

Case Report

Dystrophic epidermolysis bullosa presenting as scarring skin eruptions and nail dystrophy

失養症性大疱性表皮鬆解表現為疤痕性皮損及指趾甲失養症

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A 57-year-old Chinese gentleman presented with pruritic skin eruptions located mainly over the shins since childhood. Scratching resulted in skin blister and finally scarring. He also had nail dystrophy over the fingers and toes since childhood. Incisional skin biopsy for histology and electron microscopy was compatible with the diagnosis of dystrophic epidermolysis bullosa. His mother had "prurigo nodularis" and nail dystrophy, but she was not available for examination as she lived abroad. His siblings, children and father were free of skin diseases. He was given symptomatic treatment with topical steroid, euras cream and oral antihistamine. Antibiotics and local antiseptic solution were used to control skin infections. His pruritic symptom was under control, although the skin scarring and nail dystrophy remained the same.

57歲男性華人自童年起於雙脛前區有癢性皮炎。搔癢後皮膚起疱及形成疤痕。此外，患者自童年起便有指趾甲失養症。皮膚活組織檢查送組織學及電鏡下檢查與失養症性大疱性表皮鬆解的診斷吻合。患者母親曾患有“癢疹”和指趾甲失養症，但因身處外國未能接受進一步檢查。患者的父親、子女及兄弟姐妹均無皮膚病。患者接受局部激素、克勞米通霜劑及口服抗組胺藥作對症處理。抗生素及局部消毒液作控制皮膚感染。患者的皮膚疤痕及指趾甲失養症持續，但癢症症狀則得到控制。

Keywords: Chinese, dystrophic epidermolysis bullosa

關鍵詞：華人，失養症性大疱性表皮鬆解

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Introduction

Epidermolysis bullosa (EB) is a group of heterogeneous diseases characterised by development of blister after minor mechanical trauma. There are three types of inherited EB and they differ from one another by the level of skin cleavage.¹ Epidermolysis bullosa simplex has skin cleavage located at basal keratinocytes, whereas, site of skin cleavage of junctional epidermolysis

bullosa is localised at the intra-lamina lucida region. Dystrophic epidermolysis bullosa (DEB) is characterised by blister developing in the sublamina densa region. The latter entity, although rare, has been previously reported in Hong Kong Chinese.² We described another case of dystrophic epidermolysis bullosa in a 57-year-old Chinese.

Case report

A 57-year-old Chinese gentleman, with a known history of asthma, presented to our skin clinic in 1986 with pruritic skin eruptions. These were localised mainly over the shins. The elbows and trunk were involved to a lesser extent. The skin eruption had been developing since childhood. Scratching of the skin was followed by the formation of skin blister and, finally, scarring. He noticed that his shins were easily traumatised with minor injury. At the same time, nail dystrophy developed insidiously over his fingers and toes since childhood. There was no mucosal involvement. He had multiple dental caries with teeth extraction in the recent few years. Systemic symptoms such as weight loss, dysphagia and constipation were absent. Skin biopsy had been performed in Taiwan in the year 1970 but the patient was not sure of the result. He was given five to six courses of steroid injection in Taiwan with only temporary symptomatic relief. His parent's marriage was nonconsanguinous. He had five siblings and two children, all of them did not have any similar skin problem or nail dystrophy as recalled by the patient. His mother had a history of prurigo nodularis and dystrophic toenails. She had never received any skin biopsy but unfortunately, she could not come for examination as she resided in the United States.

Physical examination of the index patient revealed scarring and erosions located symmetrically over both shins and calves (Figure 1). There were hypopigmented scars over the upper back, abdominal walls and both elbows. Apart from



Figure 1. Symmetrical scarring and erosions over both shins of the patients.

androgenetic alopecia, there was no other hair abnormality. There was neither any milium nor blister at the time of examination. His fingernails and toenails were rudimentary and dystrophic (Figures 2 & 3). Taking into account of the timing of onset and the clinical features as summarised above, the most likely clinical diagnosis was DEB. The other clinical differential diagnoses might include lichen planus, prurigo nodularis and epidermolysis bullosa acquisita. Investigations including complete blood picture, liver and renal function tests were normal. Incisional biopsy of skin lesion over the lower limb showed re-epithelialised, pauci-inflammatory subepidermal blister with underlying dermal scarring (Figure 4). Direct immunofluorescence study was negative. However, localisation of lamina densa in blister by histochemical and immunohistochemical methods yield equivocal results. Fortunately, electron microscopy confirmed the presence of lamina densa in roof of blister in many areas. The anchoring fibrils, however, were morphologically unremarkable. The overall features were compatible with DEB. He was given topical steroid, euras cream and oral antihistamine for symptomatic relief. Topical chlortetracycline



Figure 2. Rudimentary and dystrophic toenails.



Figure 3. Rudimentary and dystrophic fingernails.

ointment and potassium permanganate solution were given for eroded areas. The pruritic symptom remained under control with treatment, although he occasionally developed blisters and erosions over his shins on minor trauma.

Discussion

DEB is a heterogeneous collection of inherited mechanobullous disorder with characteristic

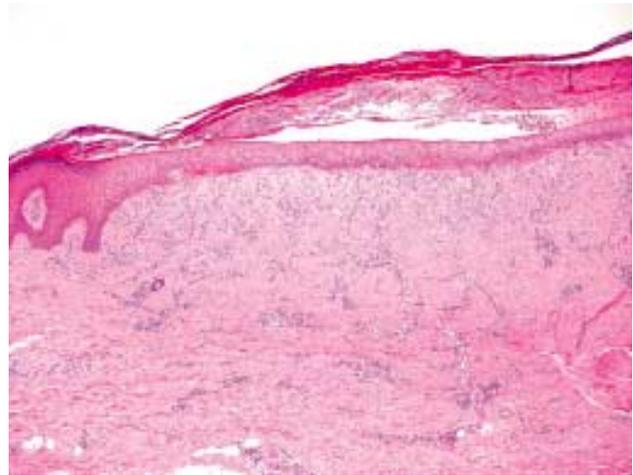


Figure 4. There is a re-epithelialised subepidermal blister with underlying dermal scarring. Note the relatively cell poor nature in the base of the blister (H&E, original magnification x 20).

trauma-induced blisters, associated with milia, scarring and nail dystrophy. Ultrastructurally, there is a sublamina densa level of blister formation and quantitative or qualitative changes in anchoring fibrils at the dermo-epidermal junction.³ DEB can be subdivided into commonly observed types and rare types.¹ Commonly observed subtypes included dominant DEB, recessive DEB-Hallopeau-Siemens (HS) and recessive DEB-non HS. The rare types were clinically striking and included dominant DEB-pretibial, DEB-transient bullous dermolysis of the newborn, dominant DEB-pruriginosa, recessive DEB-inversa, recessive DEB-centripetalis and DEB, autosomal dominant/recessive heterozygote. Our patients have pruritic eruptions involving mostly the shins. Features compatible with either pretibial EB or DEB-pruriginosa are present. Pretibial EB features recurrent blistering with scarring and milia formation predominantly in the pretibial area and variable nail dystrophy.⁴ In pretibial EB, involvement of other areas of body, besides pretibial region, is not unusual. Moreover pruritus is common and prurigo-like lesions can be present.⁴ EB pruriginosa was first described by

McGrath et al in 1994.³ It is characterised clinically by pruritus, lichenified or prurigo-nodularis like lesions, violaceous linear scarring, occasional trauma-induced blistering, milia and nail dystrophy. The lesions are mostly located over the shins, but are also prominent on forearms and sometimes on the trunk. Thus, there are substantial similarities between pretibial EB and EB pruriginosa.

Pathologically, DEB presents as subepidermal blister/cleft and the basal cells appear intact. There is a moderate to heavy upper to mid-dermal interstitial and perivascular lymphohistiocytic infiltrate. Fibrosis may be present in papillary dermis. Milia may also be seen. There are several non-molecular histological diagnostic methods for EB, namely electron microscopy, immunofluorescence antigen mapping and EB-specific antibodies.⁵ Electron microscopy demonstrates the level of skin cleavage directly and in DEB, it is in the sublamina densa. Immunofluorescence antigen mapping infers the level of cleavage from fluorescence staining of epidermal antigens and in DEB, bullous pemphigoid antigen-1, laminin-5 and type IV collagen are all in the roof of blister. LH 7:2 antibody binds to the N-terminal of type VII collagen. In recessive DEB, there is reduced or absent staining by this antibody whereas in dominant DEB, the staining is normal.

DEB results from mutations in the COL7A1 gene, which is located on chromosome 3p21 and encodes type VII collagen.⁶ Type VII collagen is the major constituent of anchoring fibrils in the dermoepidermal junction and is synthesised primarily by keratinocytes and less by dermal fibroblasts. Three polypeptides, $\alpha 1(\text{VII})$ chains, fold into typical triple helix. Type VII collagen has a central triple helix domain consisting of Gly-X-Y repeats, flanked by two noncollagen domains. Most dominant DEB patients have mutations resulting in glycine substitution in the Gly-X-Y repeats. Although a full-length polypeptide is produced, the triple helix is not as stable as the

normal type VII collagen. This leads to clinical phenotype of dominant DEB. In contrast, the more severe clinical phenotype of recessive DEB results from mutations leading to truncated type VII collagen polypeptide. Pedigree analysis is important in deducing the possible mode of inheritance and genetic counselling. But in the absence of an informative pedigree, detection of collagen mutation, if available, can be useful. This has been applied to detect a de novo mutation in dominant DEB⁷ and a recessive splice site mutation in pretibial EB.⁸ Moreover, the dominant clinical phenotype of DEB can be manifested as familial nail dystrophy, with or without skin eruptions.⁹ It is therefore important to examine skin as well as nails in relatives of DEB patients.

Treatment of DEB includes avoidance of trauma, use of nonadherent dressings for wound and treatment of wound infection if present. Skin grafts, either allografts¹⁰ or autografts,¹¹ have also been tried but there is no proper randomised trial on this treatment modality. Gene therapy is only in the early stage of development. Gene corrected fibroblasts, from patients with recessive DEB, have shown to be able to restore type VII collagen expression in skin equivalent culture and in animal models.¹² It is hoped that gene therapy can provide a final solution for DEB, especially for the recessive form, which is essentially a genetic disease.

References

1. Fine JD, Eady RA, Bauer EA, Briggaman RA, Bruckner-Tuderman L, Christiano A, et al. Revised classification system for inherited epidermolysis bullosa: Report of the Second International Consensus Meeting on diagnosis and classification of epidermolysis bullosa. *J Am Acad Dermatol* 2000;42:1051-66.
2. Tang WY, Lee KC, Chow TC, Lo KK. Three Hong Kong Chinese cases of pretibial epidermolysis bullosa: a genodermatosis that can masquerade as an acquired inflammatory disease. *Clin Exp Dermatol* 1999;24: 149-53.
3. McGrath JA, Schofield OM, Eady RA. Epidermolysis bullosa pruriginosa: dystrophic epidermolysis bullosa

- with distinctive clinicopathological features. *Br J Dermatol* 1994;130:617-25.
4. Lee JY, Chen HC, Lin SJ. Pretibial epidermolysis bullosa: a clinicopathologic study. *J Am Acad Dermatol* 1993; 29:974-81.
 5. Fine JD, Smith LT. Nonmolecular diagnostic testing of inherited epidermolysis bullosa: current techniques, major findings and relative sensitivity and specificity. In: Fine JD, Bauer EA, McGuire J, et al editors. *Epidermolysis bullosa: clinical, epidemiologic and laboratory advances and the findings of the National Epidermolysis Bullosa Registry*. Maryland: John Hopkins University Press, 1999:48-78.
 6. Jarvikallio A, Pulkkinen L, Uitto J. Molecular basis of dystrophic epidermolysis bullosa: mutations in the type VII collagen gene (COL7A1). *Hum Mutat* 1997;10: 338-47.
 7. Matsuba S, Suga Y, Mayuzumi N, Ikeda S, Ogawa H. A Japanese case of de novo dominant dystrophic epidermolysis bullosa. *Clin Exp Dermatol* 2002;27: 56-8.
 8. Betts CM, Posteraro P, Costa AM, Varotti C, Schubert M, Bruckner-Tuderman L, et al. Pretibial dystrophic epidermolysis bullosa: a recessively inherited COL7A1 splice site mutation affecting procollagen VII processing. *Br J Dermatol* 1999;141:833-9.
 9. Dharma B, Moss C, McGrath JA, Mellerio JE, Ilchyshyn A. Dominant dystrophic epidermolysis bullosa presenting as familial nail dystrophy. *Clin Exp Dermatol* 2001;26:93-6.
 10. Fivenson DP, Scherschun L, Choucair M, Kukuruga D, Young J, Shwayder T. Graftskin therapy in epidermolysis bullosa. *J Am Acad Dermatol* 2003;48:886-92.
 11. Beele H, Naeyaert JM, Monstrey S, Kint A. Ulcers in pretibial epidermolysis bullosa. Grafting with autologous meshed split-thickness skin and allogeneic cultured keratinocytes. *Arch Dermatol* 1995;131:990-2.
 12. Woodley DT, Krueger GG, Jorgensen CM, Fairley JA, Atha T, Huang Y, et al. Normal and gene-corrected dystrophic epidermolysis bullosa fibroblasts alone can produce type VII collagen at the basement membrane zone. *J Invest Dermatol* 2003;121:1021-8.



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