Dystrophic Epidermolysis Bullosa Pruriginosa: The First Report of A Family in Malaysia

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INTRODUCTION

The dystrophic forms of epidermolysis bullosa (DEB) are characterized by skin fragility, blister formation, milia and healing with atrophic scars[1]. Often they demonstrate nail dystrophy or absent nails. Both autosomal recessive and autosomal dominant subtypes of DEB have been described in numerous case series and reports. They were caused by mutations on a single gene, the COL7A1, which encodes the anchoring fibril protein, type VII collagen. Patients with DEB typically develop the skin lesions at birth or infancy. Dystrophic epidermolysis bullosa pruriginosa (DEBP), however, has been recognized as a distinct subtype of DEB in which the patients tend to present late and have severe pruritus[2]. As a result, it may be confused with other acquired pruritic skin conditions. In this report, we describe the first Malaysian Malay family with EBP resulting from a novel COL7A1mutation.

CASE REPORT

AAM is a 20 year-old student who presented to us with a 14-year history of intensely pruritic plaques all over her body, but sparing the face, palms and soles. The lesions were initially blisters located at knees and elbows, but subsequently became generalized. The blisters ruptured and healed with hyperkeratotic plaques. She was treated by primary care doctors with systemic and topical corticosteroids, systemic antibiotics and emollients, but without improvement. Apart from allergic rhinitis, she has no significant past medical history. She is the 8th child of the family (Figure 1). Her parents were non-consanguineous. Her father, 4 other sisters and a brother also have history of itchy blisters and papules of varying degree of severity over the limbs.

Clinically there were linear dyspigmented hyperkeratonic plaques over the arms, legs, abdomen, back and buttock, sparing her face and scalp. A few blisters were noted on the abdomen, right knee and legs (Figure 2(a) i). Albopapuloid lesions were noted over the dorsum of hands and feet (Figure 2(a) ii). There were onychogryphosis of both thumbs, right index, middle and ring fingers and pterygium on her toenails. She had xerosis. There was no abnormality of her teeth or hair. She did not have palmoplantar keratoderma.

Our provisional diagnoses include dermatitis artifacta, keratosis lichenoides chronica, hypertrophic lichen planus and lichen simplex chronicus. Due to the presence of strong family history, we also investigated the diagnosis of dystrophic epidermolysis bullosa pruriginosa.

The blood count showed eosinophilia ($1.9x10^9$/L) and mild hypochromic microcytic anemia with haemoglobin of 10.5g/dl. The white cell count and platelet counts were normal. Her serum iron level was 8umol/L (normal range 6.6-26.0) and the total iron binding capacity was 68umol/L (normal range 49-89). The renal profile, liver function tests and random blood sugar were normal. Antinuclear antibodies were negative. She was also found to have a very high IgE (>5000kU/L) with high serum enzyme immunoassay values for house dust mites.

Histology of a skin biopsy obtained from a hyperkeratotic plaque on the left arm showed a cell poor subepidermal blister (Figure 2(b) i & ii). The underlying dermis was infiltrated by lymphocytes and some eosinophils. Dermal fibroblasts and capillary vessels were increased. The direct immunofluorescence stainings of perilesional skin with IgG, IgA, IgM, C3 and fibrin antibodies were all negative.

With informed consent and ethical approval, DNA extraction from peripheral blood samples from the patient, her parents and 2 siblings (indicated by red arrow in Figure 1) was carried out for molecular genetic analysis with respect to the diagnosis of dystrophic epidermolysis bullosa. From the extracted DNA, the coding exons 49-118 and the neighboring intronic regions of the COL7A1 gene (Genbank NM_000094.3, NC_000003.11) were amplified by polymerase chain reaction (PCR) and sequenced directly with flanking or internal primers. Mutation was found at c.6860G>A, p.G2287E in exon 87 of the COL7A1 gene in a heterozygous state. Her father and sister (no.7 and no.34 in Figure 1) were also heterozygous for the same mutation. However her mother and sister (no.14 and no. 31 in Figure 1) did not have the mutation. These findings confirmed the diagnosis of dominant dystrophic epidermolysis bullosa in the patient and her family.

The patient and her family members were counseled in length regarding the diagnosis, the inheritance pattern and the prognosis. She was prescribed antihistamines regularly and was advised to apply emollient and moderate potency topical corticosteroids to her lesions under occlusion. Counseling was given to her to avoid trauma and rigorous scratching.

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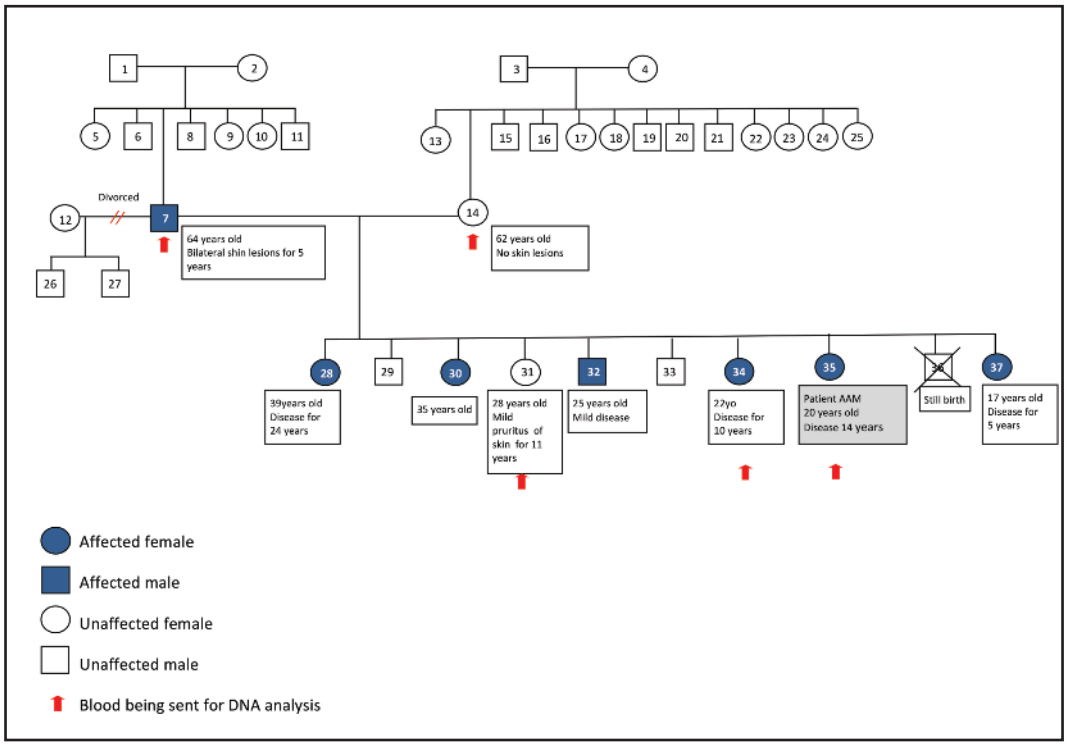

Fig. 1 : Family tree of the index patient

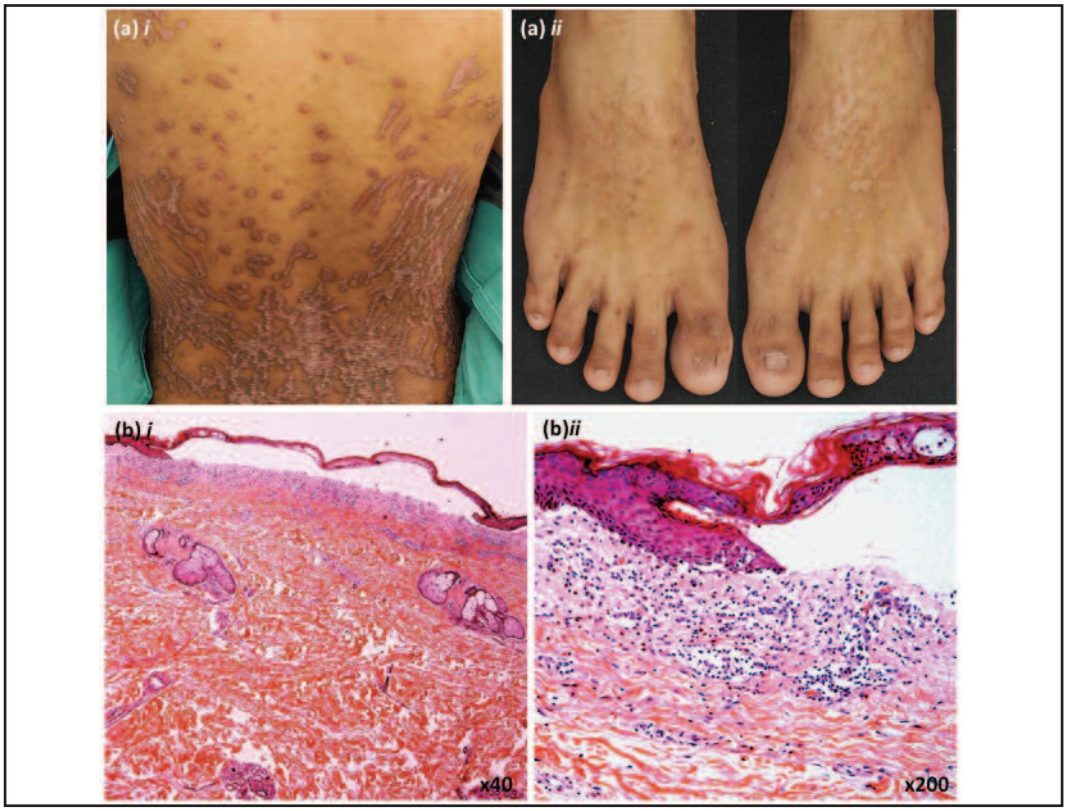

Fig. 2: (a) The clinical appearance of the cutaneous lesions in the index patient. There were extensive linear excoriated hyperkeratotic plaques with a few of tense bullae (a)i. Albopapuloid lesions were noted over the dorsum of the feet and the toe nails were atrophic (a)ii. (b)The histology of skin biopsy taken from a lesion on the abdomen. (b)i A cell poor subepidermal blister (x40); (b)ii The upper dermis was infiltrated by lymphocytes and eosinophils (x200)

Table I: Reported cases of epidermolysis bullosa pruriginosa, the mutations identified and the treatment provided

Author, year & Country	Characteristics of patients	Age of presentation (years)	Age of onset	Associated diseases	COL7A1 mutation identified	Position of mutation	Treatment
McGrath et al(2), 1994, UK	8 unrelated patients (4 males and 4 females)	14-46 14-46	Birth to 10 years	1. Atopy in a patient 2. SCC arising within the scar of the shin	Not done	-	Potent topical corticosteroids under occlusion and intralesional triamcinolone reduced the itch
Lee et al(3), 1997, Taiwan	A Chinese woman	31	10 years	None	G2242R	Ex 85	NA
Yamasaki et al(4), 1997, Japan	A Japanese male	58	10 years	None	Not done	-	Oral cyclosporin 3.6mg/kg
Mellerio et al(5), 1999, UK	6 unrelated patients	13-40	Infancy to 29 years	Elevated IgE in 2 patients	G2242R G1791E G2369S G2713R 5532+1G-to-A 7786delG 6863del16	Ex 85 Ex 61 Ex 93 Ex 110 IVS64 Ex 104 Ex 87	NA
Jiang et al(6), 2002, China	A Chinese man with 59 affected family members	35	3 years	None	6899 A-to-G	Ex87	NA
Chuang et al(7), 2004, Taiwan	A Taiwanese woman	52	20 years	None	G2366V	Ex92	NA
Das et al(8), 2005, India	3 patients, (2 were related)	14-22	1-2 years	None	Not done	-	Cryotherapy
Ozanic Bulic et al(9), 2005, UK	A white British girl	14	Infancy	Slight elevated IgE	G2040D		Thalidomide 50mg daily
Drera et al(10), 2006, Italy	7 unrelated patients, 6 females and a male	8-44	Birth to 5 months old	Elevated IgE in 5 patients, asthma and rhinoconjunctivitis in a patient	c.425A.G/c.7344G>A p.R1630X/c.7344G>A p.R51G/p.R2492X p.G1755D p.G2073V c.6900+4A>G c.6900+2delTGAT	Ex 3/Ex 95 Ex 51/Ex 95 Ex 2/Ex 98 Ex 59 Ex 75 IVS 87 IVS 87	Amelioration of skin lesion and pruritus in a patient who received methyl prednisolone for asthma.
Broekaert et al(11), 2006, Germany	A Turkish woman	29	27 years	None	C.8137G >C	Ex 110	None
Ee et al(12), 2007, Singapore	A Chinese woman	52	25 years	• History of partial thyroidectomy on thyroxine replacement • Mild anemia	G2251E	Exon 86	NA
Wang et al(13), 2007, China	A Chinese girl	23	2 years	None	G2626D	Ex106	NA
Ren et al(14), 2008, China	A Chinese male	15	2 years	None	c.6900+1G > T	IVS87	NA

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Schumann et al(15), 2008, Germany	6 central European patients and one Middle East	12-58	1-53 years	• Nickel sensitization • Elevated thyroid hormone • DM • Thyroid cancer • Elevated IgE	p.G2028R p.G2028R c.425A>G/p.E2736K c.497insA/p.G1347W p.G1755D p.R1630X/ND p.G2623V		NA
Shi et al(16), 2009, China	A Chinese man	30	10 years	Raised IgE	G2242W	Ex85	NA
Almaani et al(17), 2009, UK	A British white woman	61	40years	Lichen planopilaris	p.G2290A	Ex87	Topical tacrolimus
Hayashi et al(18), 2010, Japan	A Japanese man	71	71 years	• DM on anti-diabetic and herbal medicine • BPH	c.6859G>A;p.G2287A	Ex87	Oral prednisolone 30mg/day & topical tacrolimus
Tey et al. Arch Dermatol 2011;147:956-960	A Caucasian man	14	6 years	None	IVS55+1G>C	IVS55	Oral cyclosporin 3.5mg/kg, topical tacrolimus and high-potency topical corticosteroids
Tang et al, Malaysia current study	A Malay woman	20	6 years	High IgE Mild anemia Hypereosinophilia	c.6860G>A; p.G2287E	Ex87	Topical corticosteroids

Abbreviation: UK – United Kingdom; USA – United State of America; Ex – Exon; IVS – Intron, DM – Diabetes mellitus; BPH – Benign prostatic hyperplasia

DISCUSSION

In this report, we identified the first family in Malaysia with dominant epidermolysis bullosa pruriginosa, a subtype of dystrophic epidermolusis bullosa, with most likely involvement of 2 generations. Many cases were illustrated in the literature (Table I) ever since the first case series reported by McGrath *et al* in 1994[2]. The most prominent characteristics of DEBP are late onset, pruritus and pattern hypertrophic scars. Intact blisters are infrequently apparent and may only be described by the patients. Excoriations are marked clinically. Scars are prominent and predominantly hypertrophic instead of atrophic. As a result, DEBP is often recognized late by clinicians and commonly mistaken for dermatitis artifacta, keratosis lichenoides chronica (Nekam's disease), hypertrophic lichen planus and lichen simplex chronicus.

The reasons for the delayed onset of symptoms in DEBP remain unclear. However in the case series reported by Drera *et al*[3], all the 7 patients had typical mild dystrophic epidermolysis bullosa (DEB) to begin with, in which they had skin fragility and milia since birth or infancy. The typical hyperkeratotic cutaneous lesions only appeared after the onset of pruritus. A similar depiction by Schumann et al was published subsequenty[4]. Another 7 patients with DEBP had mild symptoms of epidermolysis bullousa (EB) since birth, infancy or early childhood which later progress to typical clinical manifestations of DEBP after they experienced pruritus. The unbearable itch will lead to scratching which is a form of trauma to fragile skin. This will promote blisters and later scar formation. Hence, many believe pruritus has a direct effect on the clinical appearance of DEBP and by managing the pruritus, the clinical conditions would have been improved.

Consequently, great effort has been exploited to find the cause of pruritus in these patients. Many clinicians attempt to relate the pruritus to various underlying systemic diseases such as atopic eczema, thyroid disease, iron deficiency, contact dermatitis, renal or liver impairment. Indeed, a few patients were described to have associated atopy, elevated IgE, anemia, thyroid gland cancer, elevated thyroid hormone, nickel sensitivity, diabetes mellitus taking anti-diabetic and herbal medicines and lichen planopilaris in the literature (Table I). Our patient AMM was also found to have mild anemia, hypereosinophilia and very high level of IgE, especially to house dust mites. Whether these underlying medical conditions unswervingly explained the mechanism of pruritus is debatable as there were many EBP patients without any medical problems that could explain the pruritus. Perhaps the morphologically altered anchoring fibrils in EBP act as itch stimuli received by unspecialized free nerve endings located close to the dermal-epidermal junction. This hypothesis certainly requires further studies to for detailed investigation.

To date, more than 30 different mutations in COL7A1 have been identified in patients with EBP (Table I). Majority of the cases is inherited in an autosomal dominant manner. The presence of a positive family history in our patient highly supported the diagnosis and we proceeded with genetic analysis without having to perform immunofluorescence mapping. We have detected a heterozygous mutation, c.6860G>A p.G2287E, in 3 affected individuals in the family. To our knowledge, the mutation p.G2287E in exon 87 identified in our patient is novel, and is associated with dominant DEB with milder phenotype.

Being an inherited mechanobullous disorder, genetic treatments for EBP are not yet available. The management includes examination of family members of the affected proband and appropriate genetic counseling to them. Collectively, successful treatment protocols for pruritus in EBP have not been established. Topical corticosteroids and topical calcineurin inhibitors have been used to ease the itch transiently (Table I). Oral cyclosporine and oral thalidomide were also described to be helpful in a few cases (Table I). As our patient is at the child-bearing age, systemic treatment with cyclosporine and thalidomide were not considered.

In conclusion, here we describe a typical EBP in a Malay family in Malaysia with the novel COL7A1 mutation p.G2287E, which expands the database of known mutations and corresponding phenotypes.

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