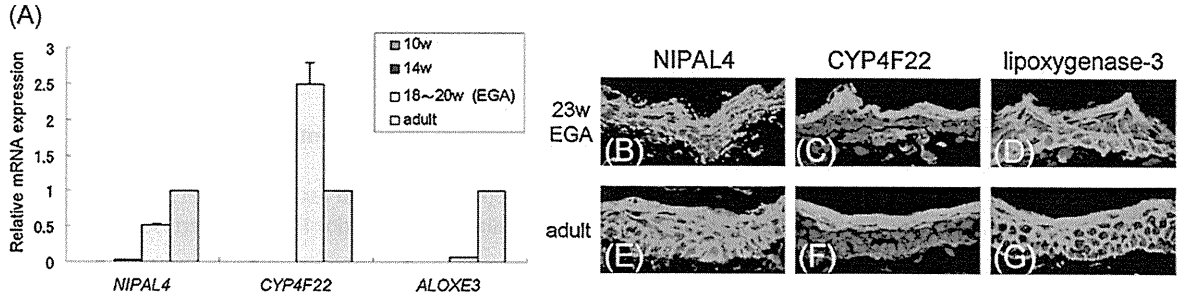

Fig. 1. NIPAL4, CYP4F22 and lipoxygenase-3 expression in developing human skin. (A) mRNA expression in developing human skin. The mRNA expression of *NIPAL4*, *CYP4F22* and *ALOXE3* in fetal human whole skin was studied by quantitative RT-PCR analysis, normalized by *GAPDH* [Applied Biosystems: Hs00398027_m1*, Hs00403446_m1*, Hs00222134_m1*, Hs03929097_ gl*]. At 10 and 14 weeks EGA, *NIPAL4*, *CYP4F22* and *ALOXE3* mRNA are hardly expressed. At 18–20 weeks EGA, the rate of *CYP4F22* mRNA expression is higher than in adult human whole skin ($n = 3$, mean ± SD). (B–G) Immunofluorescence staining of NIPAL4, CYP4F22 and lipoxygenase-3 in developing human skin. Fetal skin samples at 10–23 weeks EGA and adult skin samples were stained for NIPAL4 [Rabbit polyclonal anti-NIPAL4 antibody against a 16-amino acid sequence synthetic peptide (residues 445–461)], CYP4F22 [B01; Abnova, Taipei City, Taiwan], and lipoxygenase-3 [T-14; Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.] (Supplementary Fig. S1). For the 23 weeks EGA sample and the adult skin, CYP4F22 (C and F) is expressed in the upper layer of the epidermis, mainly in the granular layers. NIPAL4 (B and E) and lipoxygenase-3 (D and G) are expressed at the cell periphery throughout the epidermis. NIPAL4 expression is seen evenly from the basal cell layer to the granular layers, although lipoxygenase-3 expression is slightly stronger towards the granular layers. NIPAL4, CYP4F22 and lipoxygenase-3 green (FITC), nuclear stain, red (PI solution) (original magnification 40×). Data are presented as representative of triplicate experiments.

and 20 weeks EGA was higher than that in adult human skin. At 18 and 20 weeks EGA, *NIPAL4* mRNA expression was approximately half of that in adult skin, and only a tiny amount of *ALOXE3* mRNA was expressed.

We investigated protein localization by immunofluorescence staining (Fig. 1B–G). For the 10 weeks EGA sample, NIPAL4, CYP4F22 and lipoxygenase-3 were not detected. A similar pattern was obtained for the 14 weeks EGA sample. For the 23 weeks EGA sample, CYP4F22 was expressed in the upper layer of epidermis, mainly in the granular layers, and NIPAL4 and lipoxygenase-3 were expressed at the cell periphery in the entire epidermis. Staining patterns of NIPAL4, CYP4F22 and lipoxygenase-3 in the adult skin were similar to those at 23 weeks EGA. Lipoxygenase-3 is usually considered to be a partner with 12R-LOX. 12R-LOX has been visualized at the cell periphery only in the upper epidermis [2]. In our results, lipoxygenase-3 was distributed at the cell periphery in the entire epidermis. Concerning to lipoxygenase-3 in the upper epidermis, lipoxygenase-3 is thought to work with 12R-LOX, although function of lipoxygenase-3 in the lower epidermis is unknown.

In cultured keratinocytes, RT-PCR analysis (Fig. 2A) and immunoblot analysis (Fig. 2B and C) confirmed that mRNA and protein expression of CYP4F22 were increased under the high Ca^{2+} condition (1.2 mmol/L for 48 h). In contrast, there was no significant increase in the mRNA or protein expression of NIPAL4 or ALOXE3 under the high Ca^{2+} condition.

The present study of the adult human epidermis clarified that NIPAL4 and lipoxygenase-3 were expressed at the cell periphery in the entire epidermis of adult human skin. CYP4F22 was expressed in the cytoplasm of keratinocytes in the upper layer of adult human epidermis, mainly in the granular layers. One previous report [3] noted that, inconsistent with our present observations, *NIPAL4* mRNA is highly expressed in the granular layers of the epidermis with *in situ* hybridization analysis. The cause of this discrepancy is unclear, but it might be due to difference in sensitivity between *in situ* hybridization and immunostaining.

We have demonstrated that the mRNAs of *NIPAL4*, *CYP4F22* and *ALOXE3* are not expressed in the early stages of fetal development, at 10 weeks EGA or at 14 weeks EGA. At 18 and 20 weeks EGA, *NIPAL4* mRNA expression was about half that in adult skin, although *ALOXE3* mRNA was only weakly expressed. Among the keratinization-associated genes, the mRNA expression pattern of *NIPAL4* is similar to that of *ABCA12*, and the pattern of *ALOXE3* resembles those of other keratinization-related molecules, such as *TGM1*, *LOR* and *KLK7* [4].

NIPAL4 encodes a putative transmembrane protein of 404 amino acids with a molecular weight of 44 kDa [6]. The NIPAL4 protein is highly expressed in the brain, lung and stomach, and in

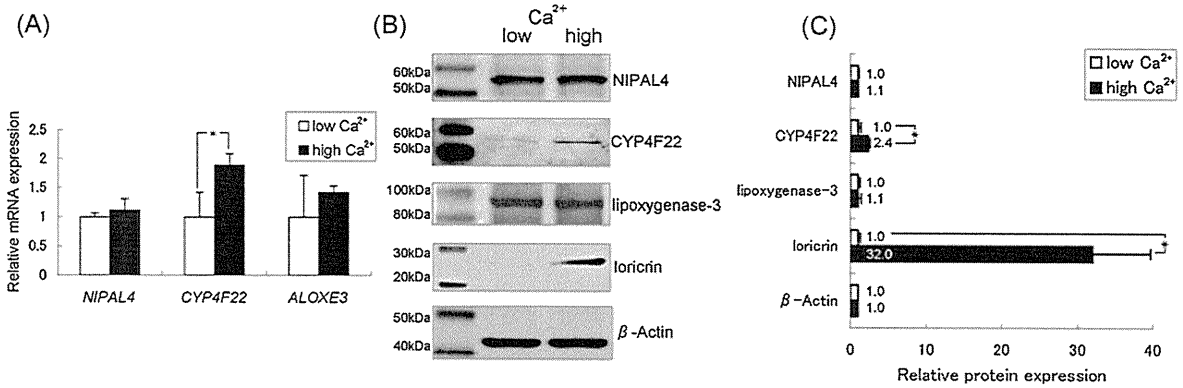

Fig. 2. mRNA and protein expression of NIPAL4, CYP4F22 and ALOXE3 in developing human skin and NHEK. (A) mRNA expression in NHEK. mRNA expression of *CYP4F22* is significantly higher in the NHEK under the high Ca^{2+} condition than in those under the low Ca^{2+} condition. There are no significant differences between the high and low Ca^{2+} conditions in terms of the mRNA expression of *NIPAL4* and *ALOXE3* ($n = 3$, mean ± SD, $^*p < 0.05$). (B) Protein expression assessed by Western blot analysis. The expression of CYP4F22 is higher in the NHEK raised under the high Ca^{2+} condition than in those raised under the low Ca^{2+} condition. However, neither NIPAL4 nor lipoxygenase-3 is increased under high Ca^{2+} condition. Anti-ALOXE3 antibody for immunoblotting: NBP1-32533; Novus Biologicals, LLC, U.S.A. (C) Quantitative analysis by Image J software revealed that the protein expression of CYP4F22 was significantly increased under the high Ca^{2+} condition. Data are presented as representative of triplicate experiments.

leukocytes and keratinocytes. The protein product of the *ALOXE3* gene, lipoxygenase-3, is thought to function as a hydroperoxide isomerase to generate epoxy alcohol [5]. CYP4F22 is a member of the cytochrome P450 family 4, subfamily F. The gene includes 12 coding exons and the cDNA spans 2.6 kb in length. All *CYP4F22* mutations reported to date are predicted to abolish the function of the encoded CYP protein and to compromise the 12(R)-lipoxygenase (hepoxilin) pathway.

Human epidermis contains 15S-lipoxygenase type 1, 12S-lipoxygenase and 12R-lipoxygenase [6]. Skin also contains cytochrome 450, and members of the CYP4 family with unknown epidermal function [3]. 12R-lipoxygenase has attracted great medical interest. 12R-lipoxygenase is expressed only in the epidermis and the tonsils [6,7] and is upregulated in psoriatic lesions [8]. It transforms 20:4n-6 to 12R-hydroperoxyeicosatetraenoic acid (12R-HPETE), which is important for the development of the water permeability barrier function in the epidermis [2]. 12R-LOX and eLOX3 play a crucial role in releasing ω-hydroxyceramide for construction of the corneocyte lipid envelope which is essential for intact skin barrier [9]. O-linoleoyl-ω-hydroxyceramide is oxygenated by the consecutive actions of 12R-LOX and eLOX3 and the products are covalently attached to protein *via* the free ω-hydroxyl of the ceramide, forming the corneocyte lipid envelope [9].

It is hypothesized that CYP4F22 may be linked to the 12R-lipoxygenase and lipoxygenase-3 pathway. Hydroxyeicosatetraenoic acids (HEETs) can be hydrolyzed to triols by epoxide hydrolases, and these products might be substrates of CYP4F members. Thus, it is possible that CYP4F22 might be involved in a downstream step in the 12R-lipoxygenase/lipoxygenase-3 pathway. CYP4F22 could be involved in the oxidation of 8R,11R,12R-HEET. However, from a systemic study of MS/MS spectra of HEETs derived from 12- and 15-HPETE, CYP4F22 did not appear to oxidize 8R,11R,12R-HEET [10]. Nilsson et al. [10] reported that recombinant CYP4F22 catalyzed the omega-3 hydroxylation of 20:4n-6; however, oxygenation of 8R,11R,12R-HEET was not detected. An additional function of CYP4F22 is to synthesize the omega-hydroxy fatty acids in the ceramide [10].

Our study revealed CYP4F22 to be highly expressed at the site and the onset of keratinization during skin development. From this it is speculated that CYP4F22 is involved in the metabolism of lipid substrates that are important to differentiation/keratinization of epidermal keratinocytes, at least during the fetal period. Further studies of the function of CYP4F22 would be needed to elucidate its function in development of the epidermis and keratinocytes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jdermsci.2011.12.006.

References

[1] Akiyama M. Updated molecular genetics and pathogenesis of ichthyoses. Nagoya J Med Sci 2011;73:79–90.
[2] Epp N, Fürstenberger G, Müller K, de Juanes S, Leitges M, Hausser I, et al. 12R-lipoxygenase deficiency disrupts epidermal barrier function. J Cell Biol 2007;177:173–82.
[3] Wajid M, Kurban M, Shimomura Y, Christiano AM. NIPAL4/ichthyin is expressed in the granular layer of human epidermis and mutated in two Pakistani families with autosomal recessive ichthyosis. Dermatology 2010;220:8–14.
[4] Yamanaka Y, Akiyama M, Sugiyama-Nakagiri Y, Sakai K, Goto M, McMillan JR, et al. Expression of keratinocyte lipid transporter ABCA12 in developing and reconstituted human epidermis. Am J Pathol 2007;171:43–52.
[5] Eckl KM, Krieg P, Küster W, Traupe H, André F, Wittstruck N, et al. Mutation spectrum and functional analysis of epidermis-type lipoxygenases in patients with autosomal recessive congenital ichthyosis. Hum Mutat 2005;26:351–61.
[6] Holtzman MJ, Turk J, Pentland A. A regiospecific monooxygenase with novel stereopreference is the major pathway for arachidonic acid oxygenation in isolated epidermal cells. J Clin Invest 1989;84:1446–53.
[7] Boeglin WE, Kim RB, Brash AR. A 12R-lipoxygenase in human skin: mechanistic evidence, molecular cloning, and expression. Proc Natl Acad Sci USA 1998;95:6744–9.
[8] Woollard PM. Stereochemical difference between 12-hydroxy-5,8,10,14-eicosatetraenoic acid in platelets and psoriatic lesions. Biochem Biophys Res Commun 1986;136:169–76.
[9] Zheng Y, Yin H, Boeglin WE, Elias PM, Crumrine D, Beier DR, et al. Lipoxygenases mediate the effect of essential fatty acid in skin barrier formation. A proposed role in releasing omega-hydroxyceramide for construction of the corneocyte lipid envelope. J Biol Chem 2011;286:24046–5.
[10] Nilsson T, Ivanov IV, Oliw EH. LC–MS/MS analysis of epoxyalcohols and epoxides of arachidonic acid and their oxygenation by recombinant CYP4F8 and CYP4F22. Arch Biochem Biophys 2010;494:64–71.

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Possible modifier effects of keratin 17 gene mutation on keratitis–ichthyosis–deafness syndrome

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MADAM, Keratitis–ichthyosis–deafness (KID) syndrome (OMIM 148210, 242150) is a rare type of ectodermal dysplasia caused by mutations in the gap junction protein beta-2 gene (*GJB2*)[1] or beta-6 gene (*GJB6*).[2] On the other hand, mutations in genes encoding keratin 6a, 6b, 16 and 17 (*KRT6A*, *KRT6B*, *KRT16* and *KRT17*) are known to cause pachyonychia congenita (PC; OMIM 16720, 17210). PC and KID syndrome share similar symptoms, such as palmoplantar hyperkeratosis and onychodystrophy. This study reports a Japanese patient with atypical KID syndrome with the combined heterozygous mutations of a recurrent mutation in *GJB2* and a novel mutation in the V1 region of *KRT17*.

The proband was a 40-year-old Japanese woman. She was the child of healthy, nonconsanguineous parents. From childhood, she had shown diffuse mutilating palmoplantar hyperkeratosis (Fig. 1a), nail dystrophy (Fig. 1b), hypotrichosis, sensorineural hearing loss, and vascularized keratitis. Periorificial hyperkeratosis was not seen. From these findings, the diagnosis of KID syndrome was made. She had had recurrent bacterial and fungal skin infections. In her twenties, painful tumours appeared on her lower limbs. In her thirties, tumours on both buttocks developed to take on a papilloma-like appearance (Fig. 1c). Etretinate with topical or systemic antibiotics and antifungal agents did not alleviate her symptoms. Skin abrasion was repeatedly conducted on the tumours. Histopathology of the lesions revealed epidermal pseudocarcinomatous hyperplasia with dilation of vessels in papillary and reticular dermis accompanied by mixed immune cell infiltrates, excluding the involvement of squamous cell carcinoma (Fig. 1d). Vacuolated keratinocytes, suggesting human papillomavirus infection, were not detected.

Genomic DNA extracted from peripheral blood was used as a template for polymerase chain reaction (PCR) amplification. Direct sequencing of *GJB2*, *GJB6*, *KRT6A*, *KRT6B*, *KRT16* and *KRT17* was performed as described elsewhere.[3–5] The medical ethical committee of Hokkaido University approved all the described studies. The study was conducted according to the Declaration of Helsinki Principles. The proband gave her written informed consent.

Mutation analysis of the proband's genomic DNA revealed a c.148G>A transition (p.Asp50Asn) in *GJB2* (Fig. 2a), which is the most prevalent mutation in patients with KID syndrome.[1] Furthermore, the proband was found to be heterozygous for a c.177C>A transversion (p.Ser59Arg) in *KRT17* (Fig. 2b). Restriction enzyme digestion of the PCR products by PvuII was carried out to confirm the c.177C>A in *KRT17* (Fig. 2c). The c.177C>A in *KRT17* was novel and was not detected in 200 alleles from 100 normal Japanese individuals. Mutation screening on the proband's parents could not be performed because the father was not alive and the mother did not consent. Keratin 17 (K17) immunohistochemistry on skin samples from several different sites revealed K17 expression in whole epidermis although its expression level did not vary between nonlesional and lesional skin specimens (data not shown).

As the clinical manifestations of the proband were atypical and more severe than those of other patients with KID syndrome – as evidenced, for example, by diffuse mutilating palmoplantar hyperkeratosis and recurrent granulation tissue formation on the buttock – we hypothesized that mutations in other genes might have affected the proband's phenotype through modifier effects. Modifier genes are defined as genes that affect the phenotypic expression of another gene, and several studies have demonstrated that modifier genes are involved in manifestations of inherited disorders.[6] *KRT6A*, *KRT6B*, *KRT16* and *KRT17*, the causative genes of PC, which affects the nails and the palmoplantar area, were selected as candidates for modifier gene investigation in our case, although we cannot exclude the possibility that there are some other genes which modify KID syndrome phenotype.

Most of the keratin mutations are within the helix boundary motifs, which are crucial for keratin monomers to form dimers and subsequent keratin networks.[7] The *KRT17* mutation found in the proband was located not within the helix boundary motifs but in the V1 region of K17 (Fig. 2d). In other keratin genes, such as *KRT5* and *KRT16*, some mutations have been reported within the V1 region, and the phenotypes resulting from these mutations are milder than those resulting from the mutations within the helix boundary motifs.[7] The V1 regions of keratin intermediate filament have glycine loops[8] and it has been suggested that these structures modulate flexibility and other unknown physical attributes of keratin filaments by interacting with similar structures in loricrin.[9] Ser^{59} is located within a highly conserved segment composed of the glycine loop in K17 (Fig. 2e). p.Ser59Arg in K17 is predicted to be probably damaging by PolyPhen-2, with a score of 0·893.[10]

Based on these findings, it is conceivable that the p.Ser59-Arg variant in K17 has a modifying effect on the pathogenic

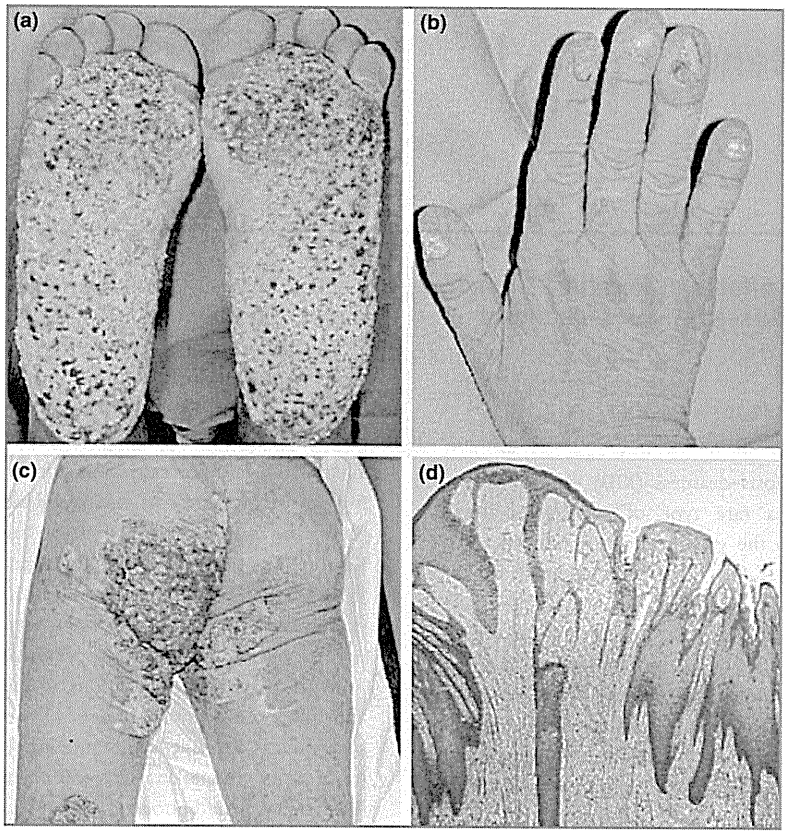

Fig 1. Clinical features of the proband. (a) Numerous erosive papules are coalesced into a hyperkeratotic plaque on the proband's soles. (b) Nail dystrophy is seen in the fingers. (c) A tumour is observed on the left buttock. Scars after skin abrasion are seen on the dorsal aspects of the thigh and on the right buttock. (d) Specimens from the tumour show pseudocarcinomatous hyperplasia of the epidermis. Dilated vessels with monocytic infiltrates are seen in the dermis (haematoxylin and eosin; original magnification × 100).

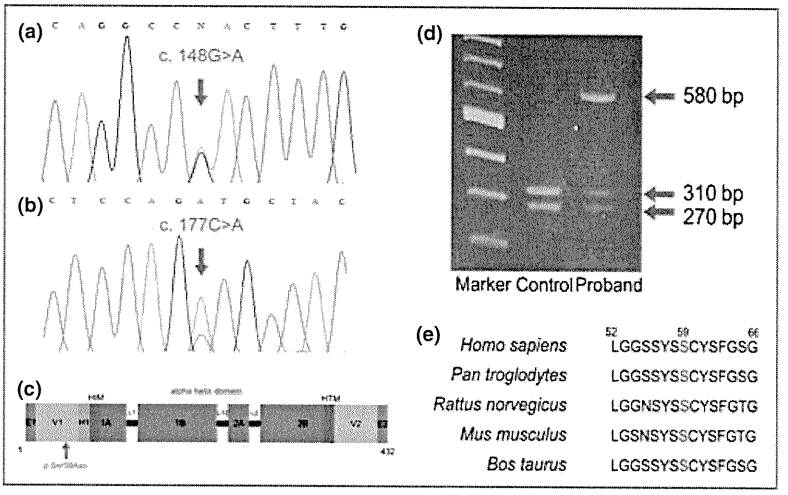

Fig 2. Mutation analysis. (a) The proband was heterozygous for a c.148G>A transition (p.Asp50Asn) mutation in *GJB2* (arrow). (b) c.177C>A (p.Ser59Arg) in *KRT17* was detected in the proband's genomic DNA (arrow). (c) PvuII restriction enzyme digestion of the polymerase chain reaction (PCR) products from genomic DNA of the proband and a normal control. c.177C>A resulted in the loss of a site for PvuII. PvuII restriction enzyme digestion of the PCR products from a normal controls reveals 270- and 310-bp bands. In contrast, 270-, 310- and 580-bp bands were detected in the proband, suggesting that she was heterozygous for c.177C>A. (d) A schematic of the structure of keratin 17. Note that Ser^{59} is located at the V1 region of the keratin molecule (arrow). HIM, helix initiation motif; HTM, helix termination motif. (e) Keratin 17 amino acid sequence alignment shows the level of conservation in diverse species of the amino acid Ser59 (red characters).

GJB2 mutation p.Asp50Asn and may contribute the proband's phenotype. Nevertheless, the limited scope of this study (single case report) does not allow us to determine the clinical significance of p.Ser59Arg in K17, and the influence of other genetic and epigenetic factors cannot be excluded.

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References

1 Mazereeuw-Hautier J, Bitoun E, Chevrant-Breton J *et al.* Keratitis–ichthyosis–deafness syndrome: disease expression and spectrum of connexin 26 (GJB2) mutations in 14 patients. *Br J Dermatol* 2007; **156**:1015–19.
2 Jan AY, Amin S, Ratajczak P *et al.* Genetic heterogeneity of KID syndrome: identification of a Cx30 gene (GJB6) mutation in a patient with KID syndrome and congenital atrichia. *J Invest Dermatol* 2004; **122**:1108–13.
3 Richard G, White TW, Smith LE *et al.* Functional defects of Cx26 resulting from a heterozygous missense mutation in a family with dominant deaf-mutism and palmoplantar keratoderma. *Hum Genet* 1998; **103**:393–9.
4 del Castillo I, Villamar M, Moreno-Pelayo MA *et al.* A deletion involving the connexin 30 gene in nonsyndromic hearing impairment. *N Engl J Med* 2002; **346**:243–9.
5 Kanda M, Natsuga K, Nishie W *et al.* Morphological and genetic analysis of steatocystoma multiplex in an Asian family with pachyonychia congenita type 2 harbouring a KRT17 missense mutation. *Br J Dermatol* 2009; **160**:465–8.
6 Nadeau JH. Modifier genes in mice and humans. *Nat Rev Genet* 2001; **2**:165–74.
7 Szeverenyi I, Cassidy AJ, Chung CW *et al.* The Human Intermediate Filament Database: comprehensive information on a gene family involved in many human diseases. *Hum Mutat* 2008; **29**:351–60.
8 Steinert PM, Mack JW, Korge BP *et al.* Glycine loops in proteins: their occurrence in certain intermediate filament chains, loricrins and single-stranded RNA binding proteins. *Int J Biol Macromol* 1991; **13**:130–9.
9 Terrinoni A, Puddu P, Didona B *et al.* A mutation in the V1 domain of K16 is responsible for unilateral palmoplantar verrucous nevus. *J Invest Dermatol* 2000; **114**:1136–40.
10 Adzhubei IA, Schmidt S, Peshkin L *et al.* A method and server for predicting damaging missense mutations. *Nat Methods* 2010; **7**:248–9.

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IJD	5352		Author Received:	No. of pages: 3	PE: Prasanna

International Journal of Dermatology

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Sweet's syndrome presenting with vegetative nodules on the hands: relationship to neutrophilic dermatosis of the dorsal hands

A 22-year-old Japanese woman was referred to our department with a 3-week history of painful eruptions on her hands, extremities, face, and buttocks. Initially, a few reddish eruptions appeared on the left hand, and these gradually developed on other sites. She had experienced sore throat and mild fever (38 °C) for a week before the eruptions. Initial examination showed elevated erythematous nodules on both hands (Fig. 1). Multiple reddish papules were distributed over the extremities, buttocks, and face. Her medical history was unremarkable except for a 5-year course of antidepressants. The biopsy specimen from the nodule on the right dorsal hand revealed neutrophilic infiltration and edematous change in the dermis, and the specimen from the papule on the left thigh showed neutrophilic infiltration of the dermis (Fig. 2). Neither of the specimens showed vasculitis. Gram, periodic acid-Schiff, Grocott, and Ziehl–Neelsen stains on the biopsy specimen, culture of skin tissue, and polymerase chain reaction analyses failed to indicate any infectious diseases. Laboratory examinations detected weakly positive antinuclear autoantibody (1 : 80), but they were negative for rheumatoid factor. Neither anti-PR3-ANCA nor anti-MPO-ANCA antibodies were detected. Complete blood counts showed increased leukocytes (11 000/μl) and slightly elevated eosinophil fraction (10%). Cytopenia, abnormal granules in the cells, and abnormal nuclear shape were not observed. Systemic examinations, including X-ray and endoscopy, detected neither internal malignancies nor inflammatory bowel diseases. To summarize the clinicopathological features and laboratory findings, the patient had: (i) abrupt onset of painful nodules; (ii) histopathological evidence of dense neutrophilic infiltration without leukocytoclastic vasculitis; and (iii) previous upper respiratory tract infection and pyrexia. These fulfilled the diagnostic criteria of Sweet's syndrome (SS).[1] Two weeks after our initial examination, the lesion resolved itself without any systemic and topical therapies, leaving residual pigmentation. No recurrence has been observed for 2 years (Fig. 1e–h).

Neutrophilic dermatosis of the dorsal hands (NDDH) was first described by Strutton *et al.*[2] In 2006, Walling *et al.*[3] reviewed 52 reported cases and proposed the concept of NDDH as a distributional variant of SS; this

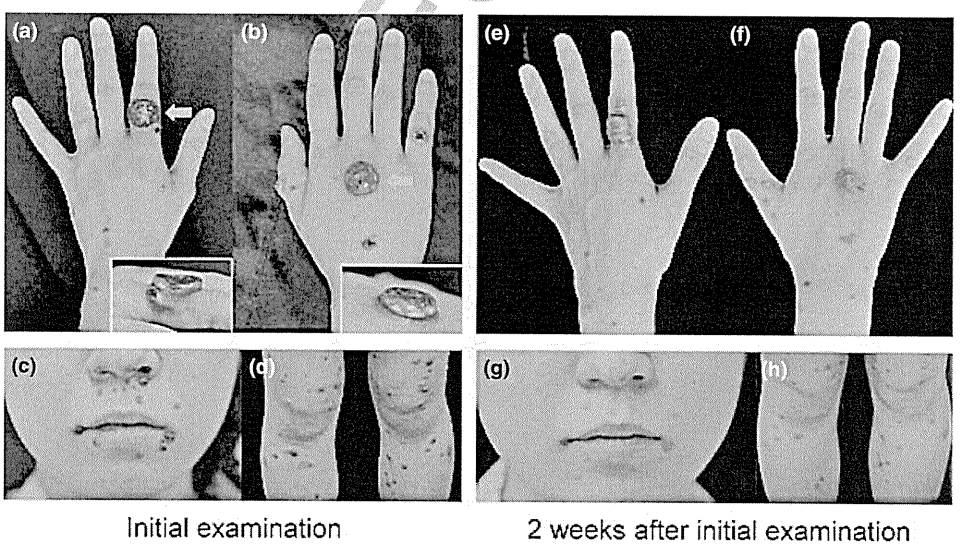

Figure 1 (a, b) Painful nodules and papules on both hands. A broad-based erythematous vegetative nodule elevated from the violaceous margin and 25 mm in diameter is observed on the left index finger (a, inset). An erythematous vegetative nodule 20 mm in diameter is noted on the right dorsal hand (b, inset). (c, d) Multiple dark red papules with partial scales and crusts on the surface ranging in size from 2 to 10 mm are observed on the face (c) and thighs (d). (e–h) Two weeks after our first examination, the lesions resolved without systemic and topical therapies, leaving residual pigmentation

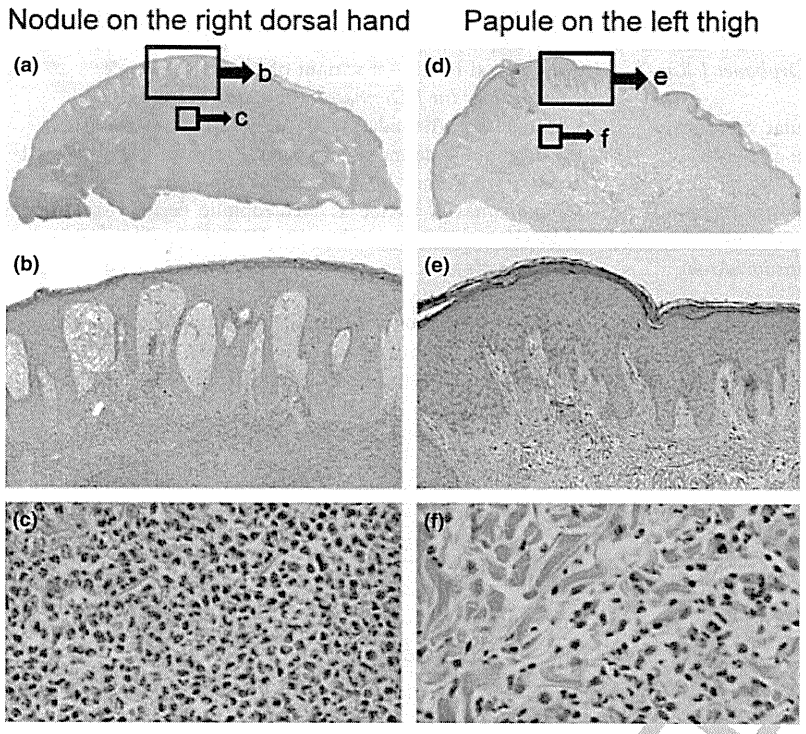

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Figure 2 Histopathological observation. (a–c) The biopsy specimen from the nodule of the right dorsal hand shows edematous change in the superficial dermis (b) and dense neutrophilic infiltration throughout the dermis (c). (d–f) The specimen from the papule on the left thigh reveals perivascular infiltration of neutrophils and lymphocytes (e, f). Neither of the specimens shows apparent leukocytoclastic vasculitis. (Hematoxylin–eosin stain, original magnification; a, d: ×4; b, e: ×100, c, f: ×400)

concept has been followed by several studies.[4–6] Recently, Takahama and Kanbe[7] reported a patient with NDDH with HLA-B51, the marker for SS, which suggests a strong relationship between NDDH and SS. Our case showed typical NDDH vegetative nodules and definitively fulfilled the criteria for SS, which also supports the disease concept of NDDH proposed by Walling *et al.*[3] NDDH lesions are usually limited to the dorsal hands; however, some patients with NDDH also have lesions at other sites.[1,3,4,8] As far as we have surveyed, there have been no NDDH cases with skin lesions distributed as widely as our patient's. From the histopathology, we speculate that the pathogenesis of all the skin lesions is similar, with lesion severity depending on the affected body site. It is not known why eruptions on the dorsal hands tended to develop vegetative nodules.

Although the patient had typical NDDH lesions on the hands, our case is unique for the wide distribution of lesions at sites other than the hands and for fulfilling the diagnostic criteria for SS. The present case further supports the notion that NDDH is a clinical variant of SS and highlights the diversity of cutaneous manifestations of SS.

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References

1 Cohen PR. Sweet's syndrome – a comprehensive review of an acute febrile neutrophilic dermatosis. *Orphanet J Rare Dis* 2007; 2: 34–62.

2 Strutton G, Weedon D, Robertson I. Pustular vasculitis of the hands. *J Am Acad Dermatol* 1995; 32: 192–198.

3 Walling HW, Snipes CJ, Gerami P, Piette WW. The relationship between neutrophilic dermatosis of the dorsal hands and Sweet syndrome: report of 9 cases and comparison to atypical pyoderma gangrenosum. *Arch Dermatol* 2006; 142: 57–63.

4 Abbas O, Kibbi AG, Rubeiz N. Sweet's syndrome: retrospective study of clinical and histologic features of 44 cases from a tertiary care center. *Int J Dermatol* 2010; 49: 1244–1249.

5 Kung EF, Arora A, Petronic-Rosic V, Tsoukas MM. Clinicopathologic challenge. Neutrophilic dermatosis of the dorsal hands – a variant of localized Sweet's syndrome. *Int J Dermatol* 2009; 48: 555–557.

6 Duquia RP, Almeida HL Jr, Vettorato G, *et al.* Neutrophilic dermatosis of the dorsal of the hands: acral sweet syndrome? *Int J Dermatol* 2006; 45: 51–52.

7 Takahama H, Kanbe T. Neutrophilic dermatosis of the dorsal hands: a case showing HLA B54, the marker of Sweet's syndrome. *Int J Dermatol* 2010; 49: 1079–1080.

8 DiCaudo DJ, Connolly SM. Neutrophilic dermatosis (pustular vasculitis) of the dorsal hands: a report of 7 cases and review of the literature. *Arch Dermatol* 2002; 138: 361–365.

Erythema Annulare Centrifugum-like Neutrophilic Dermatosis: Effects of Potassium Iodide

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Figurate erythema can be seen in various dermatological backgrounds, including erythema annulare centrifugum (EAC) and collagen diseases. Neutrophilic dermatoses clinically demonstrating figurate erythema, however, are relatively rare. We describe here a case of a 76-year-old Japanese man who presented with figurate erythema histologically characterized by neutrophilic infiltration, which was treated successfully with potassium iodide.

CASE REPORT

A 76-year-old man presented to our outpatient clinic with a one-year history of recurrent annular erythematous lesions. The eruptions had usually disappeared spontaneously within 2–4 weeks, with new lesions occurring after a few months.

On physical examination, annular oedematous erythemas were found spread over the extremities, back and gluteal regions (Fig. 1a). Some of the lesions were more than 10 cm in diameter. The lesions had elevated borders and central resolution. Scaling, vesicles and crusts were absent. The patient reported slight itching. His general condition was good, and he had not been taking any medications. The initial diagnosis was EAC, and differential diagnoses were erythema gyratum repens and Sjögren's syndrome.

Laboratory data showed slightly elevated C-reactive protein (0.48 mg/dl) and immunoglobulin E (658 IU/l). Anti-nuclear antibody was positive at a titre of 1:80, although anti-Sjögren's syndrome A (SS-A) and B (SS-B) antibodies were negative. Otherwise, the results were normal, including blood cell count, rheumatoid factor, tumour markers and serum complement. Whole-body computed tomography (CT) scanning showed only fatty liver and gallbladder stones.

Histological examination of a skin biopsy taken from the active border of an annular lesion on the left thigh showed perivascular and interstitial cell infiltration without remarkable epidermal changes. The dermal infiltrate consisted mostly of neutrophils in association with small numbers of eosinophils and rare lymphocytes (Fig. 2). Vasculitis was not detected. The case was finally diagnosed as neutrophilic figurate erythema.

Initial treatments with oral anti-histamine and topical steroid were unsuccessful. Based on the diagnosis of neutrophilic dermatosis, oral potassium iodide at 0.9 g/day was started, and the lesions disappeared completely within 2 weeks (Fig. 1b). The eruptions have been almost completely suppressed for 2 months under the potassium iodide treatment.

DISCUSSION

The eruptions had the characteristic annular figurate pattern. Figurate erythema is typically seen in EAC, erythema gyratum repens, Sjögren's syndrome and certain other disorders. However, our case showed typical histological features of neutrophilic dermatosis. A search of the English literature found only two cases described as "neutrophilic figurate erythema" in adults (1, 2): one with Hodgkin's lymphoma showed a paraneoplastic clinical course, and the other had no associated diseases or laboratory abnormalities. In children, we found three cases described as "neutrophilic figurate erythema of infancy", characterized by annular and arciform lesions with centrifugal growth and central clearing, without associated diseases and significant laboratory abnormalities (3–5).

From the viewpoint of neutrophilic dermatoses, Christensen et al. (6) described two cases of patients with chronic and recurrent outbreaks of generalized annular erythematous, oedematous cutaneous plaques, with histopathological findings suggestive of Sweet's syndrome, but without fever or general symptoms. They used the term "chronic recurrent neutrophilic dermatosis", and Cabanillas et al. (7) also reported a case of this entity. Clinicopathologically, our case can also be included in this entity, although most of the annular eruptions seen in neutrophilic dermatoses were not as large as those in our case. Our case suggests that neutrophilic dermatoses can rarely show large annular figurate erythema mimicking EAC.

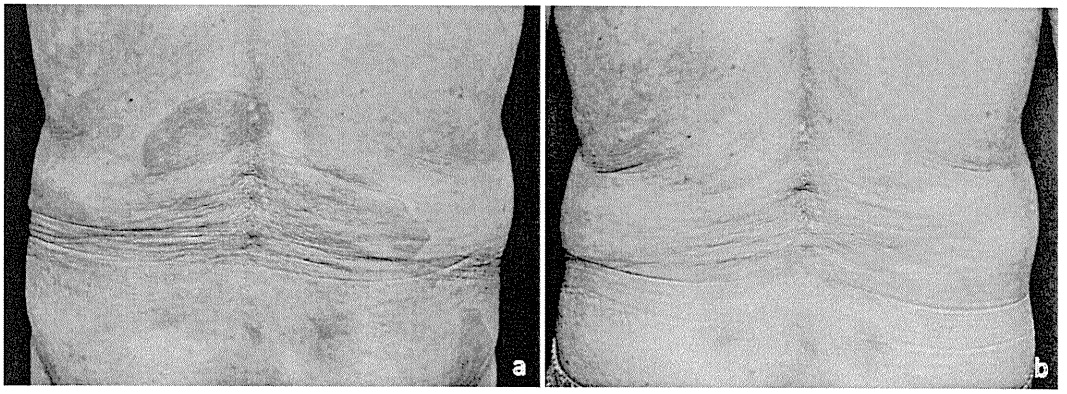

Fig. 1. (a) Annular erythematous plaques with central clearing on the back. (b) Healing after one month of potassium iodide treatment.

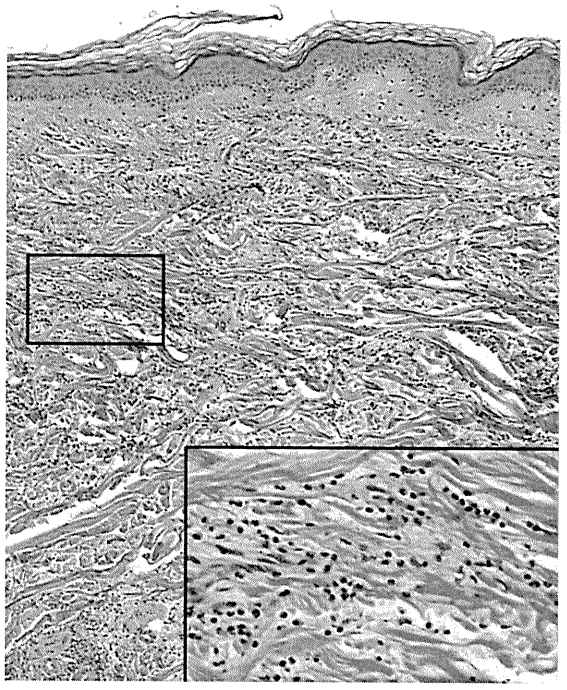

Fig. 2. Superficial and deep perivascular and interstitial dermatitis without epidermal changes (haematoxylin & eosin (H&E) ×40). Inset: the perivascular and interstitial infiltrate consists mostly of neutrophils (H&E ×200).

Treatment of neutrophilic figurate erythema includes oral prednisolone (1, 6, 7), colchicine (2), antihistamines (2, 4) and topical therapy (mild corticosteroid cream, miconazole nitrate ointment, etc.) (4, 5), although one paediatric patient presented a complete resolution with no drug treatment (3). Potassium iodide, which inhibits neutrophil chemotaxis, often has clinical benefit for neutrophilic dermatoses, and our case also showed a prompt and favourable response. We report here the first case of potassium iodide treatment for neutrophilic figurate erythema showing annulare centrifugum-like lesions.

REFERENCES

1. Trébol I, González-Pérez R, García-Rio I, Arregui MA, Saracibar N, Carnero L, et al. Paraneoplastic neutrophilic figurate erythema. Br J Dermatol 2007; 156: 396–398.
2. Ozdemir M, Engin B, Toy H, Demirkesen C. Neutrophilic figurate erythema. Int J Dermatol 2008; 47: 262–264.
3. Annessi G, Signoretti S, Angelo C I. Neutrophilic figurate erythema of infancy. Am J Dermatopathol 1997; 19: 403–406.
4. Cox NH, McQueen A, Evans TJ, Morley WN. An annular erythema of infancy. Arch Dermatol 1987; 123: 510–513.
5. Patrizi A, Savoia F, Varotti E, Gaspari V, Passarini B, Neri I. Neutrophilic figurate erythema of infancy. Pediatr Dermatol 2008; 25: 255–260.
6. Christensen OB, Holst R, Svensson A. Chronic recurrent neutrophilic dermatosis. Acta Derm Venereol 1989; 69: 415–418.
7. Cabanillas M, Suárez-Amor O, Sánchez-Aguilar D, Pereiro MM, Toribio J. Chronic recurrent neutrophilic dermatosis: a possible variant in the spectrum of neutrophilic dermatoses. Actas Dermosifiliogr 2008; 99: 61–63.

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Intractable erythematous plaques on the hands: palmoplantar eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (EPF) is an inflammatory disease characterized by plaques studded with numerous papules and sterile pustules.[1] The lesions are usually located on the face, trunk, and arms, and much less commonly on the palms and soles.[2,3] Palmoplantar EPF lesions have been reported as grouped papules and pustules on the palms and soles, resembling palmoplantar pustulosis.[4–6] Herein, we report a case of EPF that was unique in that the affected region was limited to the hands.

The present case is a 44-year-old Japanese woman with a 2-year history of itchy eruptions on her hands. Initial presentation was at a local dermatology clinic, where she was diagnosed as having hand eczema and treated with topical steroid. However, the treatment did not improve her skin lesions. The patient was referred to our department for further consultation. Upon initial examination, pruritic erythematous plaques with papules that spread centrifugally were observed on both hands, including on dorsal hands, palms and fingers (Fig. 1). Potassium hydroxide examination of the scales was negative. There were no eruptions on the face, trunk, arms, legs, or soles. General laboratory examinations revealed no apparent abnormalities except for an elevated eosinophil count (570/μl, eosinophil fraction of total white blood cells = 11.4%). Human immunodeficiency virus antibody was negative in the serum. At first, we suspected skin lesions of being dyshidrotic eczema of the hands. Treatment with antihistamine medication (bepotastine besilate) and topical steroid ointment (clobetasol propionate) slightly improved the lesions, although they relapsed soon after withdrawal of medication. The medical history revealed that the patient had received metal dental fixtures for the restoration of three teeth 1 year before. Metal patch tests on her back showed positive cutaneous reactions to palladium, nickel, and platinum at 48 h (+; ICDRG criteria). However, removal of the palladium-containing dental implants failed to improve her skin condition. As her skin lesions were intractable, we performed a skin biopsy to obtain pathological findings. Skin biopsy specimens from the left dorsal hand showed psoriasiform acanthosis of the epidermis and perivascular infiltration of eosinophils in the superficial dermis (Fig. 2). No spongiosis was observed. These histopathological observations were consistent with palmoplantar EPF.[5] We finally diagnosed her skin lesions as EPF of the hands, and we started administration of indomethacin (200 mg/day). Two weeks later, the erythematous plaques had subsided,

LOW RESOLUTION COLOR FIG

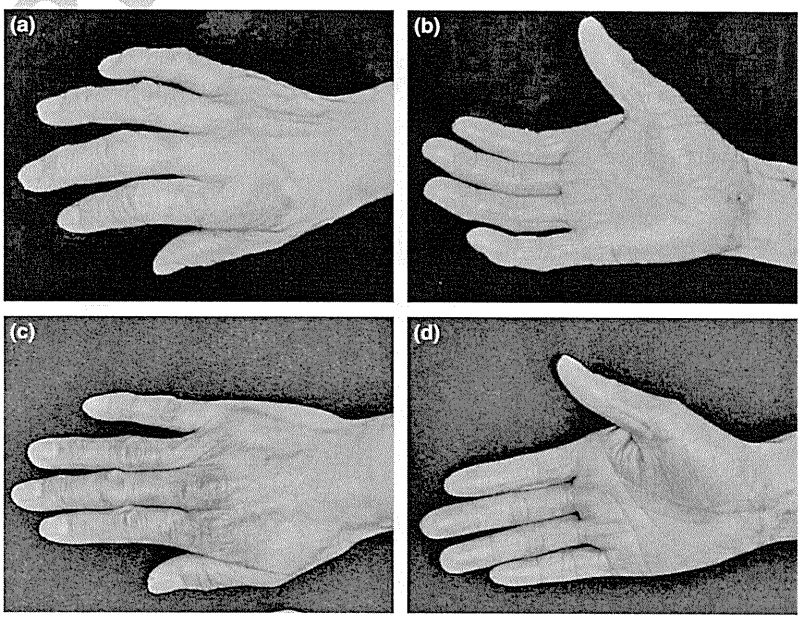

Figure 1 (a,b) Before oral indomethacin treatment. Pruritic plaques with centrifugally spreading papules are seen on the right hand. (c,d) After oral indomethacin treatment. The erythematous plaques have subsided, leaving only pigmentation

LOW RESOLUTION COLOR FIG

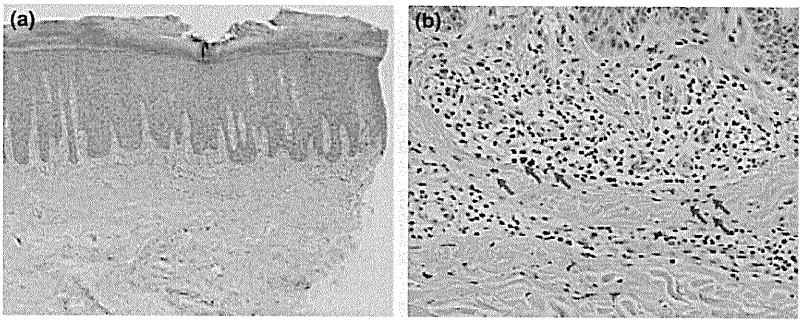

Figure 2 (a) A skin biopsy specimen was taken from the left dorsal hand. The epidermis shows psoriasiform acanthosis and parakeratosis (hematoxylin–eosin stain, original magnification ×10). (b) In the superficial dermis, perivascular inflammatory cell infiltration with eosinophils is recognized. Arrows indicate eosinophils (hematoxylin–eosin stain, original magnification ×40)

leaving residual pigmentation (Fig. 1c,d). The eosinophil count decreased from 570 to 382/μL (eosinophil fraction of total white blood cells = 7.8%) after systemic indomethacin treatment. The indomethacin dosage was decreased, and no recurrence has been observed for the following 2 years.

There have only been a few reports of palmoplantar EPF.[4–6] Aoyama and Tagami reported that palmoplantar lesions were noted in 18% of patients with EPF and that the initial skin lesions of 8% of patients with EPF were restricted to the palms or soles.[5] They described palmoplantar EPF lesions as having three characteristics: (i) palmoplantar pustulosis-like skin manifestation; (ii) poor response to topical steroids; and (iii) favorable response to indomathacin.[5] Concerning histopathology, they reported that the specimens from palmoplantar EPF lesions showed psoriasiform acanthosis and infiltration of eosinophils.[5] From the histopathological findings, we finally diagnosed the skin lesions as hand-restricted EPF, and we were able to easily manage the lesions with oral indomethacin as previously reported.[5,6] A review of the literature found no other reported cases of EPF patients with hand-restricted involvement for the entire disease course.

Our case suggests we should consider palmoplantar EPF as a candidate diagnosis when intractable erythematous plaques occur on the hands.

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References

1 Ofuji S, Ogino A, Horio T, *et al.* Eosinophilic pustular folliculitis. *Acta Derm Venereol* 1970; 50: 195–203.
2 Takematsu H, Nakamura K, Igarashi M, *et al.* Eosinophilic pustular folliculitis: report of two cases with a review of the Japanese literature. *Arch Dermatol* 1985; 121: 917–920.
3 Ofuji S. Eosinophilic pustular folliculitis. *Dermatologica* 1987; 174: 53–56.
4 Saruta T, Nakamizo Y. Eosinophilic pustular folliculitis particularly with reference to lesions on the palm of the hand and sole of the foot. *J Dermatol* 1980; 7: 239–246.
5 Aoyama H, Tagami H. Eosinophilic pustular folliculitis starting initially only with palmoplantar pustular lesions. *Dermatology* 1992; 185: 276–280.
6 Tsuboi H, Niiyama S, Katsuoka K. Eosinophilic pustular folliculitis (Ofuji disease) manifested as pustules on the palms and soles. *Cutis* 2004; 74: 107–110.

CORRESPONDENCE

Intraepidermal neutrophilic IgA pemphigus successfully treated with dapsone

A 25-year-old woman presented with a 2-month history of erythematous, intensely itchy macules and vesicles on the extremities and trunk. Before onset, she was in good health and took no medication. Physical examination revealed pinkish or reddish, edematous, well-demarcated erythema *(figure 1A)*. The lesions tended to coalesce, forming annular patterns, some of which had vesicles around the margins, forming a sunflower-like configuration. The oral cavity and genital area were unaffected. Histopathological findings of a pustule revealed intraepidermal blisters with neutrophil infiltrates without prominent acantholysis *(figure 1B)*. Laboratory examinations, including serum immunoglobulins, and ELISA for anti-desmoglein 1 and 3 were within normal ranges. Chest X-ray, electrocardiogram, and blood tests revealed no other related diseases and monoclonal gammopathy. DIF of the erythematous lesion revealed IgA deposition in the intercellular space throughout the epidermis *(figure 1C)*. IIF revealed circulating IgA autoantibodies binding to the cell surfaces of the entire epidermis of normal human skin (titer: 64×). Immunoblot analysis using epidermal extracts from normal human skin and recombinant desmocollin 3 showed no specific bands for either IgA or IgG antibodies. These findings led to the diagnosis of IEN-type IgA pemphigus. Treatment was initiated with topical corticosteroids, achieving only a slight effect; dapsone (50 mg per day) was therefore started. The pruritus and lesions improved but the symptoms recurred after four weeks. For that reason the dose was raised to 75 mg dapsone and the itchness subsided within a few days. Two weeks later, only pigmented macules with no active lesions were observed. The titer of IIF also decreased from 64× to 16×.

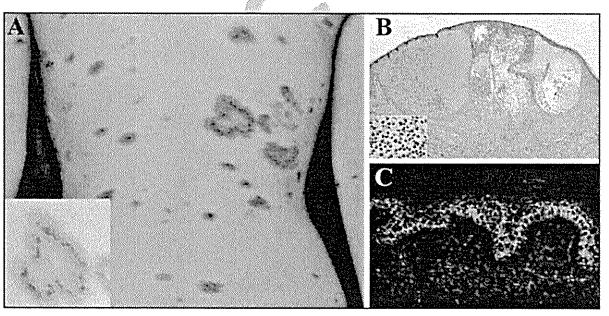

Figure 1. A) Pinkish and reddish edematous erythema with vesicles around the margins are scattered on the trunk. **B)** Histopathological findings of a pustule reveal intraepidermal blisters with neutrophil infiltrates. **C)** Direct immunofluorescence of the perilesional skin biopsy specimen reveals IgA deposits on the keratinocyte cell surfaces.

IgA pemphigus is a distinct group of auto-immune intraepidermal blistering diseases that present with vesiculopustular eruption, neutrophil infiltration with or without acantholysis. IgA autoantibodies that target keratinocyte cell surfaces and desmosomal components in the epidermis have been detected in DIF and IIF [1]. IgA pemphigus is divided into two major subtypes: the IEN type, and the SPD type. While SPD-type IgA pemphigus shows subcorneal pustules, the IEN type is characterized by pustule formation, mainly in the middle or lower epidermis.

In DIF, SPD-type IgA pemphigus involves cell surface IgA binding only in the upper epidermis, whereas IEN-type IgA pemphigus shows binding throughout the epidermis [2]. Desmocollin 1 has been identified as an autoantigen in SPD-type IgA pemphigus, suggesting that it plays an important role in the pathogenesis of this disease subtype [3]. Although autoantibodies against desmogleins [4] and desmocollins [5] have been reported in some cases of IEN-type IgA pemphigus, the specific autoantigen remains unidentified. In our case, we were also unable to detect specific autoantibodies using immunoblot analysis. Interestingly, a case with clinical and histological features compatible with SPD-type IgA pemphigus, but for which anti-desmocollins antibodies were not detected, was diagnosed as IEN-type IgA pemphigus [6]. That report suggested that the subtypes of IgA pemphigus might be considered to be divided by autoantigens.

In contrast to the common types of pemphigus, like pemphigus vulgaris, treatment for some cases of IgA pemphigus does not require corticosteroid or other immunosuppressive therapy. These cases of IgA pemphigus are well controlled using only anti-inflammatory treatments, such as dapsone, colchicine or isotretinoin [1]. Dapsone may be useful in treating IgA pemphigus due to its effect in suppressing neutrophilic infiltration. However refractory cases require plasmapheresis or cyclophosphamide. In the present case, oral administration of dapsone quickly caused the symptoms to subside. In IgA pemphigus, it is important to make the correct diagnosis and to choose a suitable therapy to avoid the side effects by the prolonged use of systemic corticosteroids. ■

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1. Hashimoto T. Immunopathology of IgA pemphigus. *Clinics in dermatology* 2001; 19: 683-689.
2. Hashimoto T, Ebihara T, Nishikawa T. Studies of autoantigens recognized by IgA anti-keratinocyte cell surface antibodies. *Journal of dermatological science* 1996; 12: 10-17.
3. Hashimoto T, Kiyokawa C, Mori O, *et al.* Human desmocollin 1 (Dsc1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. *The Journal of Investigative Dermatology* 1997; 109: 127-131.
4. Karpati S, Amagai M, Liu WL, *et al.* Identification of desmoglein 1 as autoantigen in a patient with intraepidermal neutrophilic IgA dermatosis type of IgA pemphigus. *Experimental Dermatology* 2000; 9: 224-228.
5. Yasuda H, Kobayashi H, Hashimoto T, et al. Subcorneal pustular dermatosis type of IgA pemphigus: demonstration of autoantibodies to desmocollin-1 and clinical review. *The British journal of Dermatology* 2000; 143: 144-148.
6. Iida K, Sueki H, Ohyama B, *et al.* A unique case of intraepidermal neutrophilic dermatosis-type IgA pemphigus presenting with subcorneal pustules. *Dermatology* 2011; 222: 15-19.

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British Journal of Dermatology

Case report

Title: Mucous membrane pemphigoid with generalized blisters: IgA and IgG autoantibodies target both laminin-332 and type XVII collagen

Running head: Mucous membrane pemphigoid with IgA/G reacting with laminin-332 and type XVII collagen

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What's already known about this topic?

- IgA and IgG class autoantibodies directed against type XVII collagen (COL17) or laminin-332 in patients with mucous membrane pemphigoid (MMP) have been well documented.
- MMP with IgA autoantibodies that react with both laminin-332 and COL17 has not been reported.

What does this study add?

- This is the first MMP case in which circulating IgA and IgG class autoantibodies against both laminin-332 and COL17 were detected.

Abstract

Mucous membrane pemphigoid (MMP) is a mucous membrane-dominated, subepidermal autoimmune blistering disease in which autoantibodies usually react with the C-terminal domain of type XVII collagen (COL17) or with laminin-332. Only a few cases of MMP with widespread blisters have been reported. Serologically, IgA and IgG class autoantibodies directed against COL17 or IgG autoantibodies directed against laminin-332 in patients with MMP have been well documented. MMP cases in which IgA reacts with laminin-332, however, are extremely rare. We report a case of MMP in a 67-year-old man. Clinical examination revealed extensive mucosal lesions as well as generalized blisters and erosions that healed with scar formation. He was intractable with systemic steroid treatment. Interestingly, in addition to IgG directed against laminin-332 and the noncollagenous 16A (NC16A) and C-terminal domains of COL17, circulating IgA reacted with laminin-332 and with the NC16A domain of COL17 were also detected. This is the first MMP case with circulating IgA and IgG autoantibodies against both laminin-332 and COL17.

Keywords: cicatrical pemphigoid, autoimmune blistering disease, scar

Introduction

Mucous membrane pemphigoid (MMP) is characterized by blistering and erosive lesions that occur mostly in the oral cavity and conjunctivae, leaving scarring [1]. C-terminal portions of type XVII collagen (COL17) and laminin-332 are known as major autoantigens of MMP [2,3]. IgA and IgG autoantibodies directed against COL17 or IgG autoantibodies directed against laminin-332 in MMP patients have been well described [4,5], and clarified using *in vivo* mouse models [6-9]. In contrast, MMP cases whose IgA autoantibodies react with laminin-332 are extremely rare [5].

We report a case of MMP with extensive mucosal lesions as well as generalized blisters and erosions resulting in scar formation. Interestingly, both IgA and IgG autoantibodies directed against COL17 and laminin-332 were detected.

Case report

A 67-year-old Japanese male had a three-week history of pruritic tense blisters on the hands and feet that gradually spread to entire body. On physical examination, numerous disseminated vesicles, erosions and excoriated papules were observed on the whole body (Fig. 1a, b). In addition, erosions and ulcers were found on the lower lip and the buccal and perianal area (Fig. 1d). The conjunctivae were normal. He also had a sore throat, and endoscopic examination revealed multiple erosions and ulcers on the pharyngeal, laryngeal and esophageal mucosae (Fig. 1c). A biopsy specimen taken from the edge of blister on the back showed subepidermal blister formation with eosinophilic, lymphocytic and neutrophilic infiltrates (Fig. 1h). Enzyme-linked immunosorbent assay (ELISA, MBL, Nagoya, Japan) was positive for IgG antibodies to the NC16A domain of COL17 (index value: 1074; cutoff: 9).

He was initially treated with intravenous prednisolone (1.5 mg/kg per day), followed by oral prednisolone (1 mg/kg per day) for more than a month; however, this failed to sufficiently improve the clinical condition. Since 100 mg of oral azathioprine and 50 mg of diaphenylsulfone daily were added, cutaneous and mucosal lesions started to improve slowly leaving post-inflammatory hyperpigmentation and scar formation (Fig. 1e, f, g).