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CASE REPORT

Coexistence of Dystrophic Epidermolysis Bullosa and Sickle Cell Anaemia in a Child: A Case Report

Coexistence de l'épidermolyse bulleuse dystrophique et de la drépanocytose chez un enfant: un rapport de cas

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ABSTRACT

BACKGROUND: **Dystrophic epidermolysis bullosa (DEB) is characterized mainly by intraepidermal blister formation; skin separation is at the level of the sub lamina densa of the basement membrane zone with normal or decreased number of anchoring fibrils on electron microscopy. DEB commonly appearing in neonatal period, three variants of DEB exist; the two most common variants are inherited in an autosomal recessive fashion. The dominant forms are rare and less severe.**

OBJECTIVE: **The objective of this report is to describe the case of a young boy with a rare EB, which is autosomal recessive dystrophic EB occuring concurrently with sickle cell anaemia.**

METHODS: **A five year old Nigerian male being managed at the haemato-oncology clinic of the Federal Medical Centre Yola, Adamawa State was reviewed by the physicians. Relevant clinical photographs were taken after informed consent. Treatment was mainly supportive. Parents were counseled on avoidance of trauma and friction, wound management, infection prevention and control and nutritional support. Vaseline gauze was used to separate the toes to prevent pseudofusion or acquired syndactyly. Our patient's parents were also offered genetic counseling which included the risk of recurrence in subsequent children.**

RESULTS: **A 5-year-old Nigerian male, product of non consanguineous marriage presented at birth and followed up in the clinic with recurrent blistering of the skin, mucus membranes of the mouth and oesophagus. At 9 months of age the patient was also diagnosed of sickle cell anaemia. The areas of the skin commonly and severely affected included the hands, legs, toes and toe nails, knees, elbows, tongue and the buccal mucosa, None of his siblings had similar skin lesions neither any of the parents. Physical examination, histological report and haemoglobin electrophoresis were in keeping with DEB and Sickle cell anaemia respectively.**

CONCLUSION: **Autosomal recessive DEB though very rare, does occur in our environment and can even co-exist with sickle cell anaemia another condition that can lead to skin ulcers. DEB should be suspected in any child with blistering skins and mucus membrane or skins that are fragile to trivial trauma or even spontaneous eruptions. BJM 2020; 2(1): 27–30.**

Keywords: **Dystrophic epidermolysis bullosa, Sickle cell anaemia, skin and mucus membrane, blister, Yola, Nigeria.**

ABSTRAIT

CONTEXTE: l'épidermolyse bulleuse dystrophique (DEB) se caractérise principalement par la formation de cloques intraépidermiques; la séparation cutanée se fait au niveau de la sous-lamina densa de la zone de la membrane basale avec un nombre normal ou diminué de fibrilles d'ancrage en microscopie électronique. DEB apparaissant couramment en période néonatale, trois variantes de DEB existent; les deux variantes les plus courantes sont héritées de façon autosomique récessive. Les formes dominantes sont rares et moins sévères.

OBJECTIF: L'objectif de ce rapport est de décrire le cas d'un jeune garçon avec une EB rare, qui est une EB dystrophique autosomique récessive survenant en même temps que l'anémie falciforme.

Méthode: Un homme nigérian de cinq ans pris en charge à la clinique d'hémato-oncologie du centre médical fédéral de Yola, État d'Adamawa a été examiné par les médecins. Des photographies cliniques pertinentes ont été prises après consentement éclairé. Le traitement était principalement de soutien. Les parents ont reçu des conseils sur la prévention des traumatismes et des frictions, la prise en charge des plaies, la prévention et le contrôle des infections et le soutien nutritionnel. De la gaze de vaseline a été utilisée pour séparer les orteils afin d'éviter la pseudofusion ou la syndactylie acquise. Les parents de notre patient ont également reçu un conseil génétique qui incluait le risque de récidive chez les enfants suivants.

RESULTATS: Un homme nigérian de 5 ans, produit d'un mariage non consanguin présenté à la naissance et suivi en clinique avec cloques récurrentes de la peau, des muqueuses de la bouche et de l'œsophage. À 9 mois, le patient a également reçu un diagnostic d'anémie falciforme. Les zones de la peau fréquemment et gravement touchées comprenaient les mains, les jambes, les orteils et les ongles des orteils, les genoux, les coudes, la langue et la muqueuse buccale.Aucun de ses frères et sœurs n'avait de lésions cutanées similaires ni aucun des parents. L'examen physique, le rapport histologique et l'électrophorèse de l'hémoglobine correspondaient respectivement à la DEB et à l'anémie falciforme.

CONCLUSION: le DEB autosomique récessif, bien que très rare, se produit dans notre environnement et peut même coexister avec la drépanocytose, une autre affection pouvant entraîner des ulcères cutanés. Le DEB doit être suspecté chez tout enfant présentant des cloques et des muqueuses ou des peaux fragiles à des traumatismes insignifiants ou même des éruptions spontanées. **BJM 2020; 2(1): 27–30.**

Mots clés: Epidermolyse bulleuse dystrophique, drépanocytose, peau et muqueuse, ampoule, Yola, Nigéria.

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Abbreviations: DEB, Dystrophic Epidermolysis Bullosa.

INTRODUCTION

Epidermolysis bullosa is a group of genetic conditions that cause the skin to be very fragile and to blister easily.[1] Blisters and skin erosions commonly form in response to minor injury or friction, such as rubbing or scratching. Dystrophic epidermolysis bullosa (DEB) is one of the major forms of epidermolysis bullosa.[1,2] The signs and symptoms of this condition vary widely among affected individuals.[2] To date three major types of dystrophic epidermolysis bullosa have been desbribed.[1] Autosomal recessive dystrophic epidermolysis bullosa, the Hallopeau-Siemens type (RDEB-HS) is the most severe, classic form of the condition. Affected infants are typically born with widespread blistering and areas of missing skin, often caused by trauma during birth, [1] Blisters are usually present over the whole body and mucous membranes such as the moist lining of the mouth and digestive tract. A second type of autosomal recessive dystrophic epidermolysis bullosa is known as the non-Hallopeau-Siemens type (non-HS RDEB). This form of the condition is somewhat less severe than the classic type. The third type of dystrophic epidermolysis bullosa is known as the autosomal dominant type (DDEB). The signs and symptoms of this type tend to be milder than those of the autosomal recessive forms.[1]

Sickle cell anaemia (SCA) on the other hand is an autosomal recessive hemoglobinopathy caused by an amino acid substitution from glutamic acid to valine in the beta hemoglobin chain.[3] One of the symptoms occurring in sickle cell patients is leg ulcers, which are notoriously painful, difficult to treat, and frequently recurrent.[3] The existence of these two autosomal hereditary conditions with their profound skin and mucous membrane involvement and attendant complications are very challenging with poor prognosis.

Few cases of epidermolysis bullosa have been reported from Nigeria.[4,5] to the best of our knowledge there is no reported case of dystrophic epidermolysis bullosa co-existing with sickle cell anaemia in Nigeria. This case is therefore reported with the sole aim of increasing awareness of the co-existence of these two autosomal recessive conditions.

CASE REPORT

A male Nigerian child, presented to the haemato-oncology clinic of Federal Medical Centre Yola (FMCY) in Adamawa State with history of recurrent skin blisters since birth. He is product of non consanguineous marriage, first in a monogamous setting of three children. Patient was delivered preterm at 30 weeks gestation, the pregnancy was supervised at a peripheral hospital. Mother was a known hypertensive and diabetic, said to have been having a fairly good control of her blood glucose and the blood pressure until at 30 weeks, when went into spontaneous labour and delivered at a peripheral hospital. The delivery was uneventful, the baby was then referred to our FMCY where he was admitted and treated for prematurity and very low birth weight (1.25kg).

Review of the clinical notes showed that there were bruises over the lower limbs and small area of skin loss at presentation and was having blisters during his two weeks hospital stay in the neonatology ward. The blistering lesions were at that time assumed to be part of the neonatal sepsis. After he was discharged, the patient was lost on follow-up until at age 9 months when he presented with this recurrent blistering disease especially to slightest trauma. There was also history suggestive of odynophagia probably due to ulcers along the oesophagus. Patient presented with features suggestive of SCA (Jaudice, bone pains and pallor), no family history of SCD. Haemoglobin electrophoresis confirmed the diagnosis of SCA and he was started on routine prophylactic drugs for SCA.

Over the last 5 years there has been sequential avulsion of his toe nails and blistering of the skin over the dorsum of the feet; this was attributed to frequent trauma sustained while playing. (Figures 1 and 2) Non of his other siblings had similar skin changes. None of the parents or any member of the extended family had history of blistering skin diseases, but both parents were HbAS.

Examination then revealed he was pale, jaundiced with multiple superficial ulcers mainly over the upper and lower limbs, the forehead and the scalp; there were also multiple areas of hypo-pigmented patchy skin lesions and few blistering lesions. The blisters affected the knees, ankles, wrists, elbows and buccal mucosa. Healing of the blisters was accompanied by scaring and changes in the nails (see Figures 1 and 2). (Fig 2). There were no hair changes except the involvement of the scalp in the bullous eruption and scar formation.

A diagnosis of epidermolysis bullosa Dystrophica was entertained, with the following differencial diagnoses of Bullous pemphigoid, pemphigus vulgaris, and linear IgA bullous disease of childhood.

A biopsy specimen of perilesional skin showed blistering lesions devoid of a superficial squamous epithelial lining with subepidermal tissues consisting of focal haemorrhagic and aggregate mononuclear inflammatory cells. The

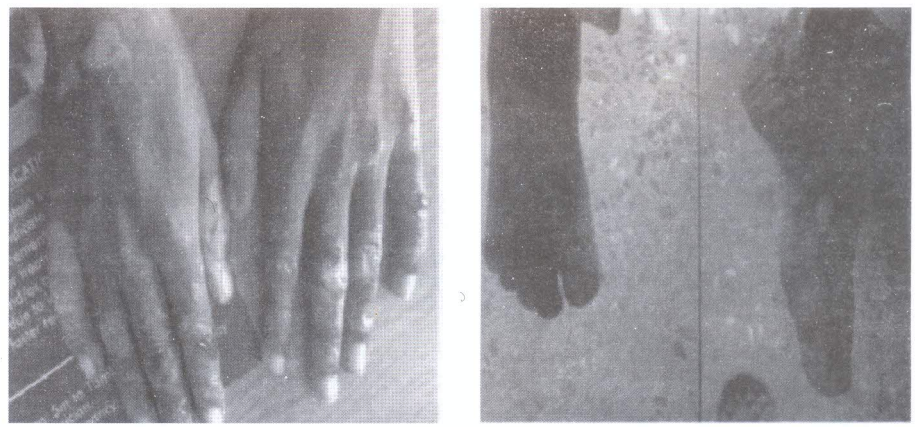

Fig. 1: Left panel: photograph showing Scars, Crust, Blisters and Fresh Ulcers on the Hands Right Panel: Dystrophic Changes, Toe Nail Avulsion, Ruptured Bullae and Extensive Scars on both Legs.

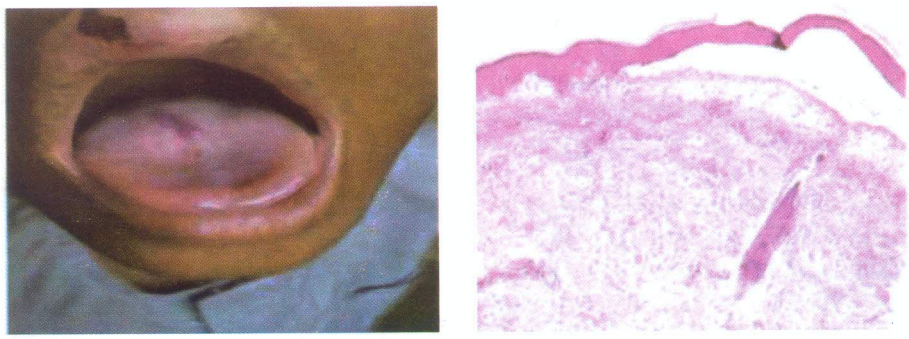

Fig. 2: Left panel: Photograph showing Bulla with Erythema on the Tongue, Crust and Healing Ulcers on the Lips and Soft Palate/Right Panel\; Photomicrograph of Perilesional Skin showing Blistering Lesions Devoid of a Superficial Squamous Epithelial Lining.

Table 1: Results of other Investigations

Investigation	Results	Remarks
FBC and Differential Count		
WBC	6.7B10^9/L	Normal counts and differential
N	40%	
L	57%	
M	3%	
Platelets	576B10^9/L	Slightly high platelets
PCV	26%	Low
Hb Electrophoresis	HbSS	Sickle cell anaemia
Wound Swap Culture	Staphylococcus aureus	Treated based on sensitivity
HIV test	Negative	Negative
Mantoux test	0mm	Negative

deeper dermis showed normal dermal appendages of sebaceous sweat glands and hair follicles. None availability of other investigative methods such as immunofluorescence mapping and transmission electron microscopy preclude further confirmatory diagnostic investigations. There was no evidence of malignancy.

Patient has been on routine drugs for SCA and regular at clinic visits. He has been thriving well but not without challenges of these recurrent mechanobullous skin lesions. Parents were counseled on the risk of recurrence.

DISCUSSION

Dystrophic epidermolysis bullosa (DEB) is one of the major variant of epidermolysis bullosa.[1,2] The signs and symptoms of this condition vary widely among affected individuals.[2] These mechanobullous disorders are characterized by blistering of the skin and mucous membranes following minor or insignificant trauma or even tractions to the affected areas. Recessive dystrophic epidermolysis bullosa (RDEB) is caused by mutations in COL7A1, the gene that encodes for C7.[4] One of the most severe types of epidermolysis bullosa, RDEB is typically inherited in an autosomal-recessive fashion. It results from transfer of the mutated COL7A1 copies from both parents, who carry the mutation, to the affected offspring.[6] C7 is the main component of anchoring fibrils, structures that attach the dermis to the epidermis at the dermalepidermal junction.[7] The inability of these anchoring fibrils to form and function properly causes the epidermis not adheres to the underlying dermis. This led to loss of structural integrity[11] which in turn cause the skin to become susceptible to even slight trauma and also hinders the skin from healing productively.[8] Most often, blisters are present over the whole body and affect mucous membranes such as the moist lining of the mouth and digestive tract. As the blisters heal, they result in severe scarring. Scarring in the mouth and esophagus can make it difficult to chew and swallow food, leading to chronic malnutrition and slow growth. Additional complications of progressive scarring can include fusion of the fingers and toes, loss of fingernails and toenails, joint deformities (contractures) that restrict movement, and eye inflammation leading to vision loss. Additionally, young adults with the classic form of dystrophic epidermolysis bullosa have a very high risk of developing squamous cell carcinoma, which tends to be unusually aggressive.[1]

The blisters either occur spontaneously or in reaction to minor trauma[1] in the index patient, the blisters on the skin were more on the hands and the legs very extensive as evident by the extensive scar. There was also involvement of the trunk and the perineum which may have been triggered by friction from his clothing and diapers while the sores on the nail beds occurred spontaneously. Gum bleeds and mucosal bleeds in the mouth were triggered by chewing solid foods and even tablets which would ordinarily not lead to bleeding in infants and underfive without this condition. Our patient was also having odynophagia probably due to ulcers along the oesophagus. These findings agree with other authors that reported similar presentations of DEB.[4,7,9]

The variant of dystrophic epidermolysis bullosa, Hallopeau-Siemens type (RDEB-HS) is the most severe, classic form of the condition. In this form, extensive, severe blistering can occur anywhere on the body, including the inside of the mouth and the oesophagus as in our patient (Figure 3). Blistering is present from birth and tends to improve with age. But in our patient such improvement with age was not observed may be because of another co-morbid condition that also can lead to skin ulcer or making ulcer healing difficult; that is Sickle cell anaemia.[3] Few reports from Nigeria,[4,5] contrary to the present report, described EB simplex which is the commonest form encountered but less

severe and less extensive compared to RDEB.

Establishing the diagnosis was challenging in our patient as it was initially mistaken for neonatal sepsis. This is in consonance with Oseni et al who highlighted in their case report such similar diagnostic challenges.[5]

Diagnosis was subsequently made upon re-establishment of contact with the patient and planned skin biopsy for histology was done. Medenica, *et al*[10] reported two cases of a 27-year-old male Caucasian and a 24-year-old female whom they had managed from birth. Both cases developed various problems ranging from pseudo fusion of the digits to difficulty with protrusion of the tongue. This highlights the problems our patient is likely to face in the future if he lives to the first and second decades. Our patient is likely to face severe challenges because of the SCA and its effect on DEB, whose association need further research.

Treatment for dystrophic epidermolysis bullosa is mainly supportive. In our patient, his parents were counseled on avoidance of trauma and friction, wound management, infection prevention and control and nutritional support. A systemic antibiotic was given based on sensitivity pattern; subsequently a topical antibiotic cream was prescribed to prevent superimposed bacterial infection. Vaseline gauze was used to separate the toes to prevent pseudofusion or acquired syndactyly, while patient was on regular prophylaxis for SCA comprising of palludrine, folic acid and vitamin C. Patient was also counseled to sleep under insecticide treated nets to prevent frequent malarial attack to reduce the frequency and severity of sickle cell crises.

Owing to its nature and severity, RDEB presents unique challenges for developing successful therapies that simultaneously alleviate the plethora of complications while having a significant impact on survival and quality of life. Recently, genome editing strategies using zinc-finger nucleases (ZFNs)[11] and transcription activator-like effectors nucleases (TALENs) have demonstrated the ability to target specific sites in the human genome and correct endogenous mutations such as the one causing RDEB.[11] Other newer therapies though still undergoing research are: HCT (hematopoietic cell transplantation); IPS (induced pluripotent stem cell).[12] These therapies are still a mirage in developing countries like ours.

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