

SHORT COMMUNICATION

Anti-laminin- γ 1 Pemphigoid Developed in a Case of Autosomal Recessive Congenital Ichthyosis

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Non-bullous congenital ichthyosis is a group of inherited scaling disorders of multiplex aetiology, always involving an epidermal barrier defect. Pemphigoid is an acquired autoimmune blistering disease with various hemidesmosomal proteins as autoantigen. Here, we describe a case of autosomal recessive congenital ichthyosis (ARCI), complicated by anti-laminin- γ 1 pemphigoid (AL γ P).

CASE REPORT

A 74-year-old Japanese man, who had a scaly skin condition since childhood, developed blistering skin lesions for one month. Physical examination revealed brown-black-coloured skin lesions with large and thick scales on the entire body (Fig. 1A and B). In addition, many exudative erythemas with tense blisters and erosions 5–20 mm in size were seen mainly on the limbs, axillae and neck (Fig. 1C and D). There were no apparent eczematous skin lesions, suggesting that the patient had neither atopic dermatitis nor Netherton syndrome. No mucosal involvement or hair abnormality, including bamboo hair, were observed.

Two sisters of the patient also had similar scaly skin lesions on the whole body since childhood. However, 3 other siblings and 7 children of the affected siblings did not exhibit any skin abnormality. Laboratory tests showed no abnormal results, including blood levels of IgE and eosinophils.

Histopathology for scaly skin lesion showed extensive hyperkeratosis with normal granular layer (Fig. 1E). Histopathology for bullous skin lesion showed subepidermal blisters with infiltration of many neutrophils and few eosinophils (Fig. 1F).

Direct immunofluorescence showed linear deposits of IgG (Fig. S1A¹) and C3 (Fig. S1B¹) to basement membrane zone (BMZ). Linear deposits of IgG and C3 to BMZ showed serrated pattern (1). No IgA deposition was found. Indirect immunofluorescence of normal human skin detected circulating IgG anti-BMZ antibodies, which reacted exclusively with dermal side of 1M NaCl-split normal human skin (data not shown).

Immunoblot analysis of normal human dermal extract identified the 200 kDa laminin- γ 1 but not the 290 kDa type VII collagen (Fig. S1C¹). Other immunoblot analyses of normal human epidermal extracts, recombinant proteins of BP180 NC16a and C-terminal domains, concentrated culture supernatant of HaCaT cells and purified human laminin-332 showed negative results, except for weak reactivity with BP230 in normal human epidermal extract (Fig. S1D¹). The results of enzyme-linked immunosorbent assays for desmoglein 1, desmoglein 3, BP180, BP230 and type VII collagen were all negative.

Extensive and severe skin lesions with thick scales did not indicate ichthyosis vulgaris. In addition, studies of Japanese



Fig. 1. Clinical appearances on the back (A), shins (B), knee (C) and axilla (D). Histopathological findings for scaly skin lesion (E) and bullous skin lesion (F). Original magnifications: $\times 400$.

mutations of filaggrin gene (2) did not show any mutations (Teye et al., manuscript in preparation), further excluding the possibility of ichthyosis vulgaris. In addition, FISH study for steroid sulphatase gene (Xp22.3) revealed no deletion of this gene which underlies X-linked ichthyosis.

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Thus, we suspected the diagnosis of ARCI, and performed extensive mutation analyses of 9 genes, which have been reported as causative genes for ARCI: *ABCA12* (3), *TGMI* (3), *ALOX12B* (3), *ALOXE3* (3), *CYP4F22* (3), *NIPAL4* and *LIPN* (4), *PNPLA1* (5), and *CERS3* (6). However, no mutation was detected.

From the above results, we made the diagnosis of AL γ P. Administration of prednisolone 40 mg/day alone did not significantly improve the bullous skin lesions. Addition of minocycline hydrochloride 200 mg/day and niacinamide 900 mg/day did not show therapeutic effects. Addition of diaminodiphenyl sulfone 100 mg/day and azathioprin 100 mg/day was effective. However, even 6 months after initiation of the treatment, the patient still occasionally showed skin lesions on prednisolone 20 mg/day. Scaly lesions did not show any improvement.

DISCUSSION

ARCI includes harlequin ichthyosis, lamellar ichthyosis and congenital ichthyosiform erythroderma (7). Brown-black-coloured large scales without flushing found in our patient suggested a diagnosis of lamellar ichthyosis, which usually shows mutation in the *TGMI* gene. However, our mutation detection system for 9 ARCI genes, including *TGMI* gene, could not show any causative gene.

Possibly our patient has mutations in a so far unidentified, new ARCI gene, because 22% of ARCI cases usually do not exhibit mutations in any known ARCI genes (7). Indeed, 6 of 24 Japanese ARCI patients did not show mutations in the 9 known ARCI genes (Nunata et al., manuscript in preparation).

AL γ P, formerly called as anti-p200 pemphigoid, is an autoimmune bullous disease caused by IgG anti-epidermal BMZ antibodies, which react with the 200 kDa protein by immunoblotting of normal human dermal extract (8, 9).

In our patient, indirect immunofluorescence of 1M NaCl split skin showed IgG anti-BMZ antibodies reactive with dermal side, and immunoblotting of normal human dermal extract showed the 200 kDa protein. No reactivity with type VII collagen or laminin-332 was detected. The n-serration pattern seen in direct immunofluorescence also excluded the reactivity with type-VII collagen.

AL γ P patients generally show good response to various treatments (10). However, our patient needed long treatments with a combination of prednisolone, dapsone and azathioprin to suppress blistering skin lesions.

In previous reports, approximately 40% of AL γ P patients were associated with various forms of psoriasis (10), (Ohata et al., manuscript in preparation). However, the pathomechanism for this preferential development of AL γ P in psoriasis patients is currently unknown.

Association of AL γ P with other skin diseases, including any types of ichthyosis, has not been clearly documented before. There was a case report of AL γ P

associated with scabies. The present paper is the first reported case of concurrent AL γ P and ARCI. Whether this is a causal or casual correlation remains to be seen, but long lasting skin lesions of ARCI might be a predisposing factor. However, because the concurrence of ARCI and AL γ P is very rare, concurrence of the 2 skin diseases in our patient may be merely accidental.

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