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CASE REPORT

Severe generalized recessive dystrophic epidermolysis bullosa (Hallopeau-Siemen's): a case report

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Abstract:

Dystrophic epidermolysis bullosa is a rare heterogenous group of genetic disorders that is clinically characterized by increased skin fragility, blister formation, followed by scarring of skin and mucus membranes, either spontaneously or after induction of minor trauma. It can either be inherited as an autosomal recessive or autosomal dominant form. We herein report a case of severe generalized recessive dystrophic epidermolysis bullosa in a 6 year old ethnic Kashmiri girl.

Keywords: *Dystrophic epidermolysis bullosa, genetic disorder*

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Introduction

Epidermolysis bullosa comprises a group of genetic mechanobullous disorders characterized by blistering of skin and mucosae following trauma and sometimes developing spontaneously [1]. Epidermolysis bullosa (EB) is broadly classified into simple, junctional and dystrophic types when the histological level of cleavage or blister formation is above, within or below the dermoepidermal junction respectively. Diagnosis of EB is based on clinical features, histopathology, immunofluorescence studies, electron microscopy and genetic studies (if available). Dystrophic EB results from mutations in COL7A1, the gene that encodes type 7 collagen. This causes a perturbation in the

anchoring fibrils lying beneath the epidermis and dermis.

Severe generalized recessive dystrophic epidermolysis bullosa (Hallopeau-Siemen's) is the most severe form of dystrophic EB.

It is responsible for widespread mucocutaneous blistering leading to fusion of digits, nail loss, flexural contractures, esophageal strictures, narrowing of trachea or larynx, orogenital ulcers and ocular erosions. Anemia, malnutrition and growth retardation have also been reported.

A multidisciplinary approach with inputs from the dermatologist, paediatrician, plastic surgeon, dentist, physiotherapist and specially trained nurses are required to achieve a good outcome.

Case report

A six year old female child, product of a consanguineous marriage was brought by her parents to the out-patient department of our institute with a history of multiple areas of denuded skin over trunk, upper limbs and lower limbs. There was a history of prior blistering over these areas which ruptured either spontaneously or with minor trauma, producing these lesions. Past history revealed that the patient has had recurrent blisters over her trunk and limbs since her birth. These blisters would rupture, leaving superficial ulcerations and later on atrophic scarring. By the age of five years, she had developed permanent loss of nails, teeth abnormalities and multiple contractures. There was a history of oral ulcers on and off, but there was no history of any ocular involvement. There was no history of seasonal exacerbation, photoaggravation or koebnerization. There was no history of atopy in the patient. There was no similar history in any of her siblings or first degree relatives. She was born at term by a Caesarean section and the immediate perinatal period was uneventful.

On examination, the patient was of normal height and weight as per her age. Systemic examination including examination of chest, cardiovascular system, abdomen and central nervous system was normal. Dermatological examination revealed multiple erosions covered



Figure 1. Multiple crusted erosions with atrophic scarring and milia formation over trunk



Figure 2. Atrophic scarring over elbow



Figure 3. Crusted lesions with atrophic scarring over knees

with granulation tissue and atrophic scarring present over the trunk (Figure 1), both upper limbs, both lower limbs, with a predominance over the bony prominences of elbows (Figure 2) and knees (Figures 3). Nikolsky's sign was positive. The fingers of both the hands showed contractures and were fused together (pseudosyndactyly) (Figure 4), while as feet were completely encased in a thick fibrous scar (mitten deformity) (Figure 5), with absent finger and toe nails.

Mucosal examination revealed multiple superficial erosions over the buccal mucosa, tongue, labial mucosa and palate (Figure 6). Teeth were carious and malformed. Ocular examination was normal.



Figure 4. Contractures of fingers with pseudosyndactyly



Figure 5. Pseudosyndactyly with mitten deformity



Figure 6. Multiple superficial erosions over tongue and labial mucosa

All the routine haematological and biochemical investigations including haemogram, blood

chemistry, urinalysis and stool examination were normal.

Urine examination for porphyrin levels was negative. Chest radiography as well as abdominal ultrasonography was normal. Skin biopsy specimen from trunk revealed subepidermal bullae. Direct immunofluorescence of the perilesional skin demonstrated no immune deposits. There were no facilities for electron microscopy or genetic studies in our hospital.

Based on the constellation of clinical and histopathological evidence, a diagnosis of severe generalized recessive dystrophic epidermolysis bullosa was entertained in this patient. The patient was managed with regular skin cleaning and dressing, topical and systemic antibacterials, along with phenytoin and vitamin E, without any marked improvement.

Discussion

EB is a complex group of mechanobullous disorders in which bullous lesions arise either spontaneously or after minor physical trauma. It can be divided into three major types, depending on the level of tissue separation or cleft formation. In case of epidermolysis bullosa simplex (EBS), blisters occur within the epidermis. In case of junctional epidermolysis bullosa (JEB), the separation is in the lamina lucida of the dermoepidermal junction and in case of dystrophic epidermolysis bullosa (DEB), the level of cleavage is in the dermis [2,3].

EBS has typically an autosomal dominant mode of inheritance, while as it is autosomal recessive in case of JEB. The mode of inheritance for DEB is either autosomal dominant or autosomal recessive [4]. As per the third international consensus meeting held in Vienna in 2007, dystrophic EB is further classified into following types [5] :

Dominant dystrophic EB:

- a) DDEB, generalized [Cockayne-Touraine and albopapuloid (Passini) variants].
- b) DDEB, acral
- c) DDEB, pretibial

- d) DDEB, pruriginosa
- e) DDEB, nails only
- f) DDEB- bullous dermolysis of the newborn

Recessive dystrophic EB:

- a) RDEB, severe generalized (Hallopeau Siemen's variant)
- b) RDEB, generalized, other (non- Hallopeau Siemen's)
- c) RDEB, inversa
- d) RDEB, pruriginosa
- e) RDEB, centripetalis
- f) RDEB, bullous dermolysis of the newborn

All cases of DEB are caused by mutations in a single gene COL7A1, which encodes for the anchoring fibril protein, type VIII collagen. Ultrastructurally, the level of blistering or tissue cleavage in all forms of DEB is immediately below the lamina densa of the epidermal basement membrane [6]. Electron microscopy and immunoelectron microscopy have shown that the anchoring fibrils in DEB are decreased in number, morphologically altered or completely absent [7]. Immunofluorescence staining of the skin of patients using the antitype VIII collagen antibodies showed that the normal bright linear staining is absent in severe generalized recessive dystrophic EB, but present in dominant dystrophic EB [8].

Severe generalized recessive dystrophic EB (Hallopeau – Siemens variant), is characterized by the appearance of bullae at birth or in early infancy. The skin is very fragile and the blisters may develop either spontaneously or after the mildest of trauma and may become haemorrhagic. Healing occurs with the the formation of scarring and milia formation. The sites of predilection are those subjected to repeated friction and physical trauma. These include the elbows, knees, hands, feet, neck, shoulders and spine. Repeated episodes of blistering with progressive scarring causes fusion (pseudosyndactyly) of adjacent fingers and toes [9]. In untreated cases, the digits may undergo progressive contractures and may progressively

become encased in a cocoon-like covering of the scar tissue, also known as the mitten hand deformity. In later cases, there may be bony resorption and muscle atrophy. Mucosal involvement may lead to oral erosions, ankyloglossia, microstomia, esophageal stricture, and anal stenosis. The main ocular complications are symblapheron, corneal corneal erosions, corneal opacity or corneal scarring [10]. There is a retardation of the physical and sexual development with increased incidence of anemia, osteoporosis and osteopenia. The most significant late complication is the development of squamous cell carcinoma of the chronically scarred skin, esophagus and mouth [11].

The management of patients with severe generalized recessive dystrophic EB requires a multidisciplinary approach with involvement of dermatologists, paediatricians, plastic surgeons, physiotherapists and specially trained nurses in order to assure an optimal outcome [12]. An attempt should be made to prevent trauma by padding of limbs. Soft diet helps to reduce oral and esophageal erosions. The patient should be regularly assessed for growth parameters. The role of dieticians is to review calorie and protein intake [13]. Regular assessment of gastrointestinal complications including oral blistering and erosions, esophageal erosions and strictures, dysphagia, diarrhea and malabsorption. Periodic dental inspection should be carried out by a paediatric dentist.

Proper skin care and wound management is the most important part of patient management. This includes antiseptic soaking solutions, topical antibiotics, systemic antibiotics, non-adherent dressings. Many cases of chronic ulcers or erosions have been treated with split skin grafts [14]. The effects of applying allogenic keratinocytes to split-skin graft donor sites have also been studied in several patients of severe recessive dystrophic EB [15]. Various skin bioequivalents have also been used in these patients with mixed results [16]. Pseudocyst (mitten-hand) deformity is a frequent complication and surgery may be required to release the adhesions. Carefull surveillance of

non-healing ulcers is very important for the early detection of squamous cell carcinoma. Established cases of squamous cell carcinoma may require wide-surgical excision and careful serial follow up.

Various systemic drugs which have been tried in dystrophic EB with mixed results include systemic steroids, phenytoin, vitamin E, minocycline, cyclosporine and retinoic acid [17-21]

Recently type VII collagen and laminin-5 gene therapy have been shown to be effective in various in-vivo models [22] Currently, these therapies are being extensively studied at the preclinical stage, in animal models. Genetic counseling and prenatal diagnosis have also an important role [23,24].

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