in the pressure areas (hands, feet, elbows) and the evolution was towards ankylosis.

Recently, the patient was admitted to the Dermatology Clinic of Sibiu County Clinical Emergency Hospital for the appearance of ulceration, in the recent months, located on the semimucoasa of the lips, especially the lower lip. Ulcer's surface was proliferative with a tendency to easy bleeding, with mouth opening maneuvers being painful, endurated base, no tendency to local epithelialization under various treatments performed in the past (figure no. 2).

Figure no. 1. a. "In confetti" eritrodermia. b. Cicatricial retraction of the flexors of the hand

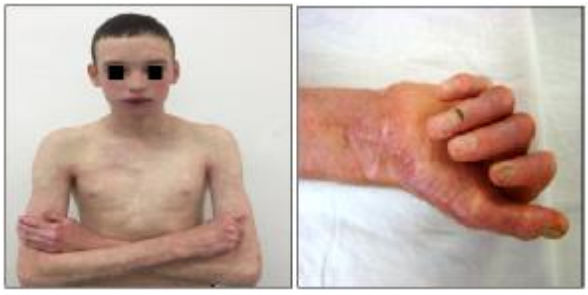
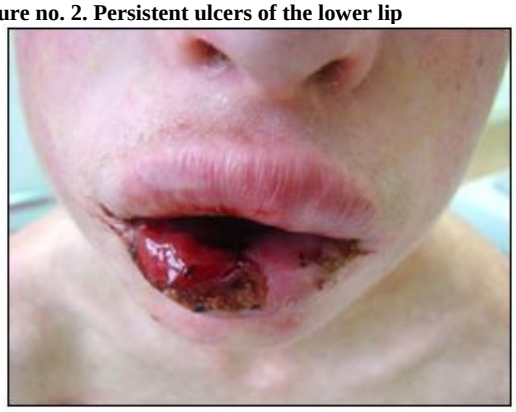


Figure no. 2. Persistent ulcers of the lower lip



General clinical examination revealed a longilin asthenic constitution, with underrepresented fat tissue, atrophic and xerotic skin, ectropion, latero-cervical and supraclavicular lymph node enlargement that were mobile and painless.

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The dermatological examination revealed on the lower lip and comisures two irregular ulcers, covered by sero-hematic crusts, approx. 3/1.5 cm, with no tendency to epithelialization, post traumatic ulcers on the abdomen, the back sides of the fingers, elbows, hands, legs. The entire skin looked xerotic with reticulate telangiectasia, surrounding islands of atrophic skin, with appearance of "in confetti" erythroderma (figure no. 1.a.) Further on, there has been highlighted scar retraction of the tendon of flexor muscles of hands bilaterally, more expressed on the right, pseudosindactily of fingers and toes, right hand functional impotence, disappearance of natural skin lines (figure no. 1.b.) Nails were dystrophic, thickened, yellow with longitudinal streaks. Multiple anal fissures and phimosis scar were also highlighted.

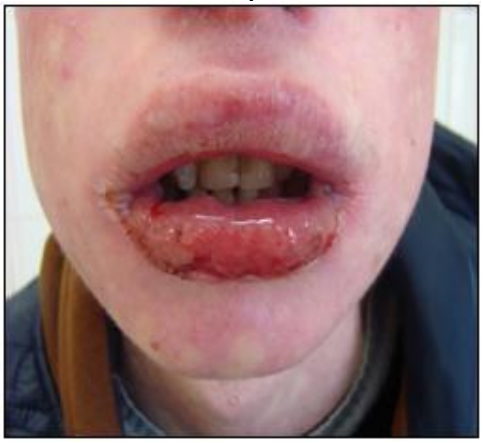
Based on history and clinical examination, there has beenn confirmed the diagnosis of congenital dystrophic epidermolysis bullosa, recessive form. Arguments considered were: the early onset of the disease, the clinical appearance of blisters followed by erosions and ulcers after minor trauma on the extremities, on extension areas, mucosal and semimucosal evolving from the early years of life and progressive worsening with formation of atrophic scars "in onion sheet" with mutilated hands and feet, phimosis, retractile scars, perianal and periorificial fissures. Recently, there has been raised the suspicion of SCC developed on the chronic ulcers of the lower lip, with no tendency to heal, despite numerous specific treatments performed.

Laboratory explorations revealed: cholestatic syndrome (FA-154 U/l), erythrocyte sedimentation rate slightly increased (12 to mm/h) candida albicans in the throat. The histopathological exam performed from the ulceration of the lower lip was in morphologically normal limits, with acellular amorphous material aspect of mucin, without inflammatory elements, without atypia. Also, skin biopsy was taken from the right arm and showed: atrophic epidermis with all the layers present, mild fibrosis in the dermis, adnexal glands absent. There has been ruled out the diagnosis of SCC of the lower lip, initially considered because of the clinical appearance and the evolution of ulcerations. To support the diagnosis of distrophic epidermolysis bullosa, we would have needed mapping by immunofluorescence and electron microscopy of the skin that would have revealed a deficiency of collagen VII or even their disappearance, but this investigation was unavailable in our clinic. Analysis of gene mutations also represents the latest step that determines the mode of transmission of the disease, the type and location of the mutation, requiring sequencing of the entire gene to determine the specific site. This investigation is very expensive and time consuming and not necessary now, genetic analysis being recommended especially for prenatal diagnosis.

The differential diagnosis of DEB should be made with epidermolytic hyperkeratosis or epidermolytic ichthyosis, in which the blisters also appear in the first days of life and are replaced over time by localized or diffuse hyperkeratosis, maintaining a skin fragility and increased possibility of developing contracture of the hands. Another condition entering in the differential diagnosis is ichthyosis bullosa Siemens characterized by the appearance of bullous lesions early in life, highlighting on the histopathology slides, an epidermal vacuolization associated with hyperkeratosis. These disorders were excluded on clinical criteria and by HP examination. There has been raised the suspicion of a progressive scleroderma, which was excluded by the negative result of specific antibodies and uncharacteristic histopathological aspect for this pathology.

The treatment consisted in systemic antibiotic (cefuroxime 1 g/day), antifungal (fluconazole 150 mg/day) for 10 days, for the infectious complication that appeared and local treatment that consisted in disinfection of the ulceration with antiseptic solutions, epithelising ointment (silver sulphadiazine) calcium alginate dressings and hydrogels. Evolution in time was fickle, with periods of diminished dimensions in the lower lip ulceration, followed by periods of extension, including the upper lip. The patient was admitted to our department during the winter of 2015 showing expansion of the ulcerative lesions all over the lower lip (figure no. 3).

Figure no. 3. Extension of the lip ulcer



We applied locally wet dressings with Ringer solution, then alginate dressings with visible favourable evolution and reduction in size of ulcerations.

The particularity of the case lies in the severe form of the disease with ankylosing pseudosindactily, phimosis, anal fissures, "in confetti" erythrodermia and also in the persistence of chronic ulcers of semimucosa of the lips, with high risk of transformation into SCC, requiring continuous monitoring for the early identification of such neoplastic process.

DISCUSSIONS

In DEB, there is a defect in the anchoring fibers in the papillary dermis, having an abnormal structure or being entirely absent, as in recessive DEB. There has been evidenced a mutation in the gene encoding collagen VII, the COL7A1. In order to set the correct diagnosis and determine the form of EBD we can do electron microscopy and imunofluorescence mapping of the skin.

There is no curative therapy, only supportive, but many experimental studies on gene therapy and molecular therapy that performed cutaneous microinjection of deficient protein synthesized by recombinant methods or by the use of viral vectors for gene transfer, provide encouraging results with growth of the VII collagen expression in lamina densa.(3,4)

Tolar et al. have demonstrated that pluripotent stem cells taken from subjects with DEB, after COL7A1 gene defect correction, can produce collagen VII, deficient in this disease, with the possibility of their use in the treatment of cutaneous and mucosal erosions that characterize this group of diseases.(5)

Also, autografts with keratinocyte cultures were proved to be effective in treating lingering erosion and the use of special splints can prevent deformation of hands.(6,7,8)

The severe phenotype of the disease in our patient correlates with autosomal recessive DEB. Patients diagnosed or suspected with DEB at birth or shortly after birth should be evaluated periodically at short and regular intervals in order to shape the evolution and the clinical picture of the disease, but also to detect the onset of complications. The evolution depends on the form of epidermolysis bullosa disease but also on how the

child is being cared.(9)

In the case presented, there were several elements that converged to an unfavourable evolution and poor adherence to treatment, such as: sporadic presentation to a specialist only in times of worsening events that led to the installation of early debilitating and irreversible complications, with scar retraction of tendons of the hand flexor muscles bilaterally, pseudosindactily of fingers and toes, mutilated hands and feet and right hand functional impotence.

In the case of our patient, there has been raised the possibility of developing a squamous cell carcinoma on the lower lip, because of the persistent ulcers, with extensive bleeding and a tendency to grow, given the increased risk that these patients have to develop such cancers. An argument against this can be the young age, but the persistence of chronic ulcers on mucosa and semimucosa of the lips can be a trigger factor for the occurrence of carcinomas on this level. Weber et al. showed that the risk of developing a SCC increases with age, from 7.5% at 20 years, 21.7% at the age of 25 years to 39.6%, 67.8% and 90.1% for ages 30,35 and 55 years. There has been also revealed that the location of SCC is mainly on the extremities that was histologically well differentiated, but showing a more aggressive evolution with rapid growth and metastasis.(10,11,12) In 2009, it was reported a case of metastatic SCC in a patient with autosomal recessive EB, treated with Cetuximab, which responded favourably without worsening of skin lesions and with similar side effects in patients without this genodermatosis.(13) Taken into account that in the case of our patient, the histopathological examination did not reveal characteristics for SCC, the diagnosis was excluded, but with a necessity of close monitoring of the patient and immediate biopsy if proliferative lesions and lingering ulcers develop. Also, mention must be made of the fact that histopathological examination of suspicious lesions should be performed by an experienced pathologist due to difficulties in differentiation of granulation tissue of chronic wounds and pseudoepiteliomatous hyperplasia.(9,11)

CONCLUSIONS

EB is a disabling disorder with a strong psychosocial, physical and professional impact, without cure to date. The prognosis of this disease is clouded due to infectious complications that may be associated with the disease, but also with an increased incidence of aggressive CSC, with great metastatic potential. These patients require regular assessments at short intervals of time (3-6 months) to a professional healthcare. Studies show that gene and molecular therapy promise effective results with optimistic prognosis in management of distrophic EB.

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