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Case Report

ROLE OF ORAL LESIONS IN DIAGNOSING GENERALISED RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA- A RARE CASE REPORT

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ABSTRACT
Epidermolysis bullosa (EB) is a heterogeneous group of genetically determined, vesiculo-bullous disorders characterized by blister formation in response to mechanical trauma. Three major subgroups, simplex, junctional, and dystrophic EB, contain more than 20 genetically and clinically distinct subtypes. In the present case, we described a patient diagnosed with a milder variant of generalised recessive dystrophic epidermolysis bullosa with specific oral and cutaneous lesions, which was previously named as non-Hallopeau-Siemans subtype.

Keywords: *Epidermolysis Bullosa, Genetically Determined, Recessive Dystrophic Subtype*

INTRODUCTION
Epidermolysis bullosa (EB) comprises a group of genetically determined skin fragility disorders characterized by blistering of the skin and mucosa following mild mechanical trauma. Dystrophic Epidermolysis Bullosa (DEB) is a subtype of EB with a well understood pathogenesis. The main presenting feature of DEB is trauma induced blisters followed by healing with scarring. The dystrophic forms of EB are characterized by deformities of the skin including coalescence of the fingers, nail changes and milia formation, and have either autosomal recessive (RDEB) or dominant (DDEB) inheritance (Serrano-Martínez *et al.,* 2003). Prevalence of DEB is not known precisely though it is found to occur in all races worldwide with equal predilection in both the genders (Leena, 2010). There are three main subtypes of RDEB- severe generalized RDEB (formerly named Hallopeau-Siemens RDEB), non-Hallopeau-Siemens RDEB, and inverse RDEB. Each has its onset at birth. The most severe subtype, severe generalized RDEB, is clearly one of the most devastating multi-organ, genetically transmitted disorders seen in mankind. Prototypic findings include generalized blistering at birth, progressive and often leading to mutilating scarring of the skin, corneal blisters or scarring (Fine *et al.,* 2004), profound growth retardation (Fine *et al.,* 2008), multifactorial anemia, failure to thrive (less common than in JEB-H), esophageal strictures (Fine *et al.,* 2008), and debilitating hand and foot deformities ("mitten deformities"; pseudosyndactyly etc.). The non-Hallopeau-Siemens RDEB, on the other hand, has similar but milder manifestations (Fine *et al.,* 2005), as will be presented here.

CASES
A 25 year old female patient reported to our outpatient clinic with the chief complaint of decayed painful teeth and difficulty in cleaning teeth. Parents reported that she had been having oral and skin blisters and ulcerations since birth for which she had been diagnosed as a case of Epidermolysis bullosa five years back at some private dermatology clinic and was under medication since then. There family history was not significant. They reported that she usually avoided brushing her teeth and was under soft diets since birth to avoid frictional trauma to the oral mucosa.
General physical examination revealed a dwarf and thinly built physique with normal phonation. Toe nails and finger nails were missing with atrophic nail beds (Figure 2B and C) and constricted distal inter-phalangeal joints of fingers. Skin on the arms, legs, neck, and face was dry, wrinkled, atrophic and shiny with hypopigmented confluent scars present and crusting at some places (Figure 2B-E). Fresh bullae

were present on the skin surface with serous hemorrhagic fluid. Scarring alopecia was present on the scalp (Figure 2A).

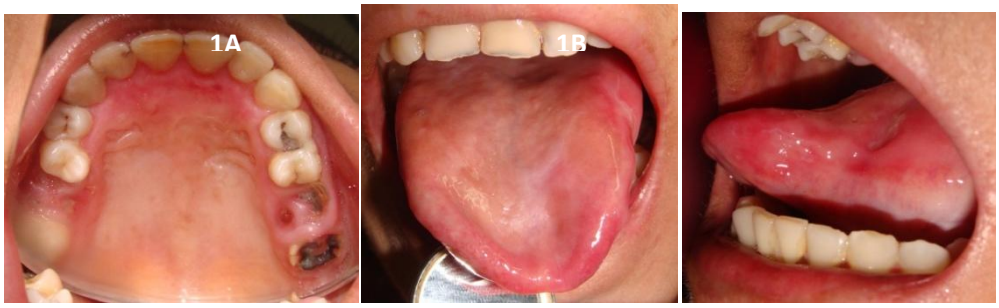

Figure 1: Intraoral pictures: A Pale, shiny, atrophic oral mucosa, while all the teeth are normal in appearance and morphology with grossly carious posterior teeth B Pale, atrophic, shiny surface of tongue with loss of papillae C Atrophic tongue mucosa with ulceration irt left lateral aspect of tongue

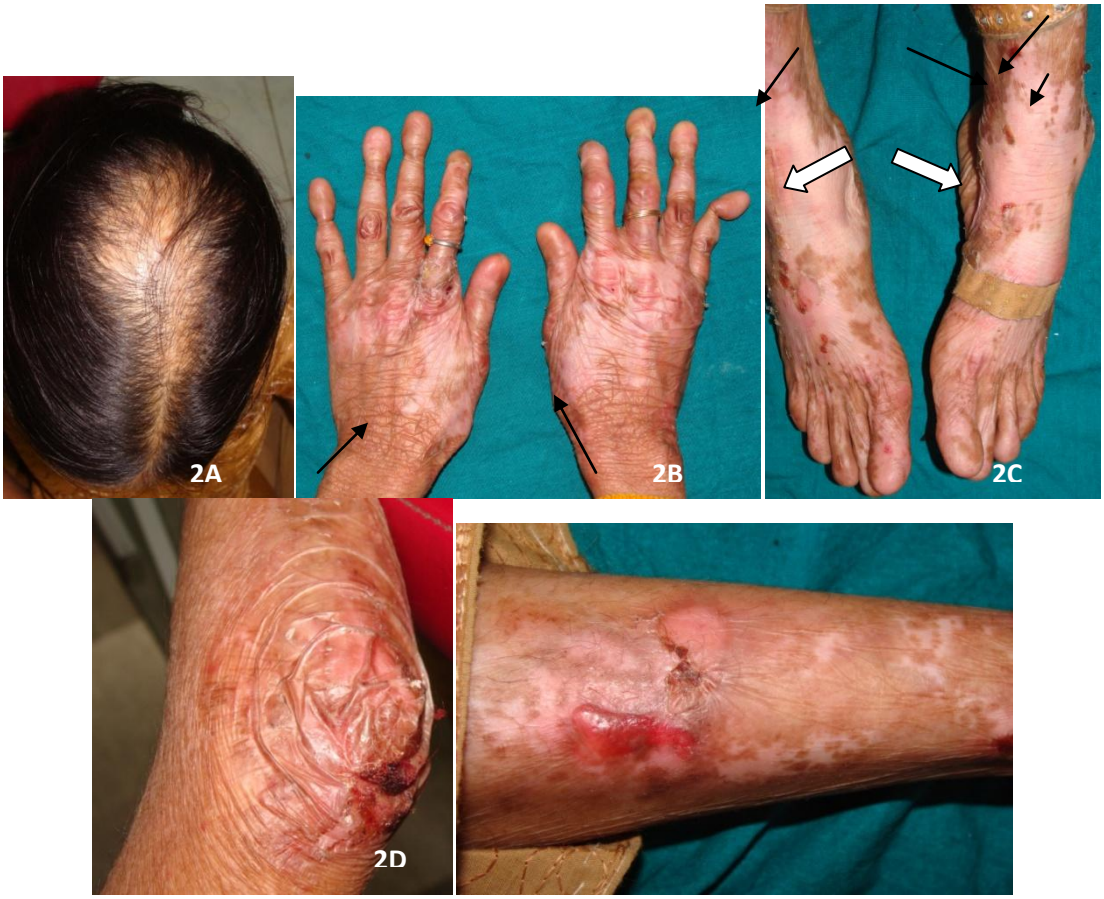

Figure 2: Extraoral pictures: A Sparse hair and scarring alopecia irt parietal region of scalp B Atrophic scarring and post-inflammatory hypopigmented areas in a flame shaped, sock-like distribution (arrows) and wrinkled skin of forearm, with complete absence of nails and with shrunken atrophic nailbeds and constricted distal inter-phalangeal joints C Atrophic scarring with hypopigmented areas in a flame shaped (thin arrows) and sock-like (thick arrows) distribution and wrinkled skin with complete absence of nails irt lower extremity D Skin on the elbow has become shiny, wrinkled, atrophic and crusted after repeated blistering E Fresh bulla formation on skin, containing serous hemorrhagic fluid, with surrounding hypopigmented scars due to previous blisters

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Intra-orally, generalised mucosal atrophy and pallor was seen. There was complete atrophy of lingual mucosa with loss of filliform papillae (Figure 1B and C) and palatal mucosa with loss of rugae pattern (Figure 1A). All the permanent teeth were present with grossly carious posterior teeth. All the non-carious teeth were intact in morphology and appearance (Figure 1A). Hence, based on the clinical findings, the case was provisionally diagnosed as dystrophic recessive epidermolysis bullosa (RDEB) (non-hallopeau type). Histopathological examination of skin revealed dermo-epidermal split, and immunopathological examination revealed that collagen band VII was absent at basement membrane zone (BMZ), while keratin 4 and laminin band V showed a normal pattern. After correlating the clinical and histopathological findings, the diagnosis of DREB was confirmed. Extraction of the grossly carious teeth was advised and patient was counselled to maintain good oral hygiene and to avoid cariogenic food.

DISCUSSION

There are four major types of inherited EB: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (Alper *et al.,* 1978). These differ not only phenotypically and genotypically but more importantly by the site of ultrastructural disruption or cleavage. Intra-epidermal blistering is the hallmark feature of EB simplex. EB simplex patients are then further subclassified, based on whether blisters arise within the basal or suprabasal layers of the epidermis (Fine *et al.,* 2008). In contrast, JEB and DEB patients develop their blisters within the lamina lucida and sub-lamina densa of the skin basement membrane zone ("dermoepidermal junction"), respectively. In Kindler syndrome, multiple cleavage planes may be seen within the same biopsied specimen of skin (Shimizu *et al.,* 1997).

DEB further occurs as recessive (RDEB) and dominant (DDEB) forms. There are mutations in the COL7A1 gene, encoding type-VII collagen which is the major component of anchoring fibrils, in the RDEB (Hashimoto *et al.,* 1976; Kahofer *et al.,* 2003). The resulting abnormal structuring in type-VII collagen prevents the organizational structuring of anchoring fibrils (Kahofer *et al.,* 2003). In RDEB, bullae are present at birth or appear in early infancy, especially affecting the hands, feet and lower legs in a flame shaped or sock-like distribution and leave atrophic scarring after healing (Wojnarowska *et al.,* 1983). In our case as well, the lesions and hypopigmented scars typically presented in a flame shaped, sock-like distribution on feet (Figure 2C) as well as hands (Figure 2B). Although the whole of the skin is fragile, the main sites of predilection for blister development are those subjected to repeated friction or trauma, as on knees (Figure 2D), elbow, hands (Figure 2B and E), and feet (Figure 2C), back of the neck, shoulders, and spine. Chronic ulcers tend to become covered with a slough, often associated with heaped up crusting and scarring. Scalp is often involved. Hair growth on scalp and body is impaired and scarring alopecia may occur (Fine *et al.,* 2005), as seen in our case (Figure 2A). Pseudosyndactyly may result in mitten like deformity of hands. Disuse of hands results in bony resorption and muscular dystrophy (Sweet *et al.,* 1999), as was apparent in our case (Figure 2B), constricted inter-phalangeal joints and thin, atrophied fingers. Non-cutaneous epithelia are also at risk of developing blisters, erosions and scars. Oral lesions may be severe, leading to marked ankyloglossia and microstomia. The gingivae are fragile and even gentle brushing may induce epithelial disruption and bleeding resulting in poor oral hygiene. The lingual papillae are lost and the surface of tongue becomes smooth, shiny and atrophic (Sweet *et al.,* 1999), as in our case (Figure 1B and C). In RDEB, esophageal strictures and pseudosyndactyly are of particular importance, since they occur early in childhood and continue to negatively impact the functionality of these patients throughout life (Fine *et al.,* 2008). Similarly, about 30% of severe generalized RDEB patients have signs of pseudosyndactyly as early as 2 years of age and virtually 100% develop this by age 20 (Fine *et al.,* 2005). Although secondary caries occurs, no primary enamel defects exist in any type or subtype of dystrophic EB (Sweet *et al.,* 1999; Fine *et al.,* 2004), as seen in our case (Figure 1A). Enamel hypoplasia is seen exclusively in all subtypes of JEB and is therefore a highly useful diagnostic finding (Wright *et al.,* 1993). Chronic renal failure, the result of poststreptococcal glomerulonephritis or renal amyloidosis, occurs within the RDEB subtype, and may eventually lead to death in about 12% of the patients (Fine *et al.,* 2004). A low but real risk of potentially fatal dilated cardiomyopathy (cumulative risk of 4.5% by age 20, 30% of whom eventually die of this complication)

exists in patients with severe generalized RDEB. Although the exact etiology is still not known, data suggest the possibility that this may result from a micronutrient deficiency (carnitine; selenium) or chronic iron overload (Fine *et al.,* 2008).

Although the risk of infantile death from any cause is low in RDEB, nearly all patients with severe generalized RDEB will develop at least one cutaneous squamous cell carcinoma (arising as early as within the second decade of life), and most (about 87% by age 45) will then die of metastatic squamous cell carcinoma within five years of the time of diagnosis of the first squamous cell carcinoma, despite apparent complete surgical removal of each primary carcinoma. Rare children with severe generalized RDEB are also at risk of developing malignant melanoma (cumulative risk of 2.5% by age 12) although none of the latter has resulted in metastasis (Fine *et al.,* 2009). General physical development is retarded.

Most patients are very thin and have a short stature. Some blood vitamins and trace metal levels are low and natural killer cell activity is impaired (Fine *et al.,* 1989). A more common RDEB subtype, which was the diagnosis in our case, formerly known as non-Hallopeau-Siemens RDEB (and probably best referred to as generalized mitis RDEB), has similar but less severe cutaneous involvement and a much lower risk of esophageal strictures, corneal injury, or hand or foot deformities (Fine *et al.,* 2009), tend to be more localised and similar to those seen in classical dominant dystrophic EB (Briggaman, 1992). Growth retardation and anaemia are extremely uncommon.

However, these patients still have a significant risk of developing squamous cell carcinomas (47.5% by age 65), although the risk of death from metastases (60% by age 65) is lower than that which is seen in severe generalized RDEB (Fine *et al.,* 2009).

Conclusion

There is no effective treatment for epidermolysis bullosa, only palliative care is given. In case of severe oral lesions, nutritional support must be provided as coarse foods are not well tolerated, and a high caries rate is often the norm. Autologous skin grafting can be performed on non-healing skin lesions (Wright *et al.,* 1993; Gache *et al.,* 2011). Preventive strategies may include topical fluoride application to prevent dental caries and physical removal of bacterial plaque supplemented with chemical inhibition by the use of chlorhexidine gluconate mouthwash. Neutral pH sodium fluoride mouthwashes are useful compared to acidic ones as the later cause discomfort during oral ulceration. Nutritional advice may be indicated (Wright *et al.,* 1993).

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