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Case Report

Paediatrics Section

Junctional Epidermolysis Bullosa in a 30-day-old Infant: A Case Report

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ABSTRACT

Epidermolysis bullosa is a group of hereditary mechanobullous disorders which are associated with appearance of bullae secondary to physical stress like heat or mechanical trauma or sometimes without any trigger. There are four major subtypes: Epidermolysis Bullosa Simplex (EBS), Junctional Epidermolysis Bullosa (JEB), Dystrophic Epidermolysis Bullosa (DEB) and Kindler syndrome. Diagnosis is by skin biopsy histopathology, immunofluorescence staining and genetic testing. The treatment is mainly supportive consisting of avoiding trauma, good skin care and careful wound management. A rare case of JEB in an infant is being presented here. A 30-day-old male infant presented with fluid filled blisters and multiple raw areas over the fingers, buttocks, legs, scalp and elbow were seen. Nail changes were also present. Crusting was present over some lesions. Skin histopathological and immunofluorescence studies were done. Final diagnosis of JEB was made and patient was managed with supportive management. Minimal handling and strict asepsis was advised to the parents. The patient was discharged and prognosis was explained to them. The child was not brought for regular follow-up and he died at four months of age.

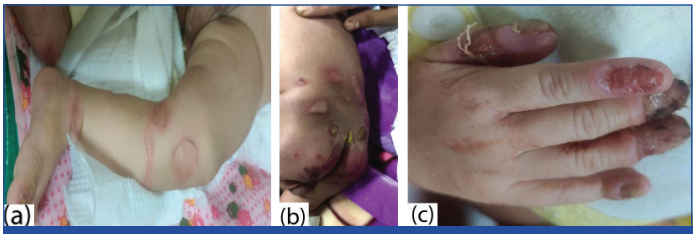
Keywords: Blisters, Hereditary, Mechanobullous

CASE REPORT

A 30-day-old male infant presented to the Outpatient Department (OPD) with complaints of fluid filled lesions and multiple raw areas over the body since birth. The child was born of second-degree consanguineous marriage, at 38 weeks of gestation, with a birth weight of 2.8 kg, by normal vaginal delivery. It was an institutional delivery with no complications. The mother was registered, immunised, had no medical illnesses during pregnancy and all her antenatal scans were normal. There was no history of similar complaints in any of the family members. The lesions started over nail folds with involvement of nails which progressed to form raw areas and resulted in the loss of nails. Lesions over the other sites started as red flat pin point size lesion which increased in size and formed fluid filled blisters which initially involved the bilateral legs. The lesions then progressed to involve the buttocks, lower back, elbows and scalp.

The blisters ruptured on its own to form multiple erosions. Some lesions discharged pus. The child was initially taken to a local clinic where he was given some oral syrup and topical medications for three days, details of which were unavailable. Thereafter, patient was shown to multiple doctors where he was prescribed cefalexin drops, hydroxyzine drops, betamethasone, gentamycin ointment and candid powder. He was also diagnosed to have allergic rash by a private practitioner and syrup amoxicillin, hydroxyzine drops and fluocinolone acetonide+miconazole ointment were prescribed. As there was no relief in symptoms, the patient was taken to a private children hospital where a provisional diagnosis of epidermolysis bullosa was made and the child was started on Intravenous (i.v.) piperacillin plus tazobactam and injection amikacin. Antibiotics were started in view of fever since one day and pus was oozing from the lesions. But as parents could not afford the treatment, they decided to continue further treatment in a government hospital and reported to the present institution.

On physical examination, the patient had an axillary temperature of 98.8°F, heart rate of 140 beats/minute and respiratory rate of 60/minute. The child was taking breastfeeding well. On cutaneous examination, there were multiple blisters and erosions on the legs (anterior aspect), bilateral elbows, lower back and scalp [Table/Fig-1a]. Some of the blisters were intact while the blisters over the points of friction were ruptured. Crusting was present over some lesions and pus was oozing from lesions on the buttocks. There was sparing of palms and soles. The largest lesion was present over the buttocks near gluteal fold measuring almost 5×2.5 cm [Table/Fig-1b]. In addition, finger nails on both hands had dystrophic changes with loss of nails and erosions over the nail beds and nail folds [Table/Fig-1c]. Oral and genital regions were normal.

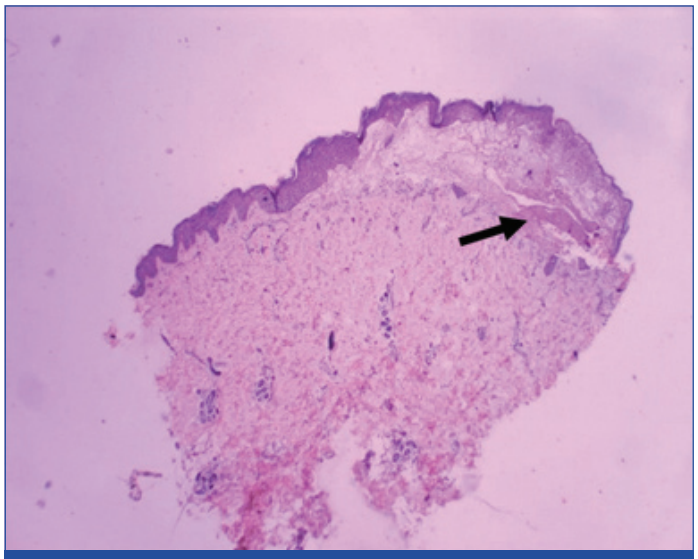


[Table/Fig-1]: a) Bullous erosions over the leg; b) Multiple lesions over the back and buttocks; c) Dystrophic nail changes.

The complete blood count was normal. C-reactive protein was normal (3.14 IU/mL). Blood and pus were sent for culture and sensitivity. A provisional diagnosis of epidermolysis bullosa was made and a Dermatology opinion was taken. Topical antibiotic (mupirocin), non adherent wet dressing (sterile white petroleum impregnated gauzes), minimal handling (avoiding unnecessary touching and lifting child, putting child on frictional surfaces etc.,), strict asepsis in form of hand washing with soap before handling child and care of wound were advised. Skin biopsy was done under local anaesthesia from the new lesions over the medial aspect of the right ankle. The sample was sent for histopathological examination and immunofluorescence studies.

Histopathological study of skin biopsy showed basket weave striatum corneum with normal looking epidermis with few keratinocytes with subepidermal blister cavity consisting of neutrophils and eosinophils [Table/Fig-2]. Upper dermis showed sparse lymphocytic perivascular infiltrate. For the immunofluorescence, frozen section of patient's skin was stained with monoclonal antibodies against type IV, VII, K 14 and Laminin 332 proteins. There was subepidermal split in the sections

studied. There was marked reduction in staining of Laminin 332 as compared to normal skin which was used as control. Staining with other monoclonal antibodies was seen in the dermal side of split, the intensity of which was comparable to normal human skin. These features were suggestive of Junctional Epidermolysis Bullosa (JEB) and hence, the final diagnosis of JEB was made.



[Table/Fig-2]: Skin biopsy showing: Epidermis is detached from the dermis forming a subepidermal cleft (Black arrow) (H&E;10X).

Blood culture sensitivity and pus culture reports were suggestive of no growth; hence, antibiotics were stopped. The child recovered over time and was discharged after eight days of hospitalisation. At the time of discharge, parents were advised minimal handling of the child to avoid trauma, no rubbing of skin and to avoid any kind of jewellery. Local application of mupirocin ointment was advised along with non adherent wet dressing.

The parents were counselled and prognosis was explained to them. The child was not brought for regular follow-up and baby died at four months of life at home. His death was informed over phone.

DISCUSSION

Epidermolysis bullosa is a heterogeneous group of rare inherited mechanobullous disorders of skin and mucous membranes which are characterised by increased skin fragility thereby resulting in blistering of skin and mucosa [1]. Blistering usually occurs in response to some minor stress which may be mechanical trauma or heat. Sometimes there may not be an apparent cause [2]. The condition was first identified and reported in 1870 by von Hebra. A very low incidence has been reported throughout the world. A study by Sharma S and Bedi S, published in 2013 reported that the disease affects 1 in 50000 live births [3]. Data from other sources also present a similar epidemiological picture. Incidence is estimated to be around 19.6 per million live births according to the National Epidermolysis Bullosa (EB) registry project from United States of America (USA). According to the registry, the majority (92%) of the patients suffered from EB simplex, 5% had Dystrophic EB and only 1% presented with JEB [4]. Australia reports a prevalence of 10.3 per million population [5]. On the other hand, epidemiological data from Scotland reports a higher incidence (33.2 per million live births) in 2001 [6].

On the basis of the level of tissue separation and the type of inheritance, three major types of EB have been recognised: Epidermolysis Bullosa Simplex (EBS), JEB and Dystrophic Epidermolysis Bullosa (DEB) [7-9]. In the third international consensus meeting held in Vienna in 2007, a fourth group was also added to the classification named as mixed or Kindler syndrome [10]. The major forms of JEB are generalised severe (formerly herlitz), generalised intermediate, localised and generalised with pyloric atresia [9]. These variants can sometimes be distinguished clinically, but molecular studies are confirmatory. This disorder presents with a wide range of manifestations as well as complications and may result in neonatal death [1,11]. Patients, particularly suffering from JEB are at an increased risk of death [12,13].

A neonate presenting with blisters makes the clinicians consider various differentials such as staphylococcal scalded skin syndrome, toxic epidermal necrolysis and bullous impetigo (infectious aetiology); bullous pemphigoid or pemphigus (immunological aetiology) and hereditary diseases such as EB [14]. The hallmark of EB is the skin fragility followed by blisters and erosions and sometimes milia, nail dystrophy and scar formations may be seen [12]. The present case also presented with these hallmark findings of blisters and erosions over the skin along with the nail changes. Similar findings have been reported in patients suffering from EB [1,15]. Infants continue to have blisters that heal without scarring in majority of the cases. Rarely, extensive lesions may heal by scarring in the patients leading to complications such as scarring pseudosyndactyly of the hands and feet [3,12,16]. Although the index case did not present with any oral ulceration or erosion, it has been reported as a common symptom in patients [1]. Absence of oral cavity symptoms have been reported in some cases [8]. Pitting of tooth enamel is a very common finding associated with diagnostic significance in this condition but unless primary dentition is present, this finding cannot be examined [16,17]. The index case did not have primary dentition at the time of presentation.

Junctional epidermolysis bullosa is also associated with gastrointestinal complications such as pyloric atresia and oesophageal narrowing. Duodenal atresia is also reported as a rare complication [12,16,18-21]. Urogenital complications are generally associated with JEB and these complications due to involvement of epithelium can cause dysuria, urinary retention, urinary tract infection and ultimately lead to kidney failure. Anomalies such as dysplastic/polycystic kidneys and hydronephrosis have also been reported [16,18,22,23].

In JEB, the underlying defect lies in the hemi desmosomes which tend to be sparse and very small, especially in the more severe forms of the disease and the majority of mutations have been found in the LAMB3 gene [14,24]. Dystrophic EB, on the other hand, is caused by mutations in the gene encoding type VII collagen leading to the separation of the sub-basal lamina. Different homozygous variants in COL7A1 were identified as the most common genetic defects identified among the patients [25].

Immunofluorescence mapping is a rapid and reliable method in order to detect the level at which tissue has separated [2]. The method of immunofluorescence staining relates the level of cleavage to specific markers for structural proteins which are expressed in both EB patients as well as normal patients. In JEB, the roof of the blister is stained by the anti BP180 (anticollagen type XVII) antibody, whereas the floor is stained by collagen type IV antibodies [26].

The management for JEB is mostly supportive [27]. Wound care is of paramount importance in the management of JEB in order to prevent secondary bacterial infection [28]. Care should be taken in order to prevent the appearance of new blisters and other complications. Nutritional support should be given simultaneously. Mupirocin ointment helps in controlling lesions that are infected and wet non adhesive dressing helps in healing of old lesions [1]. Trauma should be avoided in order to decrease the appearance of new lesions. Systemic agents have not shown much promise in the treatment of EB. Trials with phenytoin and tetracyclines have not provided conclusive results [29,30]. Other systemic agents such as retinoids, vitamin E etc., have also been studied but there is no reliable clinical

evidence for their efficacy [31]. For certain complications caused by the wounds, surgical procedures may have to be advised [32]. Repeated blistering on hands and feet leads to contractures and fusion of the web spaces, adduction contracture of the thumb, flexion contracture of the fingers at the interphalangeal joints, and flexion or extension contracture at the metacarpophalangeal joints. Surgical corrections for the contractures as well as skin grafting are required for such patients. Postoperative splinting may also be needed [1,33].

Terrill PJ et al., found pseudosyndactyly to have recurred in 13.3% of patients one year postoperatively, in 37% of patients at four years and in 66.6% of patients at five years in a series of 122 operations with split skin grafting [34]. Gene therapy may be promising in the future. The goal of the gene therapy in recessive type of EB is to replace the mutant allele with a normal allele whereas in the dominant forms of EB, it is to suppress downregulate or inactivate the mutant allele [35-37]. Successful gene therapy for JEB was demonstrated in a 49-year-old woman and a seven-year-old boy by Bauer J et al., and Hirsch T et al., respectively in 2017 by transplantation of epidermal stem cells [38,39]. Both these cases had LAMB3 mutation resulting in decreased Laminin 332 protein. Experimental approaches involving transplantation of fibroblasts are also being explored. They can provide a source of normal collagen for wound healing [40]. Recently, a clinical trial studying genetically corrected, C7-expressing autologous human dermal fibroblasts injected into the skin of Recessive Dystrophic Epidermolysis Bullosa (RDEB) patients was started and five patients have already been reported as treated [41].

The prognosis of EB varies according to the subtype. Most of the EB patients who suffer from EBS or dystrophic EB usually have normal life expectancies. On the other hand, JEB patients have a high mortality during the first few years of life [12]. Hence, it is important to identify the subtype of EB as early as possible. Attempt at an early and definitive diagnosis should always be made. Genetic counselling and psychosocial support should be provided to the parents and prognosis should be explained.

CONCLUSION(S)

Epidermolysis bullosa is a rare genetic disorder. It has four major subtypes. The disease is characterised by increased skin fragility resulting in blisters and erosions over the body. Prevention of trauma to the skin, proper wound care and nutritional support is very essential for the management. Early diagnosis is important so that families of affected parents can be offered prenatal diagnosis and genetic counselling.

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