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CASE REPORT

A rare and fatal cause of blisters in a newborn

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Abstract

Newborns may develop blisters and erosions due to multiple entities, including infections, congenital or hereditary diseases. In this report we describe a male newborn who presented with pustular lesions on the first day of life and progressively developed blisters and erosions. Due to disease progression even with intravenous antibiotic therapy after suspicion of bullous impetigo, other diagnoses had to be considered and a multidisciplinary approach with the support of dermatology was necessary. A skin biopsy and genetic study were performed, which allowed the definitive diagnosis of Epidermolysis Bullosa, a group of rare hereditary bullous diseases. Because of the absence of curative therapy, supportive treatment was performed, which did not prevent the patients death at 2 months of life. It is therefore essential for pediatricians to identify this entity as early as possible in order to improve the prognosis.

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INTRODUCTION

In the neonatal period, blisters and skin erosions can be manifestations of several entities, namely infections, congenital or hereditary diseases and therefore constitute a diagnostic challenge[1,2]. Bullous lesions can be benign and transient, but they can also be the first manifestation of a chronic skin disease or systemic disease[1,3].

Due to the diversity of differential diagnoses, a systematic approach is fundamental. Initially, it is essential to exclude an infection, which is the most common cause of blistering[1,4,5], namely herpes simplex virus, bullous impetigo, staphylococcal scalded skin syndrome, congenital syphilis and neonatal varicella[4-6]. Most infections that present with blisters show signs of systemic disease, except bullous impetigo[1,5]. Since the signs of infection are nonspecific, treatment with antimicrobial therapy is usually necessary while the investigation is underway[1,2,4]. When infection is not suspected or has already been excluded, the assessment can be guided by the predominance of bullae or erosions and by its distribution. If blisters predominate, with isolated and non-progressive lesions, sucking blisters, bullous impetigo and aplasia cutis should be thought. If there are multiple or progressive lesions, genodermatosis — such as epidermolysis bullosa, epidermolytic ichthyosis, incontinentia pigmenti and congenital porphyria must be considered. Autoimmune/immunomediated lesions caused by maternal antibody transfer or cases of diffuse cutaneous mastocytosis must also be excluded. Instead, localized erosions may constitute precursors of hemangiomas or aplasia cutis and generalized erosions may correspond to Langerhans cell histiocytosis, toxic epidermal necrolysis or congenital erosive and vesicular dermatosis[1].

Obtaining blister or vesicle liquid for direct microscopy, culture and antimicrobial sensitivity testing and/or polymerase chain reaction may be useful[4]. Skin biopsy may be required for histology, tissue culture and immunophenotyping[1].

Because blisters and erosions are related to skin barrier defects that can lead, if extensive, to hydro-electrolyte imbalances and secondary infections, it is essential to keep watch for signs of dehydration and sepsis. In addition, injuries can be painful and therefore analgesia, especially in wound care, should be used. Moreover, due to the increased metabolic needs, it is essential to monitor the weight gain and adjust the caloric intake[1].

CASE REPORT

A male preterm weighing 2395g was delivered vaginally at 35 weeks after premature rupture of membranes, with good adaptation to extra-uterine life. At birth, pustular lesions were observed on the scalp and, on the next day, scalp lesions became erosions and blisters appeared on the left ear, periumbilical area, buttocks and perineum, with no inflammatory signs. An arterial blood gas test showed hyponatremia (sodium 128mmol/L) and the Complete Blood Count was normal (haemoglobin 19.9g/dL, platelets 171.000/ul, leukocytes 7300/ul (47%neutrophils, 34%lymphocytes)).

The diagnosis of bullous impetigo was admitted and antibiotic therapy was initiated using IV vancomycin and gentamicin, as well as topical mupirocin and topical vitamin A.

On the 6th day of life, due to worsening of previous lesions, appearance of new ones and negative Nikolsky's sign, dermatology consult was asked and Bullous Pemphigoid was though and investigated. A biopsy for anatomopathological examination and a Direct Immunofluorescence (DIF) was taken. Prednisolone (1mg/kg/day) was started and vancomycin was discontinued due to case reports of Vancomycin-Induced Linear IgA Bullous Dermatosis.

The anatomopathological examination result was available on Day16, describing a subepidermal bullous detachment with a perivascular and interstitial infiltrate consisting of lymphomononuclear cells, neutrophils and eosinophils. DIF was negative. An Indirect Immunofluorescence study was performed on the newborn and his mother and were both negative, which ruled out Bullous Pemphigoid.

On Day24, after being in an incubator for a day, there was a significant worsening of skin lesions, now with a positive Nikolsky's sign (Figures 1 and 2). At this point, Epidermolysis Bullosa (EB) was considered and a new biopsy and a blood test for genetic study were performed. Considering the shift of diagnosis hypotheses, progressive decrease in prednisolone dose was started.

By Day33, after placing a Central Venous Catheter (CVC) under general anesthesia, the infant developed a dysphonic crying, probably related to mucosal lesions during intubation. Prescription of oral nystatin and morphine was given to coincide with every dressing change. Due to increased nutritional needs and excessive fluid loss through skin, IV immunoglobulin, plasma and erythrocyte transfusions were given. Albumin and furosemide were started and parenteral nutrition initiated opportunistically.

The second biopsy showed bullous subepidermal detachment associated with minimal lymphomononuclear infiltrate in the underlying superficial dermis. DIF was negative. These histological alterations favoured the hypothesis of EB.

Dermatological consult suggested the use of IV gentamicin for a 3-week period due to its ability to increase laminin levels in the skin. The patient was placed in a positive pressure room, because of the enormous risk of hospital-acquired infection.

The results of the genetic study came on Day54, describing "a pathogenic variant c.283C>Tp(arg 95*) in homozygous on LAMC2 gene. This variant is described in patients with Junctional EB-Herlitz (JEB-H), which is assumed as the diagnosis due to clinical compatibility".

There was a progressive worsening of lesions and repeated trends of hyperglycaemia, hyponatremia/hypochloraemia, hypocalcaemia, hypoalbuminemia and





Figures 1 e 2. Newborn skin lesions on Day 24.

increased C-Reactive Protein and Procalcitonin. In collaboration with the palliative care team, it was decided, after the second loss of CVC, oral medication would be used regardless of its limitations. Cannabidiol was introduced and morphine and fentanyl were given for continued analgesia. Folic acid was initiated as a co-factor for cell mitosis.

On Day63, the infant presented with eyelid edema, central cyanosis, pulmonary rales and heavily exsudative dressings. At this time only pain medication was administered. On Day64, progressive hypothermia, bradypnea and pulmonary congestion were present, which culminated in death.

DISCUSSION

Epidermolysis Bullosa comprises a group of rare hereditary blistering diseases characterized by extreme fragility of the skin and mucosa to minor frictional trauma, resulting in blisters and erosions[1,4,6-8]. The clinical spectrum ranges from localized skin disease to a life-threatening and disabling disease with extensive extracutaneous involvement[6]. The incidence of all forms of EB is estimated to be 20 per million births[1,6,8]. It can affect every racial and ethnic groups and both sexes equally[8]. More than 100 mutations have been described in 16 genes that encode basement membrane proteins, that connect the dermis to the epidermis, responsible for clinical manifestations' diversity[9]. According to the latest 2020 Consensus[9], EB is classified into four major types based on the ultrastructural level of blister formation: simplex, junctional, dystrophic and Kindler syndrome; and subtypes, according to its presentation and genetic mutation, with varying prognosis[1,4]. In some, disease manifestations are limited and life expectancy is normal; other subtypes can be fatal in infancy or associated with lifelong disability and be fatal only in early adulthood[1].

EB may be present at birth, as in our case and others in the literature[10], or shortly thereafter with varying degrees of blisters and erosions[1]. When skin lesions are apparent at birth, they are usually located in peripartum mechanical trauma areas, such as the head and face, or can be more extensive[1]. After the perinatal period, they are seen in sites of handling and friction, such as the hands, perineum, and back, after removal of adhesive or in skin areas prepared for procedures[1]. Sometimes, there may be mucosal involvement and therefore feeding difficulties[1]. Our patient presented with dysphonic crying, probably related to mucosal lesions during intubation.

Diagnosis depends on biopsies of a blister or skin, analysed with immunofluorescence and transmission electron microscopy or/and molecular genetic testing[1,4,6]. Knowing the EB subtype may be important for parents' counselling, in terms of prognosis and their likelihood of having another affected child. In addition, molecular testing is crucial in the assessment of possible extracutaneous involvement and in deciding the best therapeutic approach and follow-up[1,4]. Given the variable extracutaneous, a multidisciplinary approach is essential[11], as our case report shows.

Currently, there is no cure for EB and treatment is based on supportive care and should focus on minimal, nontraumatic handling, use of nonadherent wound care dressings, pain control, nutritional support and prevention of complications[1,4,6]. Due to diagnostic delay, minimal handling was only started later, which may have contributed to worst prognosis.

Recently, translational therapies are being investigated, including cell, gene, protein and drug approaches to correct the underlying molecular pathology, promising a more effective and long-lasting treatment[11].

EB may be inherited in an autosomal dominant or recessive pattern[11]. JEB-H represents the least common, but the most severe form[6,8]. Patients usually present with widespread blistering at birth[6,8], which heals with atrophic scarring, and milia and nails are often dystrophic or absent[6]. Involvement of the airway, eyes and gastrointestinal and genitourinary systems is also common[6,8]. JEB-H is associated with high mortality within the first 2-3 years of life[6,12], with accumulative risk of death of 44.7% by 1 year of age[6]. The most common causes of death are failure to thrive, sepsis and respiratory failure[6,12].

CONCLUSION

There is a wide range of differential diagnosis to neonatal blistering, with infections being the most common cause. Epidermolysis Bullosa is rare and includes multiple phenotypes, with a broad spectrum of clinical manifestations. A skin biopsy for immunofluorescence antigen mapping is the first-line diagnostic test for EB, but is not available in our country. Genetic testing is usually necessary to confirm the diagnosis, to allow parent counselling, to assess the possible extracutaneous involvement and to eventually guide treatment. Multidisciplinary approach is beneficial. No curative therapy exists for EB, and thus current treatment consists of supportive care that should focus on minimal, nontraumatic handling, use of nonadherent wound care dressings, pain control, nutritional support and prevention of complications. Other promising treatments are under investigation.

It is therefore essential for pediatricians to identify this entity as early as possible in order to improve the prognosis.

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