A family with epidermolysis bullosa pruriginosa due to a novel mutation in the *COL7A1* gene

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Introduction

Epidermolysis bullosa pruriginosa (EBP) is a subtype of dystrophic epidermolysis bullosa characterised by intensely pruritic, trauma induced blistering mainly over the pre tibial area[1]. We report a family with EPB where seven members from three generations were affected, clearly showing an autosomal dominant pattern of inheritance. Genetic analysis revealed a novel mutation in the *COL7A1* gene.

Case histories

Case 1 (index case)

A 55 year-old male from Hingurakgoda presented to the skin clinic General Hospital, Polonnaruwa with severely itchy, trauma induced blistering over the shins since childhood. The blisters were treated with atrophic scarring (Figure 1), but some hypertrophic scars were also present. The severity of the lesions had worsened with age, extending to the lower thighs and dorsa of feet. His toe nails were dystrophic with pterygium formation (Figure 2). Upper limbs were spared.

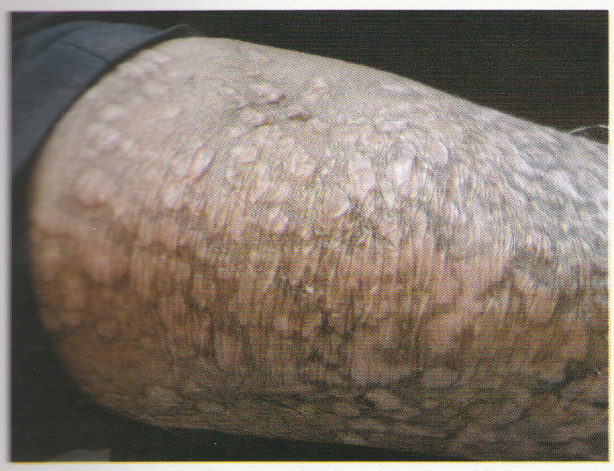

Figure 1. *Atrophic scars over the shins of case 1 following trauma induced blisters.*

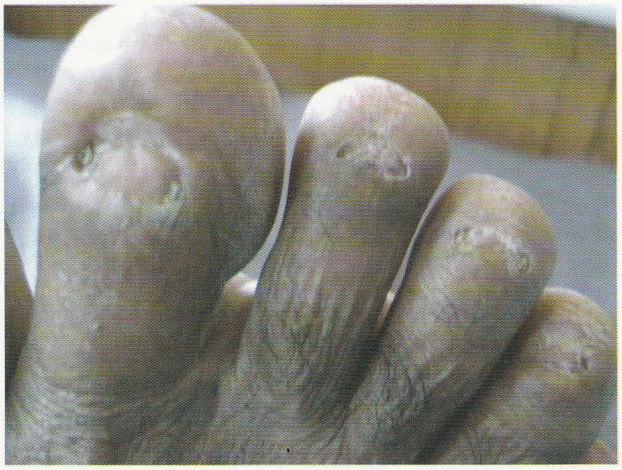

Figure 2. *Pterygium formation of the toes in case 1.*

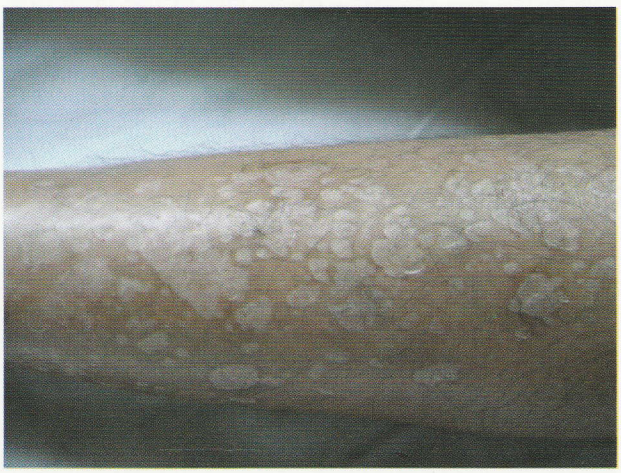

Figure 3. *Atrophic scars over the shin of case 2.*

The patient was a known diabetic and hypertensive, being followed up in the medical clinic, GH Polonnaruwa. He had been previously started on dapsone based on a skin biopsy finding of atrophic lichen planus.

On direct questioning he admitted that several members of his extended family were affected by a

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similar illness. His mother, deceased now, had been the first member of the family to manifest the disease. He had two other siblings (a 70 year old brother and a sister who is deceased) with similar skin problems. According to the history given by the index case the offspring of his siblings were not affected. Out of the 4 daughters of the index case three were suffering from similar blistering. His youngest daughter, who is 16 years of age, was not affected.

Case 2 (eldest daughter of the index case)

This patient is a 33-year old mother of a 13-year old son and 8-year old daughter, who are so far unaffected.

She has had trauma induced itchy blistering over the shins since infancy (Figure 3). These blisters heal with atrophic scars. Her toe nails had been affected since childhood. Unlike other members of the family she had started to develop haemorrhagic blisters in the finger nails recently.

Case 3 (daughter 2)

A 31-year old, mother of a 9 month old daughter who is healthy so far. Blistering is similar to that of the sister. She reported worsening of the blistering during pregnancy. She too had involvement of toe nails.

Case 4 (daughter 3)

This 29-year old mother of two was not seen at our clinic. She was reported to have blistering similar to her sisters. She too has atrophic scars and nail involvement. Her 9 year old daughter and 6 year old son were not affected.

Investigations

Skin biopsy was not done as the clinical presentation was typical and light microscopic features are non specific.

Blood from cases 1, 2 and 3 were sent to the St. John's Institute of Dermatology for genetic analysis. Molecular screening of the *COL7A1* gene showed a heterozygous G>A single nucleotide substitution at position c.6900 in exon 87 designated p.Q2300Q.

Management

All patients were advised on avoidance of trauma. The young women were also counselled on the possibility of their offspring being affected. All patients were also alerted to the possibility of malignant change in long standing scars and were asked to report any untoward changes in scars.

Case 1 was initially treated with potent topical corticosteroids and emollients with minimal improvement of symptoms. He was later started on topical tacrolimus 0.03% ointment for symptomatic relief but was subsequently lost to follow up.

Discussion

Epidermolysis bullosa (EB) is a group of inherited disorders in which blistering of the skin and the mucosae occur on trivial trauma. Dystrophic EB, a subgroup of EB is characterised by anchoring fibril abnormalities and sub-lamina densa blistering. Epidermolysis bullosa pruriginosa (EBP) is a subtype of dystrophic EB characterised by intensely pruritic, trauma induced blistering mainly over the pre tibial area[1]. Other feature include nodular prurigo like lesions, nail dystrophy and variable presence of albopapuloid lesions[1]. Skin fragility usually becomes evident in early childhood but may be delayed till the second or third decade. Autosomal dominant, autosomal recessive and sporadic cases have been reported.

The differential diagnosis includes other forms of epidermolysis bullosa and lichen planus. With the degree of scarring and the nail changes it may be difficult to make a distinction between lichen planus and EBP.

The underlying genetic mutations are in the type VII collagen gene (*COL7A1*)[1]. Several mutations like glycine substitution, deletion mutations and splice site mutations have been reported[2]. These mutations are identical to mutations leading to non-itchy variants of dystrophic EB which has led to the assumption that factors other than the inherent genetic mutation may lead to EBP[2].

Genetic analysis was done in three members of the family reported here and they all showed a heterozygous G>A substitution in position c.6900. Although this mutation does not result in an amino acid change it occurs in the last nucleotide of exon 87 and is expected to alter splicing resulting in the skipping of exon 87. To the best of our knowledge this mutation has been previously detected in one instance only[3].

Treatment of EBP is generally disappointing as targeted therapies are not available. Due to the rarity of the condition no clinical trials on the efficacy of any treatment modality are feasible. There are case reports of the successful use of topical tacrolimus 0.03%

ointment,[4] systemic ciclosporin[5] and liquid nitrogen cryotherapy[6]. These treatment modalities offer symptomatic treatment only and the scarring and cosmetic disfigurement remain unchanged.

Other than the medical management it is important to educate the patients on avoidance of trauma. Genetic counseling should be offered to patients with a family history of the disease. As this is a condition leading to scarring they should also be alerted to the possibility of malignant transformation which could occur within scars[7].

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