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CLINICAL REPORT

Localized Linear IgA/IgG Bullous Dermatosis

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Linear IgA/IgG bullous dermatosis (LAGBD) is an autoimmune blistering disease characterized by the local accumulation of IgA- and IgG-class anti-basement membrane autoantibodies. It typically presents as a generalized pruritic vesiculobullous eruption. No cases of localized LAGBD have yet been reported. We report a case of a 78-year-old man with LAGBD localized to the perianal area. The patient complained of suffering from persistent ulcers around the anus for more than 3 years. Physical examination revealed several blisters and ulcers up to 2-cm in diameter around the anus. No lesions were found elsewhere on the body. Histological analysis of a skin biopsy revealed subepidermal blistering, while direct immunofluorescence showed the linear deposition of IgA and IgG antibodies at the dermoepidermal junction. Indirect immunofluorescence of normal human skin whose layers had been separated using 1M NaCl showed the binding of both IgA and IgG to the epidermal side. Immunoblotting demonstrated the presence of circulating IgA and IgG autoantibodies that bound to a 120-kDa protein. This is the first case of localized LAGBD whose skin lesions were restricted to the perianal region. ***Key words: Linear IgA/IgG bullous dermatosis; linear IgA bullous dermatosis; bullous disease; BP180; collagen XVII; immunoblotting.***

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Linear IgA bullous dermatosis (LABD) is an autoimmune blistering disease characterized by subepidermal blisters and linear deposition of IgA autoantibodies at the dermoepidermal junction (1). In LABD, IgA autoantibodies most commonly recognize a 120-kDa or 97-kDa soluble ectodomain of collagen XVII or BP180 (2). Recently, linear IgA/IgG bullous dermatosis (LAGBD) was designated a subepidermal blistering disease in which linear deposition of both IgA and IgG anti-basement membrane autoantibodies occurs. It comprises a heterogeneous group of diseases, with the majority of cases being treated as a subgroup of LABD (3). Clinical features of both LAGBD and LABD vary. They usually present as annular vesiculobullous lesions over the whole body. Several cases of localized LABD have been described (4–7). In contrast, no cases of localized linear IgA/IgG bullous dermatosis (LAGBD) have yet been reported.

We herein describe a case of localized LAGBD in which the location of the lesions had been restricted for more than 3 years.

CASE REPORT

A 78-year-old man visited us complaining of a 3-year history of a perianal skin lesions. Topical steroid cream had not improved his condition. His medical history included stomach cancer (stage 1) and he had been treated for almost 10 years with a range of medicines, included teprenone, ursodeoxycholic acid and trimebutine maleate.

Physical examination revealed several ulcers and blisters on a well-demarcated, 5-cm plaque around the anus (Fig. 1). No skin lesions had appeared elsewhere on his body during the previous more than 3 years and the oral and ocular mucosae were not affected. Pruritus was absent, but defecation was painful. The rectal mucosa was unaffected and anal function was normal. A full blood count and tests of liver and renal function revealed no significant abnormalities, although the patient's HbA1c level was slightly raised (6.0%; normal range 4.3–5.8%).

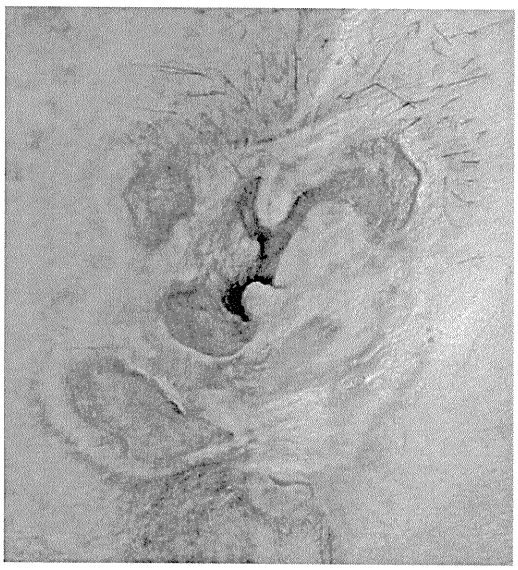

Fig. 1. Clinical manifestation. Ulcers on a well-demarcated plaque around the anus.

A biopsy was taken from the edge of the skin lesion. Histopathological analysis revealed subepidermal blistering and infiltration by lymphocytes, as well as neutrophils and eosinophils (Fig. 2a). Direct immunofluorescence (IF) analysis of lesional skin showed marked deposition of IgA (Fig. 2b), IgG (Fig. 2c) and C_3 at the dermo-epidermal junction. Indirect IF using 1M NaCl split human skin demonstrated whose layers had been separated with the binding of both IgA and IgG class autoantibodies to the epidermal side of the dermoepidermal junction. No dermal binding was observed. Epidermal extracts of normal human skin, supernatants of cultured HaCaT cells and recombinant proteins (NC16A and the C-terminal domain of BP180) were prepared as described previously (8–11) and used in immunoblot analysis of IgA and IgG class antibodies. While the patient's serum failed to react with 180- and 230-kDa antigens in epidermal extracts of normal human skin (Fig. 3a), it carried IgA and IgG class autoantibodies that bound to a 120-kDa protein in concentrated supernatants of cultured HaCaT cells (Fig. 3b). Immunoblotting with the recombinant NC16A domain of BP180 produced no specific binding (Fig. 3c). Further immunoblotting revealed that the patient's serum contained IgG, but not IgA, antibodies specific for the recombinant C-terminal domain of BP180 (BP915) (Fig. 3d). Based on these observations, we diagnosed the patient with LAGBD. Within 2 weeks of starting oral prednisolone treatment (0.5 mg/kg per day), the formation of new lesions ceased. When, however, the prednisolone dose was tapered to 0.1 mg/kg daily, new lesions again began to form. We therefore administered dapsone and gradually tapered the prednisolone dose. No new lesions appeared during 6 months of treatment with dapsone (25 mg daily).

DISCUSSION

LAGBD and LABD typically present as a generalized pruritic vesiculobullous eruption. Although 8 cases of localized LABD have been reported (4–7, 12–15), no cases of localized LAGBD have been described. We believe this to be the first case of localized LAGBD whose skin lesions were restricted to the perianal area.

LAGBD comprises an heterogeneous group of diseases characterized by subepidermal blistering and the specific binding of IgG and IgA antibodies to the epidermal basement membrane (3). Most patients carry autoantibodies against 97-/120-kDa antigens. Some, however, carry autoantibodies against a 230-kDa antigen, as well as additional, as yet uncharacterized epidermal antigens (3, 16). Some cases of LAGBD have been reported as LABD, even though they satisfy the criteria for diagnosis of LAGBD (17). Recent immunoserological studies detected circulating IgA and IgG autoantibodies specific for certain epitopes of BP180 in bullous pemphigoid and LABD patients (18, 19). These findings suggest that there may be considerable overlap between bullous pemphigoid, LABD and LAGBD. In only a few cases of LAGBD have clinical characteristics been described in detail. Most of these displayed a vesiculobullous appearance similar to that of LABD, and were effectively controlled with low-dose prednisolone, dapsone or sulfapyridine (16). More cases are needed to clarify the clinical differences between these disease categories.

The present case carried circulating IgA and IgG antibodies that bound to the 120-kDa soluble ectodomain of BP180. IgG class antibodies also reacted with BP915, the recombinant C-terminal domain of BP180,

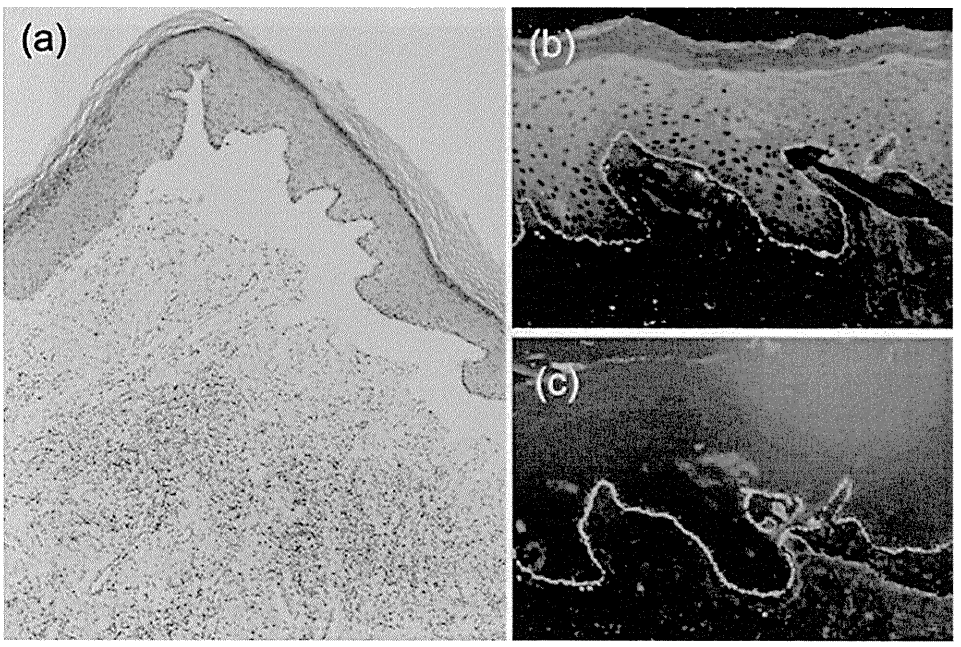

Fig. 2. (a) Biopsy of lesional skin revealed subepidermal blistering and lymphocytic infiltration. (Haemotoxylin&Eosin, original magnification ×100). (b, c) Direct immunofluorescence analysis of a lesional skin biopsy. Linear deposition of IgA (b) and (c) IgG at the dermoepidermal junction.

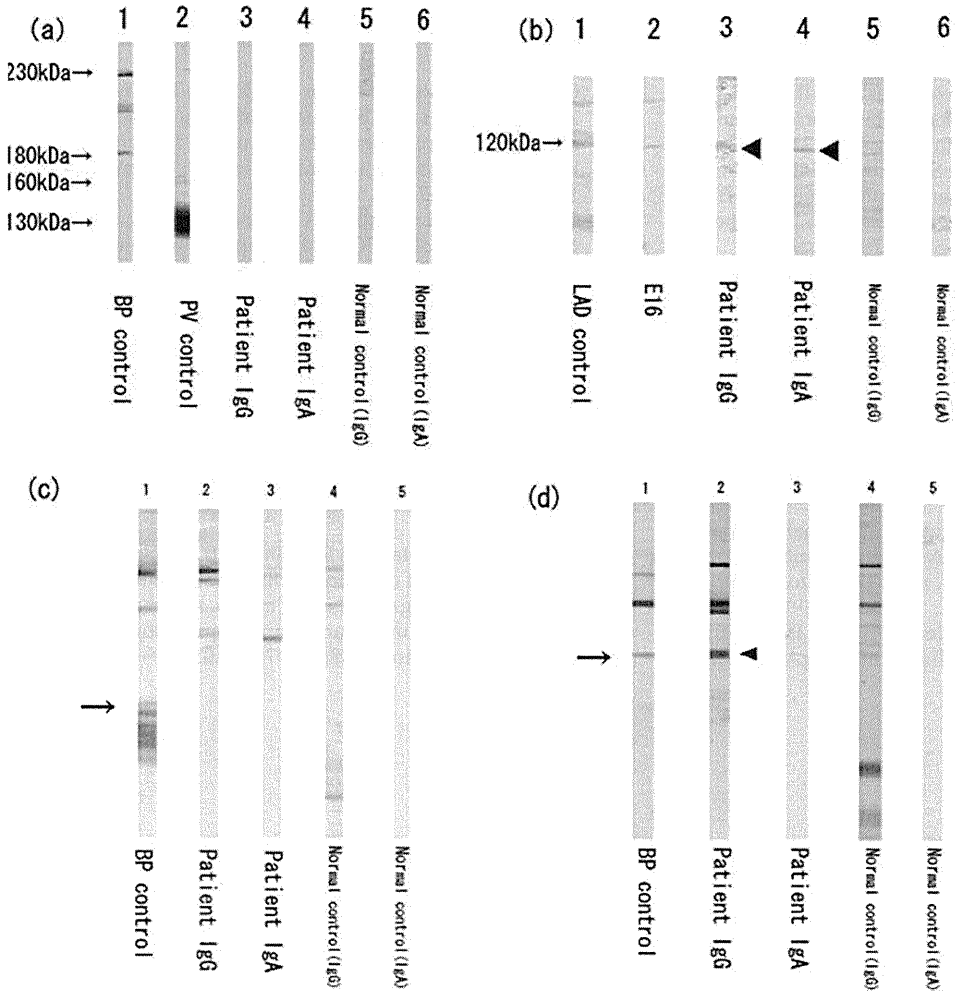

Fig. 3. (a) Immunoblotting using normal human epidermal extracts. Control bullous pemphigoid (BP) serum (lane 1) reacted with 180- and 230-kDa antigens. Control pemphigus vulgaris (PV) serum (lane 2) reacted with 130- and 160-kDa antigens. The patient's serum (lanes 3 and 4) and normal controls (lanes 5 and 6) showed no reactivity. (b) Immunoblotting using conditioned medium of cultured HaCaT cells. Control linear IgA bullous dermatosis (LABD) serum (lane 1), E16 (a goat polyclonal antibody raised against the C-terminus of BP180; Santa Cruz) (lane 2), and the patient's IgG and IgA antibodies (lanes 3 and 4, arrowheads) reacted with a 120-kDa antigen. Normal control samples (lanes 5 and 6) showed no reactivity with the 120-kDa antigen. (c) Reactivity with the NC16A domain of BP180 (arrow) (lane 1). Patient IgA and IgG (lanes 2 and 3) and normal control (lanes 4 and 5) showed no reactivity in immunoblotting analyses. (d) Reactivity with BP915 (recombinant C-terminal domain of BP180). A bullous pemphigoid control (arrow) (lane 1) and the patient's IgG (arrowhead) (lane 2) showed reactivity (lane 1, 2) in immunoblotting analyses. The patient's IgA (lane 3) and normal controls (lanes 4 and 5) showed no reactivity.

which is the protein that is primarily targeted in mucous membrane pemphigoid (MMP) (11). In a study by Georgi et al. (17) BP915 was bound by IgA in 44% of lamina lucida-type LABD serum samples tested and by IgG in 33% of such samples (17). The authors concluded that the C-terminus of BP180 represents the primary target on the BP180 ectodomain for both IgA and IgG antibodies in the serum of LABD patients (17). Healing with scarring is characteristic of MMP but it is also found in some lamina lucida-type LABD patients (17, 20). This clinical overlap may well be explained by overlap in the antigenic sites on the BP180 ectodomain targeted by autoantibodies.

In summary, we have described an unusual case of LAGBD localized to the perianal region for more than 3 years that reveals the heterogeneous nature of LAGBD. LAGBD should be considered when diagnosing the cause of perianal blistering.

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The authors declare no conflict of interest.

REFERENCES

1. Leonard JN, Haffenden GP, Ring NP, McMinn RM, Sidgwick A, Mowbray JF, et al. Linear IgA disease in adults. Br J Dermatol 1982; 107: 301–316.
2. Zone JJ, Taylor TB, Meyer LJ, Petersen MJ. The 97 kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180 kDa bullous pemphigoid antigen, BPAg2. J Invest Dermatol 1998; 110: 207–210.
3. Zone JJ, Pazderka Smith E, Powell D, Taylor TB, Smith JB, Meyer LJ. Antigenic specificity of antibodies from patients with linear basement membrane deposition of IgA. Dermatology 1994; 189 Suppl 1: 64–66.
4. Condon C, Cotter P, Lyons JF. Localized linear IgA disease and platelet abnormalities. Br J Dermatol 1994; 131: 139–141.
5. He C, Xu H, Xiao T, Geng L, Chen HD. Localized linear IgA dermatosis induced by UV light-treatment for herpes zoster. Int J Dermatol 2007; 46: 500–502.
6. Yoneda K, Yokoi I, Demitsu T, Matsuda Y, Matsuoka Y, Miyamoto I, et al. Localized linear IgA disease showing contact dermatitis-like eruption. Eur J Dermatol 2007; 17: 339–340.
7. Shimanovich I, Rose C, Sitaru C, Brocker EB, Zillikens D. Localized linear IgA disease induced by ampicillin/sulbactam. J Am Acad Dermatol 2004; 51: 95–98.
8. Dmochowski M, Hashimoto T, Bhogal BS, Black MM, Zone

JJ, Nishikawa T. Immunoblotting studies of linear IgA disease. J Dermatol Sci 1993; 6: 194–200.
9. Schacke H, Schumann H, Hammami-Hauasli N, Raghunath M, Bruckner-Tuderman L. Two forms of collagen XVII in keratinocytes. A full-length transmembrane protein and a soluble ectodomain. J Biol Chem 1998; 273: 25937–25943.
10. Zillikens D, Rose PA, Balding SD, Liu Z, Olague-Marchan M, Diaz LA, et al. Tight clustering of extracellular BP180 epitopes recognized by bullous pemphigoid autoantibodies. J Invest Dermatol 1997; 109: 573–579.
11. Nie Z, Hashimoto T. IgA antibodies of cicatricial pemphigoid sera specifically react with C-terminus of BP180. J Invest Dermatol 1999; 112: 254–255.
12. Cauza K, Hinterhuber G, Sterniczky B, Brugger K, Pieczkowski F, Karlhofer F, et al. Unusual clinical manifestation of linear IgA dermatosis: a report of two cases. J Am Acad Dermatol 2004; 51: S112–117.
13. Benbenisty KM, Bowman PH, Davis LS. Localized linear IgA disease responding to colchicine. Int J Dermatol 2002; 41: 56–58.
14. Walsh SN, Kerchner K, Sangueza OP. Localized palmar vancomycin-induced linear IgA bullous dermatosis occurring at supratherapeutic levels. Arch Dermatol 2009; 145: 603–604.
15. Gamo R, Aguilar A, Gonzalez-Valle O, Houmani M, Martin L, Gallego MA. Localized linear IgA disease associated with monoclonal gammapathy of undetermined significance. J Eur Acad Dermatol Venereol 2007; 21: 544–545.
16. Chan LS, Traczyk T, Taylor TB, Eramo LR, Woodley DT, Zone JJ. Linear IgA bullous dermatosis. Characterization of a subset of patients with concurrent IgA and IgG antibasement membrane autoantibodies. Arch Dermatol 1995; 131: 1432–1437.
17. Georgi M, Scheckenbach C, Kromminga A, Partscht K, Messer G, Brocker EB, et al. Mapping of epitopes on the BP180 ectodomain targeted by IgA and IgG autoantibodies in patients with the lamina lucida-type of linear IgA disease. Arch Dermatol Res 2001; 293: 109–114.
18. Kromminga A, Scheckenbach C, Georgi M, Hagel C, Arndt R, Christophers E, et al. Patients with bullous pemphigoid and linear IgA disease show a dual IgA and IgG autoimmune response to BP180. J Autoimmun 2000; 15: 293–300.
19. Horiguchi Y, Ikoma A, Sakai R, Masatsugu A, Ohta M, Hashimoto T. Linear IgA dermatosis: report of an infantile case and analysis of 213 cases in Japan. J Dermatol 2008; 35: 737–743.
20. Wojnarowska F, Marsden RA, Bhogal B, Black MM. Chronic bullous disease of childhood, childhood cicatricial pemphigoid, and linear IgA disease of adults. A comparative study demonstrating clinical and immunopathologic overlap. J Am Acad Dermatol 1988; 19: 792–805.

Medical genetics

An Indian family with Sjögren-Larsson syndrome caused by a novel *ALDH3A2* mutation

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Abstract

Sjögren-Larsson syndrome is an autosomal-recessive hereditary disorder characterized by congenital ichthyosis, mental retardation and spastic diplegia or tetraplegia. It is known that mutations in the fatty aldehyde dehydrogenase (FALDH) gene (*ALDH3A2*) underlie SLS. We report two Indian sisters showing typical clinical features of SLS. Direct sequencing of the entire coding region of *ALDH3A2* revealed a novel homozygous mutation, c.142G>T (p.Asp48Tyr) in exon 1, in both patients. Their parents harbored the mutation heterozygously. Mutant-allele-specific amplification analysis using PCR products as a template verified the mutation in the patients. The aspartic acid residue at the mutation site is located in the C-terminal portion of the second a-helix strand, a2, of N-terminal four helices of FALDH and the FALDH amino-acid sequence alignment shows that this aspartic acid residue is conserved among several diverse species. Until now, a number of mutations in *ALDH3A2* have been shown to be responsible for SLS in Europe, the Middle East, Africa, and North and South America. However, in Asian populations, *ALDH3A2* mutations have been identified only in Japanese SLS patients. Here we report an *ALDH3A2* mutation for the first time in SLS patients in the Asian country other than Japan. The present results suggest that *ALDH3A2* is a gene responsible for SLS in Asian populations. We hope *ALDH3A2* mutation search will be globally available including many Asian countries in the future.

Case

Two sisters were born in an Indian nonconsanguineous family. The patient was a 1.5-year-old girl. She had had severe ichthyosis on the entire body since birth, especially prominent on the bilateral lower limbs (Fig. 1a–c). She showed mental retardation and spastic tetraplegia. Ocular fundus evaluation revealed white dots in the maculae. The elder sister also had icthyotic lesions all over the body at birth and had global developmental delay. She had had seizures since 2.5 years of age that had been controlled with multiple antiepileptic medications. At the age of four, severe hyperkeratosis appeared on the chest, back, axillae and predominantly over the limbs (Fig. 1d,e). She has hypertelorism, dolichocephalic head, large low-set ears, long eyelashes and short 3rd, 4th, and 5th metatarsals. Neurological evaluations revealed severe spastic tetraplegia with persistent ankle clonus and complete head lag. She showed serious mental retardation. She had severe photophobia, and ocular fundus evaluation showed white glistening dots in the maculae bilaterally. Severe auditory startle reaction was a characteristic feature. Magnetic resonance imaging of the brain showed bilateral symmetrical diffuse white matter at high intensity in T2-weighted images in the frontal, temporal, and parietal regions. Both sisters were diagnosed with Sjögren-Larsson syndrome (SLS) from these clinical features and laboratory data.

Fatty aldehyde dehydrogenase (FALDH) gene (*ALDH3A2*) mutational analysis was performed on the affected girls and their parents, as previously described.[1,2] In the patients, a novel homozygous mutation, c.142G>T (p.Asp48Tyr) in exon 1, was identified. Their parents harbored the mutation heterozygously (Fig. 2a). This mutation was not found in 200 normal unrelated alleles (100 individuals) by direct sequence analysis. Mutant-allele-specific amplification (MASA) analysis verified the mutation in this family (Fig. 2b).

Discussion

Sjögren-Larsson syndrome (MIM# 270200) is an autosomal-recessive hereditary disorder characterized by congenital ichthyosis, mental retardation and spastic diplegia or

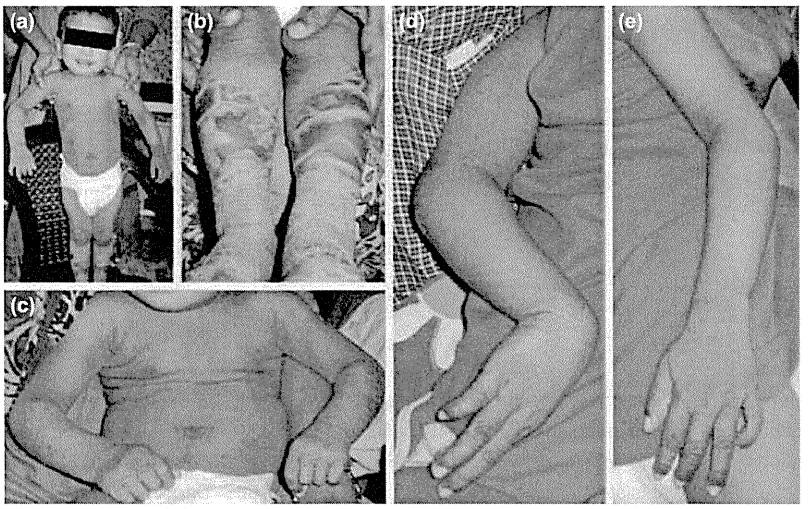

Figure 1 Clinical features of the Indian sisters with SLS. (a–c) The younger sister. Hyperkeratosis and scales cover whole body surface at 1.5 years of age (a). Dark brown scales are seen on the bilateral legs (b), the arms and the trunk (c). (d, e) The elder sister shows hyperkeratosis and brown scales on the bilateral arms at 4 years of age

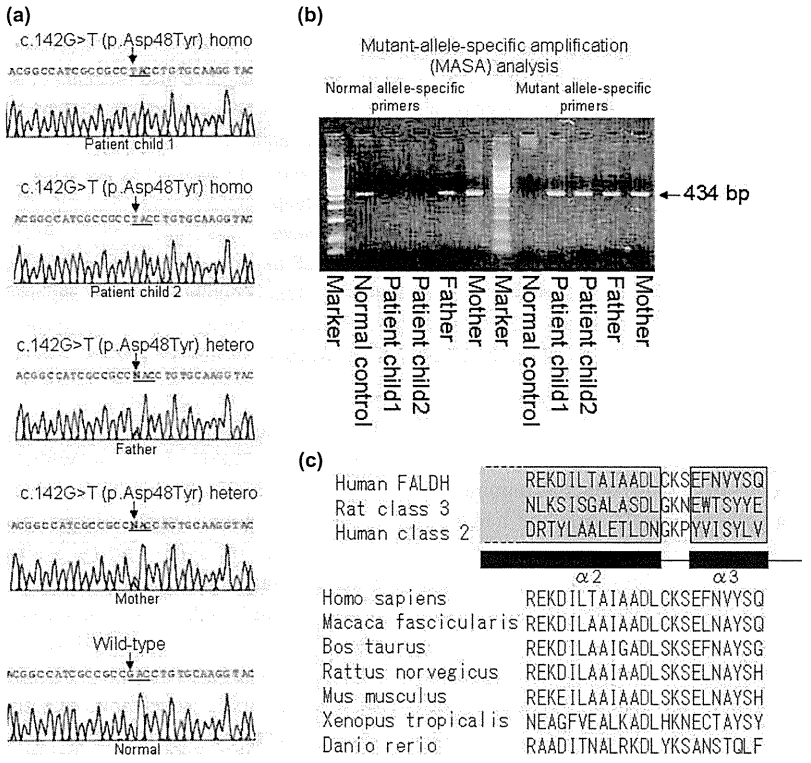

Figure 2 *ALDH3A2* mutation in the present SLS patients, and sequence alignments around the missense mutation. (a) Sequence analysis of *ALDH3A2*. In both patients, the younger sister (child 1) and the elder sister (child 2), a homozygous missense mutation c.142G>T (p.Asp48Tyr) in exon 1 derived from their parents was detected. The parents were heterozygous for the mutation. (b) Mutant allele-specific amplification analysis. With normal allele-specific primers, no amplification band is seen in the PCR products from the patients' DNA samples, suggesting that they have no normal allele. With mutant allele specific primers, the amplification band from the mutant alleles is detected as a 434-bp fragment in the PCR products from the DNA samples from the patients and their parents, and not in the PCR products from control DNA samples. This confirms the presence of the mutation c.142G>T in the patients. (c) Top: a sequence alignment between FALDH, rat class 3 and human class 2 ALDHs. Aspartic acid residue at codon 48 of FALDH is conserved. Secondary structure components found in the class 3 rat ALDH structure by Liu *et al.*[6] are presented with bars representing α-helices. Bottom: FALDH amino acid sequence alignment shows the level of conservation in diverse species of aspartic acid residue at codon 48 (D48) (red characters), which was altered by the missense mutation in the present family

tetraplegia.[3] In 1996, De Laurenzi *et al.*[4] reported that mutations in *ALDH3A2* underlie SLS. The present study reports a novel homozygous mutation in *ALDH3A2* in an Indian family with SLS.

The FALDH amino-acid sequence alignment shows that this aspartic acid residue at codon 48 is conserved among several diverse species. Compared with other aldehyde dehydrogenase (ALDH)-related sequences identified by Perozich *et al.*,[5] this aspartic acid is highly conserved among many members of the ALDH family (Fig. 2c). Analysis of the crystallized 3-D structure of the related class 3 rat cytosolic ALDH revealed that this aspartic acid is located in the C-terminal portion of the second α-helix strand, α2, of N-terminal four helices (Fig. 2c).[6] These findings strongly suggest that this aspartic acid residue is essential for the normal function of the FALDH. In the literature, missense mutation p.Ile45Phe in the α2 helix, three codons upstream of the present mutation site, was reported and the mutant enzyme was revealed to have only 9% residual enzyme activity compared with the wild-type enzyme.[7]

Until now, a number of mutations in *ALDH3A2* have been shown to be responsible for SLS in Europe, the Middle East, Africa, and North and South America.[1,7] However, in Asian populations, *ALDH3A2* mutations have been identified only in Japanese SLS patients.[1,2,8–10] Here, we report an *ALDH3A2* mutation for the first time in SLS patients in the Asian country other than Japan. The present results suggest that *ALDH3A2* is a gene responsible for SLS in Asian populations. Mutation analysis of the *ALDH3A2* gene is a highly sensitive method of confirming a diagnosis of SLS. It does not require a skin biopsy or FALDH enzymatic assays. We hope *ALDH3A2* mutation search will be globally available including many Asian countries in the future.

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References

1 Rizzo WB, Carney G, Lin Z. The molecular basis of Sjögren-Larsson syndrome: mutation analysis of the fatty aldehyde dehydrogenase gene. *Am J Hum Genet* 1999; 65: 1547–1560.
2 Shibaki A, Akiyama M, Shimizu H. Novel ALDH3A2 heterozygous mutations are associated with defective lamellar granule formation in a Japanese family of Sjögren-Larsson syndrome. *J Invest Dermatol* 2004; 123: 1197–1199.
3 Sjögren T, Larsson T. Oligophrenia in combination with congenital ichthyosis and spastic disorders; a clinical and genetic study. *Acta Psychiatr Neurol Scand Suppl* 1957; 113: 1–112.
4 De Laurenzi V, Rogers GR, Hamrock DJ, *et al.* Sjögren-Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nature Genet* 1996; 12: 52–57.
5 Perozich J, Nicholas H, Wang B-C, *et al.* Relationships within the aldehyde dehydrogenase extended family. *Protein Sci* 1999; 8: 137–146.
6 Liu Z-J, Sun Y-J, Rose J, *et al.* The first structure of an aldehyde dehydrogenase reveals novel interactions between NAD and the Rossmann fold. *Nat Struct Biol* 1997; 4: 317–326.
7 Rizzo WB, Carney G. Sjögren-Larsson syndrome: diversity of mutations and polymorphisms in the fatty aldehyde dehydrogenase gene (*ALDH3A2*). *Hum Mutat* 2005; 26: 1–10.
8 Tsukamoto N, Chang C, Yoshida A. Mutations associated with Sjögren-Larsson syndrome. *Ann Hum Genet* 1997; 61: 235–242.
9 Aoki N, Suzuki H, Ito K, Ito M. A novel point mutation of the FALDH gene in a Japanese family with Sjögren-Larsson syndrome. *J Invest Dermatol* 2000; 114: 1065–1066.
10 Sakai K, Akiyama M, Watanabe T, *et al.* Novel ALDH3A2 heterozygous mutations in a Japanese family of Sjögren-Larsson syndrome. *J Invest Dermatol* 2006; 126: 2545–2547.

Case Report

Dermatology

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Pyoderma Gangrenosum of the Eyelid: Report of Two Cases and Review of the Literature

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Key Words
Pyoderma gangrenosum · Eyelid

Abstract
Pyoderma gangrenosum (PG) of the eyelid is extremely rare, and its proper management is essential for the preservation of visual function. Here, we report 2 cases of PG of the eyelid with intraorbital involvement. In both cases, the skin and intraorbital lesions improved after systemic immunosuppressive therapies; however, corneal perforation occurred in 1 case. In order to assess the clinical features of PG of the eyelid and to obtain clues for optimal treatment, we reviewed 15 well-documented cases in the literature, including the present cases. Corneal perforation occurred in 4 cases and defective ocular motility in 1 case. Three patients eventually underwent enucleation of the affected eye. Our cases and the literature review clearly indicate that MRI is a powerful tool for evaluating the extent of extracutaneous PG lesions around the eye and that early diagnosis and immediate immunosuppressive therapy are crucial for the preservation of visual acuity.

Introduction

Pyoderma gangrenosum (PG) is a destructive and necrotising skin disease characterised by neutrophilic infiltration. PG lesions have a predilection for the lower extremities and trunk although they can occur at any site [1]. PG of the eyelid is extremely rare and the clinical features, prognosis and optimal treatments have yet to be fully described. In order to clarify the characteristics of PG affecting the eyelid and to obtain clues as to the most efficient treatment, we report 2 cases and review 13 well-documented cases in the literature.

Case Reports

Case 1

A 75-year-old Japanese man was referred to our department with a two-year history of recurrent ulcers on his right upper eyelid. Two and a half years before his visit, a twig had stuck into the upper right eyelid. The painful wound had gradually enlarged and become an eroding ulcer. The lesion was suspected to be an adnexal tumour by plastic surgeons. However, neither repeated surgical operations nor antibiotic administration improved the ulcer on the eyelid. Initial physical examination at our outpatient clinic showed an eroding ulcer extending from the right upper eyelid to the right cheek along the surgical operation wound. The ulcer on the right upper eyelid involved the superior tarsus, resulting in a lagophthalmos (fig. 1a, b). Skin biopsy specimens from the edge of the ulcer on the right cheek showed dense neutrophil infiltration (fig. 1c, d). Light microscopic observations did not show giant cells, ballooning degeneration or reticular degeneration. Negative results for Gram, PAS, Grocott and Ziehl-Neelsen stains, culture of skin tissue or polymerase chain reaction analyses failed to indicate any infectious diseases with bacteria, mycobacteria, atypical mycobacteria and fungi. Neither the Tzanck test nor immunofluorescence studies of herpes viral antigens showed any herpes virus infection. In laboratory examination, neither anti-proteinase 3, anti-myeloperoxidase antibodies nor atypical anti-neutrophil cytoplasmic antibodies were detected. From these clinical features and histopathological findings, we diagnosed the ulcers as PG.

Detailed examination failed to detect any systemic complications including inflammatory bowel diseases, haematolog-

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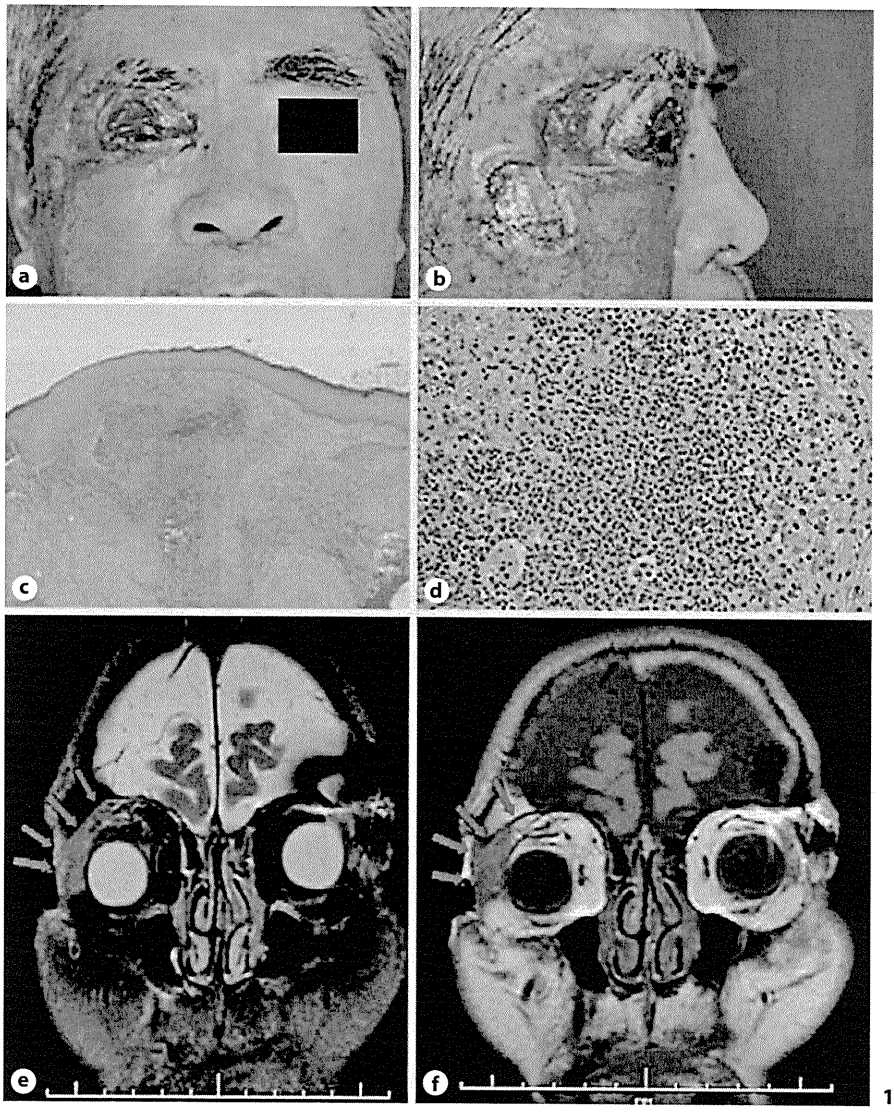

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Fig. 1. Clinical, histopathological and MRI features of case 1. **a**, **b** An eroding ulcer extended from the right upper eyelid to the right cheek along the surgical operation wound margin. **c**, **d** Skin biopsy specimens from the edge of the ulcer on the right cheek showing dense neutrophil infiltration. HE. Original magnifications: ×20 (**c**), ×60 (**d**). **e**, **f** Orbital MRI showing homogeneous hyperintensity on fat-saturated T_2-weighted image (**e**, red arrows) and hypointensity on T_1-weighted image in the right lachrymal gland and upper eyelid (**f**, red arrows), indicating acute inflammation.

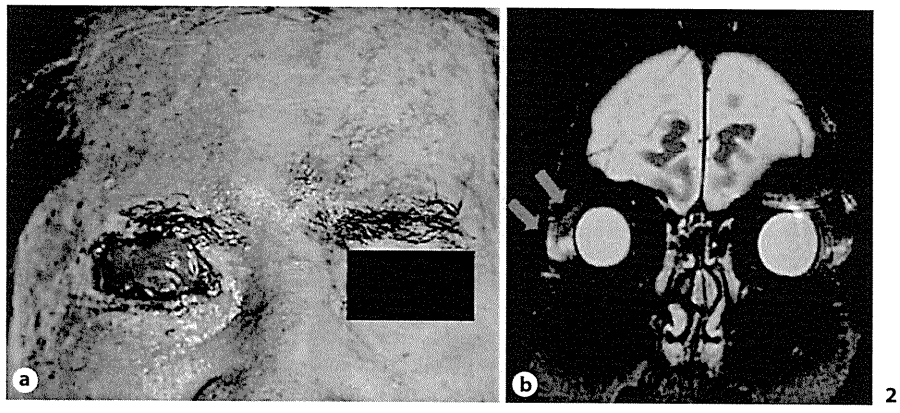

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Fig. 2. Clinical and MRI features of case 1 after PG remission. **a** The eroding ulcer healed with scarring. Corneal opacity appeared. **b** Orbital, fat-saturated T_2-weighted image after 4 months of immunosuppressive therapy showing that the hyperintense area had diminished (red arrows).

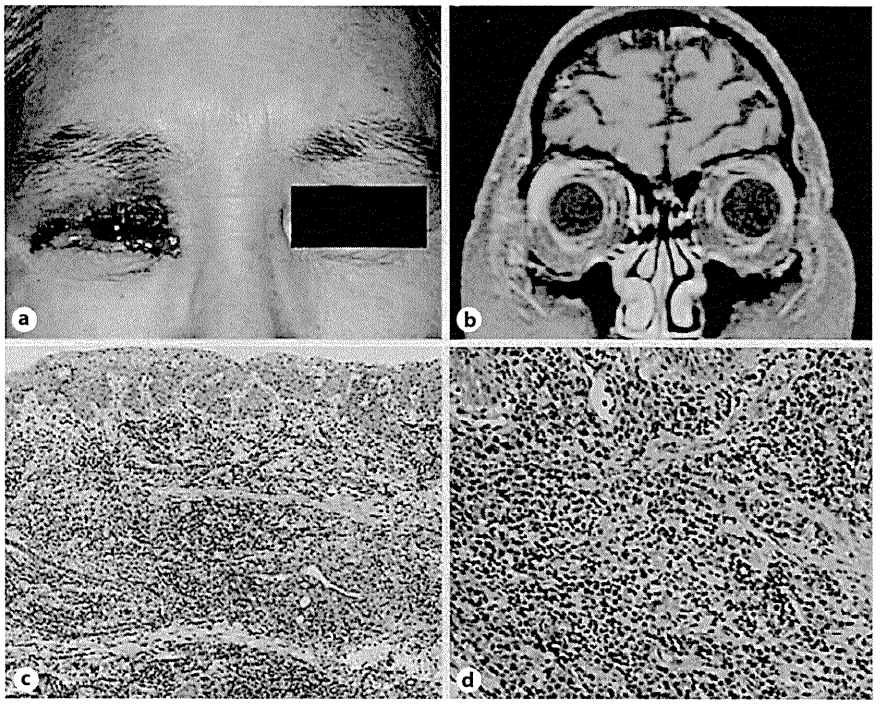

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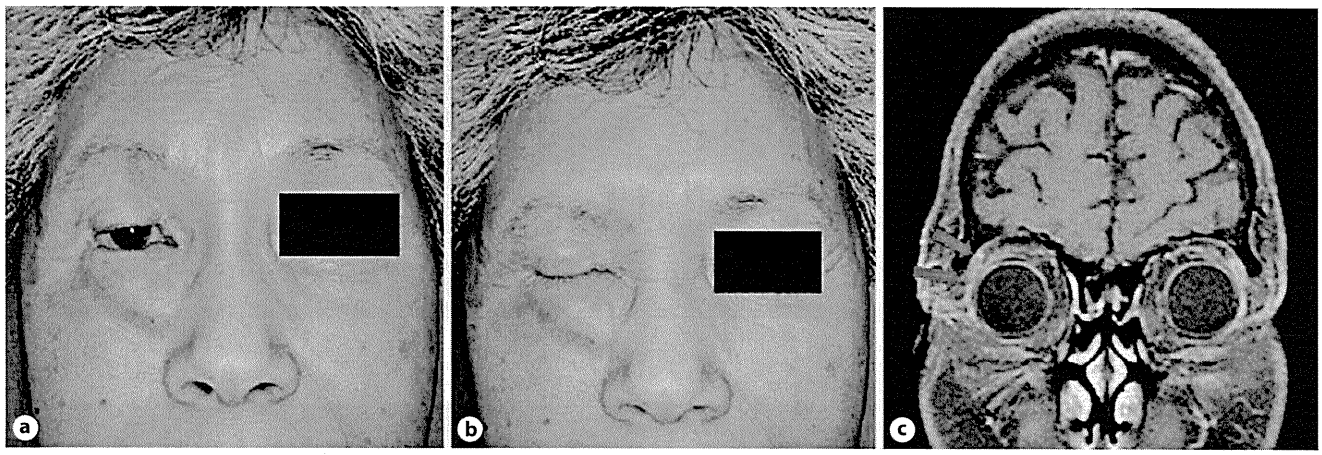
Fig. 3. Clinical, histopathological and MRI features of case 2. **a** An ulcer with surrounding erythema on the right upper eyelid. **b** Orbital MRI showing area of hyperintensity on T_1-weighted image in the right lachrymal gland and upper eyelid. **c**, **d** Skin biopsy specimens showing dermal abscesses with dense aggregates of plasma cells. HE. Original magnifications: ×20 (**c**), ×60 (**d**).

Fig. 4. Clinical and MRI features of case 2 two years after the eyelid repair operation. She was able to open (**a**) and close her eyes (**b**). **c** Orbital fat-saturated T_1-weighted image after immunosuppressive therapy revealing the area of hyperintensity had diminished (red arrows).



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ical disorders or rheumatoid arthritis. Orbital MRI showed homogeneous hyperintensity areas on fat-saturated T_2-weighted image, and hypointensity areas on T_1-weighted image in the right lachrymal gland and upper eyelid (fig. 1e, f), suggesting an acute inflammation of the extracutaneous areas. An initial combined therapy with prednisolone (1 mg/kg/day) and cyclosporin A (5 mg/kg/day) improved the skin lesions as well as intraorbital involvement (fig. 2a, b). PG disease activity was controlled and the eroding ulcer on the upper portion of the right eyelid and cheek healed with scarring. However, the destruction of the right eyelid led to poor eye closure and continuous corneal exposure to air. Two months after the remission of the cutaneous lesions of PG, perforation of the right cornea occurred and the right eye had to be enucleated. Treatment with prednisolone and cyclosporin A was continued and no recurrence was observed for 4 months after the enucleation of the eye.

Case 2

A 65-year-old Japanese woman was referred to our department with a 9-month history of a facial ulcer. A painful erythema and ulcer appeared on her right upper eyelid without any preceding episodes. At first, the patient visited an ophthalmology clinic. The lesion was initially diagnosed as

Table 1. Summary of the clinical information on reported cases with PG of the eyelid

Patient No.	Age, years	Sex	Distribution of PG	Initial diagnosis	Initial treatment	Duration from onset to diagnosis	Treatment	Outcome and prognosis	Complications	Ref.
1	64	male	left temple, scleral conjunctivitis, anterior uveitis, corneal opacity	N/A	antibiotics	N/A	PSL, azathioprine	recurrence	arthritis	Happle et al. [2]
2	62	male	left upper eyelid	N/A	N/A	14 days	chlorhexidine gluconate	recurrence	none	Browning et al. [3]
3	63	male	left eye	N/A	N/A	25 years	clofazimine	recurrence	N/A	Mensing [4]
4	67	female	right lower eyelid	N/A	antibiotics	60 days	PSL	recurrence, corneal perforation, evisceration of the eye	diabetic	Newman and Frank [5]
5	80	female	bilateral eyelids	N/A	antibiotics	N/A	PSL	no recurrence	ulcerative colitis	Tirpitz et al. [6]
6	47	female	right lower eyelid, left eyelid	N/A	N/A	8 days	mPSL (500 mg) 3 days, PSL	no recurrence	rhinosinusitis	Sidwell et al. [7]
7	28	female	left upper eyelid, right eye, left orbit, liver, spleen	nodular scleritis, orbital inflammation	N/A	3 years	PSL, cyclosporin	defective ocular motility	arthritis	Miserocchi et al. [8]
8	61	female	right upper eyelid, right necrotising scleritis	chalazia	antibiotics	30 days	PSL, cyclophosphamide	no recurrence	none	Rose et al. [9]
9	56	male	left upper eyelid, ischemic sclerokeratitis, corneal perforation	bacterial infection	antibiotics	14 days	immunosuppressive therapy	eyelid construction, keratoplasty	rheumatoid arthritis	Rose et al. [9]
10	75	female	left upper eyelid	N/A	N/A	a few weeks	PSL	eyelid construction	interstitial pneumonia	Rose et al. [9]
11	67	N/A	lower eyelid, lateral canthus, lateral orbit	N/A	antibiotics	N/A	PSL, clofazimine	corneal perforation, subtotal orbital exenteration	none	Rose et al. [9]
12	82	male	left lower eyelid, left cheek	chronic wound	antibiotics, surgical operation	2.5 years	PSL, cyclosporin	recurrence (after operation)	none	Lindberg-Larsen and Fogh [10]
13	19	female	right lower eyelid	N/A	N/A	N/A	PSL, dapsone	eyelid construction	none	Procianoy et al. [11]
14	75	male	right upper eyelid, lachrymal gland	adnexal tumour	surgical operation	1.8 years	PSL, cyclosporin	corneal perforation, subtotal orbital exenteration	none	present case 1
15	65	female	right upper eyelid, lachrymal gland	chalazia	antibiotics	180 days	PSL	eyelid construction	none	present case 2

N/A = Not available; PSL = prednisolone.

a chalazion although neither several incisions nor antibiotics improved it. The initial skin biopsy was performed at the ophthalmology clinic, and the lesion was diagnosed as PG from the histopathological findings. Systemic prednisolone (initial dose: 1 mg/kg/day) improved the lesion; however, the skin lesion recurred when the prednisolone dose was reduced to 0.2 mg/kg/day. The patient was referred to our department for further consultation.

At the initial examination, an ulcer with surrounding erythema was observed (fig. 3a). Skin biopsy specimens showed a dermal abscess containing dense aggregates of plasma cells (fig. 3c, d). Light microscopic observations did not show giant cells, ballooning degeneration or reticular degeneration. Gram, PAS, Grocott and Ziehl-Neelsen stains, and culture of skin tissue failed to identify infectious diseases due to bacteria, mycobacteria, atypical mycobacteria and fungi. Using a laboratory examination and endoscopy, no systemic complications were detected. Anti-proteinase 3, anti-myeloperoxidase antibodies or atypical anti-neutrophil cytoplasmic antibodies were not detected. Orbital MRI showed hypointensity areas on T_2-weighted image and hyperintensity areas on T_1-weighted image, suggesting fibrosis in the right lachrymal gland and eyelid (fig. 3b). From the clinical features and histopathological findings, the lesion was also diagnosed as PG in our department. We started high-dose systemic prednisolone (1.2 mg/kg/day), and it improved not only the lesion of the eyelid but also the intraorbital involvement (fig. 4c). The systemic prednisolone was then gradually tapered for 15 months. In order to obtain adequate ocular surface protection, an eyelid repair was performed 12 months after the cessation of systemic prednisolone (fig. 4a, b). No recurrence of skin ulcers or ocular involvement was observed without systemic steroid administration for 5 years.

Discussion

Here, we report 2 cases with PG of the eyelid and review well-documented reports from the literature [2–11]. We summarise the clinical information of the 15 PG cases of the eyelid including the present 2 patients in table 1. It seems to be difficult to make an early diagnosis of PG of the eyelid. In fact, 5 cases (33%) out of 15 were initially misdiagnosed as bacterial infections, chalazia or adnexal tumours (table 1). In 7 cases (47%) it took more than 1 month to be diagnosed as PG. Two cases (13%) were treated by surgical operation, resulting in enlargement of the PG lesions. Seven cases (47%) showed extracutaneous PG lesions including the lachrymal gland, orbit, sclera and uvea as well as internal organ involvement [2, 8, 9]. The eyelids are indispensable for protection of the eye, especially the cornea. Destruction of the eyelid often leads to serious visual disability. Eyelid defects due to PG caused corneal perforation in 4 cases (27%) including the present case 1 [5, 9]. In 3 patients (20%), the affected eyes were required to be enucleated [5, 9]. One patient had defective ocular motility due to severe fibrosis involving the orbital cavity [8].

In the present case 1, surgical intervention made the skin lesion worse. A new distinct PG lesion appeared along the postoperative wounds, affecting the right upper eyelid and cheek. Despite the systemic treatment with immunosuppressive agents, the defect in the right upper eyelid remained, leading to a continuous corneal exposure and perforation of the cornea. Eventually, the right eye had to be enucleated. In contrast, the visual function in case 2 was preserved owing to early diagnosis and immunosuppressive therapy.

Although there has been no report which described the usefulness of MRI, our 2 cases suggest that MRI is effective in detecting PG lesions within intraorbital tissues. In case 1, MRI showed marked homogeneous hyperintensity on fat-saturated T_2-weighted image and hypointensity on T_1-weighted image in the right lachrymal gland, indicating acute inflammation. In case 2, MRI revealed marked hypointensity on T_2-weighted image and hyperintensity on T_1-weighted image in the right lachrymal gland, suggesting the presence of fibrosis. MRI also demonstrated improvements after immunosuppressive therapy in both cases. The present 2 cases suggest that MRI is a powerful tool for evaluating the extent of subcutaneous PG lesion involvement.

In conclusion, our cases and the review of the literature indicate that successful management of PG and the preservation of visual acuity depend on early diagnosis and the induction of an adequate immunosuppressive therapy.

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References

1 Ruocco E, Sangiuliano S, Gravina AG, Miranda A, Nicoletti G: Pyoderma gangrenosum: an updated review. J Eur Acad Dermatol Venereol 2009;23:1008–1017.
2 Happle R, Schiffer HP, Kovary PM: Ocular involvement in pyoderma gangrenosum. Arch Dermatol 1977;113:1612.
3 Browning DJ, Proia AD, Sanfilippo FP: Pyoderma gangrenosum involving the eyelid. Arch Opthalmol 1985;103:551–552.
4 Mensing H: Clofazimine in dermatitis ulcerosa (pyoderma gangrenosum). Dermatologica 1988;177:232–236.
5 Newman WD, Frank HJ: Pyoderma gangrenosum of the orbit. Eye 1993;7:89–94.
6 Tirpitz C, Buchwald HJ, Lang GK, Adler G, Reinshagen M: Simultaneous onset of pyoderma gangrenosum and bitemporal abscesses of the upper eyelids during a flare of ulcerative colitis. Inflamm Bowel Dis 1998;4:98–100.
7 Sidwell RU, Petel NN, Francis N, Staughton RCD: Pyoderma gangrenosum of the eyelid and acute rhinosinusitis. Clin Dermatol 2001;26:680–682.
8 Miserocchi E, Modorati G, Foster CS, Brancato R: Ocular and extracutaneous involvement in pyoderma gangrenosum. Ophthalmology 2002;109:1941–1943.
9 Rose GE, Barnes EA, Uddin JM: Pyoderma gangrenosum of the ocular adnexa. Ophthalmology 2003;110:801–805.
10 Lindberg-Larsen R, Fogh K: Traumatic pyoderma gangrenosum of the face: pathergy development after bike accident. Dermatology 2009;218:272–274.
11 Procianoy F, Barbato MT, Osowski LE, Bocaccio FJL, Bakos L: Cicatricial ectropion correction in a patient with pyoderma gangrenosum. Arq Bras Oftalmol 2009;72:384–386.

Generalized exacerbation of systemic allergic dermatitis due to zinc patch test and dental treatments

Contact Dermatitis 2010: 62: 372–373

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Key words: Dental metal fillings; lymphocyte stimulation test; patch test; systemic allergic dermatitis; zinc.

Nickel, gold, palladium, and chromate are well-known allergens; however, zinc is much less commonly reported as an allergen (1).

We report a severe case of systemic allergic dermatitis to zinc in which generalized flare-up reactions occurred from a zinc patch test, as well as with each replacement of the patient's zinc-containing dental fillings.

Case Report

A 37-year-old Japanese man was referred with a one-year history of multiple pruritic eruptions covering his entire body. The skin lesions had been refractory to topical corticosteroids and anti-histamines. Examination showed an oedematous erythema with lesions 3–10 mm in diameter that were distributed over his entire body. A detailed history revealed that the patient had had dental fillings 3 months prior to the onset of the rash.

We suspected systemic allergic dermatitis because of the dental fillings. We performed patch test with a metal series (Torii Pharmaceutical Co., Ltd., Tokyo, Japan) consisting of aluminium chloride, gold chloride, tin chloride, iron chloride, platinum chloride, palladium chloride, indium chloride, manganese chloride, silver bromide, cobalt chloride, potassium dichromate, nickel sulfate, and zinc chloride. He developed a positive (+) reaction (ICDRG criteria) to zinc chloride on D2 (Table 1) and this persisted to D7. During patch testing, the skin lesions dramatically flared at previous lesion sites (Fig. 1). Serum zinc concentration was within normal limits; there was an eosinophilia. Lymphocyte stimulation test revealed a reaction to zinc chloride with a stimulation index of 518% (normal is <180%). A skin biopsy from erythema lesion on the back showed spongiosis and perivascular lymphocytic infiltration. Based on these clinical and histological findings, we diagnosed his pruritic eruption as systemic allergic dermatitis because of zinc.

Dental inspection showed that he had 11 teeth with zinc-containing metal fillings. We have been removing the fillings one by one, but with each

Table 1. Results of patch testing to 13 dental allergens

	D2	D3	D7
Zinc chloride 2.0% pet.	+	+	+
Other 12 dental allergens	–	–	–

Conflict of interests: The authors have declared no conflicts.

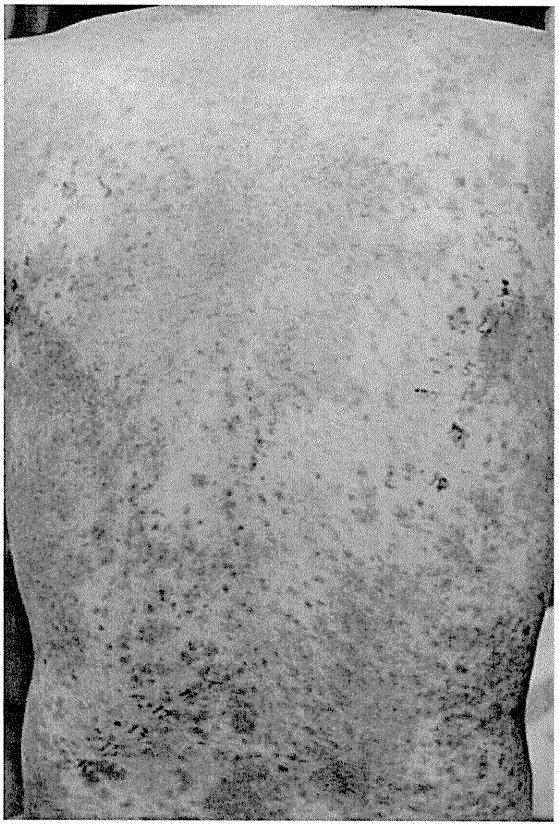

Fig. 1. Flare-up reaction is observed on the trunk after the patch test on D3. Diffuse oedematous erythema and pigmentation developed on the previous lesion.

procedure, a severe flare-up reaction has been observed. Oral corticosteroid at 10 mg/day has proved necessary prior to the removal of each zinc filling. Most of the zinc fillings have now been replaced and the patient's skin eruption has improved.

Discussion

Zinc is widely used in dental restoration. However, it is rare for zinc to cause systemic allergic dermatitis. Previously reported dental metal eruptions caused by zinc have been oral lichen planus (2, 3), palmoplantar pustulosis (4), and a maculopapular rash (5). Our case of generalized flare-up reactions to a zinc patch test and dental treatments suggests that systemic allergic dermatitis from this dental material is caused by the absorption of the metal through the skin or oral mucosa. However, one may suspect the amount of zinc that can be absorbed through the skin or oral mucosa compared with that obtained through dietary zinc intake to be small.

In conclusion, even widely used dental metals such as zinc may cause systemic allergic dermatitis that may flare-up by a patch test and metal removal treatments. Our case suggests that we should suspect systemic allergic dermatitis and take a detailed medical history when patients present with diffuse pruritic eruptions that fail to respond to conventional therapy.

References

1. Raap U, Stiesch M, Reh H, Kappo A, Werfel T. Investigation of contact allergy to dental metal in 206 patients. *Contact Dermatitis* 2009: 60: 339–343.
2. Wöhrl S, Hemmer W, Focke M, Götz M, Jarisch R. Oral symptoms due to zinc as a minor component of dental amalgam. *Contact Dermatitis* 2001: 44: 252–253.
3. Ido T, Kumakiri M, Kiyohara T, Sawai T, Hasegawa Y. Oral lichen planus due to zinc in dental restorations. *Contact Dermatitis* 2002: 47: 51.
4. Yanagi T, Shimizu T, Abe R, Shimizu H. Zinc dental fillings and palmoplantar pustulosis. *Lancet* 2005: 366: 1050.
5. Shimizu T, Kobayashi S, Tanaka M. Systemic contact dermatitis to zinc in dental fillings. *Clin Exp Dermatol* 2003: 28: 675–676.

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ORIGINAL ARTICLE

Revised nomenclature and classification of inherited ichthyoses: Results of the First Ichthyosis Consensus Conference in Sorèze 2009

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Münster, Heidelberg, and Cologne, Germany; Milano, Italy; Sapporo, Fukuoka, and Asahikawa, Japan; Paris, Lavaur, Evry, Toulouse, Bordeaux, and Dijon, France; Providence, Rhode Island; San Francisco, California; Seattle, Washington; Lausanne, Switzerland; London, United Kingdom; Pretoria, South Africa; Salt Lake City, Utah; New Haven, Connecticut; Chicago, Illinois; Gaithersburg and Rockville, Maryland; Innsbruck, Austria; Tel Aviv, Israel; Maastricht, The Netherlands; and Uppsala, Sweden

Background: Inherited ichthyoses belong to a large, clinically and etiologically heterogeneous group of mendelian disorders of cornification, typically involving the entire integument. Over the recent years, much

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progress has been made defining their molecular causes. However, there is no internationally accepted classification and terminology.

Objective: We sought to establish a consensus for the nomenclature and classification of inherited ichthyoses.

Methods: The classification project started at the First World Conference on Ichthyosis in 2007. A large international network of expert clinicians, skin pathologists, and geneticists entertained an interactive dialogue over 2 years, eventually leading to the First Ichthyosis Consensus Conference held in Sorèze, France, on January 23 and 24, 2009, where subcommittees on different issues proposed terminology that was debated until consensus was reached.

Results: It was agreed that currently the nosology should remain clinically based. "Syndromic" versus "nonsyndromic" forms provide a useful major subdivision. Several clinical terms and controversial disease names have been redefined: eg, the group caused by keratin mutations is referred to by the umbrella term, "keratinopathic ichthyosis"—under which are included epidermolytic ichthyosis, superficial epidermolytic ichthyosis, and ichthyosis Curth-Macklin. "Autosomal recessive congenital ichthyosis" is proposed as an umbrella term for the harlequin ichthyosis, lamellar ichthyosis, and the congenital ichthyosiform erythroderma group.

Limitations: As more becomes known about these diseases in the future, modifications will be needed.

Conclusion: We have achieved an international consensus for the classification of inherited ichthyosis that should be useful for all clinicians and can serve as reference point for future research. (J Am Acad Dermatol 10.1016/j.jaad.2009.11.020.)

Key words: autosomal recessive congenital ichthyosis; epidermolytic ichthyosis; genetics; histology; keratinopathic ichthyosis; mendelian disorders of cornification; superficial epidermolytic ichthyosis; ultrastructure.

The ichthyoses form part of a large, clinically and etiologically heterogeneous group of mendelian disorders of cornification (MEDOC) and typically involve all or most of the integument.[1-3] During the past few years, much progress has been made in defining the molecular basis of these disorders, and in establishing genotype-phenotype correlations.[4-11] However, there is no universally accepted terminology and classification of the diseases considered under the umbrella term "ichthyosis." Classification schemes and terminology continue to vary greatly among European, North American, and Asian countries. For example, the same entity may be referred to as epidermolytic hyperkeratosis, bullous congenital ichthyosiform erythroderma (CIE), or bullous ichthyosis, depending on where it is diagnosed.[9] Therefore, a new consensus project was initiated at the First World Conference on Ichthyosis 2007 in Münster, Germany (http://www.netzwerk-ichthyose.de/fileadmin/nirk/uploads/Program.pdf). The subsequent process of correspondence involved more than 37 dermatologists, skin pathologists, biologists, and geneticists active in the field of ichthyoses. The discussions led to the 2009 Ichthyosis Consensus Conference on the terminology and classification of inherited ichthyoses, held in Sorèze, France (http://www.netzwerk-ichthyose.de/index.php?id=28&L=1).

Abbreviations used:

ARCI:	autosomal recessive congenital ichthyosis
CDPX2:	chondrodysplasia punctata type 2
CIE:	congenital ichthyosiform erythroderma
EI:	epidermolytic ichthyosis
EKV:	erythrokeratodermia variabilis
EM:	electron microscopy
HI:	harlequin ichthyosis
IV:	ichthyosis vulgaris
KPI:	keratinopathic ichthyosis
LB:	lamellar body
LI:	lamellar ichthyosis
MEDOC:	mendelian disorders of cornification
NS:	Netherton syndrome
PPK:	palmoplantar keratoderma
RXLI:	recessive X-linked ichthyosis
SC:	stratum corneum
SG:	stratum granulosum
TGase:	transglutaminase
TTD:	trichothiodystrophy

Subcommittees were formed to address controversial issues including both terminology and nosology. The consensus achieved is presented in Tables I to III. Tables IV to XII summarize the clinical and morphologic findings of the inherited ichthyoses. Importantly, the clinical classification developed at the conference is consistent with current understanding of molecular causes and pathophysiology, as summarized in Table

XIII, and should be amenable to modification as new information emerges.

AIMS AND LIMITATIONS OF THE CONSENSUS REPORT

The overall goal of the revised classification is to clarify the terminology of this heterogeneous group of inherited skin diseases (Table I). The classification scheme and nosology should be easily understandable for all clinicians, biologists, and students. It should guide clinicians toward the correct genotyping of their patients and facilitate communication with investigators. The proposed classification (Tables II and III) will need to be modified or expanded as new information accrues. A pathophysiologic classification of the ichthyoses and all MEDOC should be initiated in the future (Table XIII).

CAPSULE SUMMARY

- Inherited ichthyoses belong to a large and heterogeneous group of mendelian disorders of cornification and involve the entire integument.
- A conference of experts was convened to reach a consensus on terminology and classification and to provide an internationally accepted frame of reference.
- The classification remains clinically based and distinguishes between syndromic and nonsyndromic ichthyosis forms.
- Bullous ichthyosis/epidermolytic hyperkeratosis is redefined as keratinopathic ichthyosis. Autosomal recessive congenital ichthyosis refers to harlequin ichthyosis, lamellar ichthyosis, and congenital ichthyosiform erythroderma.

RECOMMENDED REVISION OF THE TERMINOLOGY AND CLASSIFICATION OF INHERITED ICHTHYOSIS

The generic term "inherited ichthyosis" refers to diseases that are MEDOC affecting all or most of the integument. The skin changes are clinically characterized by hyperkeratosis, scaling, or both. Despite concern among some participants that the term "ichthyosis"[2] is outmoded and sometimes inaccurate, the consensus was to retain it, as it is too firmly entrenched in the literature and minds of clinicians to be abandoned. Inherited ichthyoses are regarded as one disease group within the greater group of MEDOC. For greater clarity, we redefined some important clinical and dermatologic terms that are in common usage (Table I). Specifically, the revised classification is based on consent to a specific definition of the term "autosomal recessive congenital ichthyosis" (ARCI), and a major change to nomenclature of the ichthyoses caused by keratin mutations (see below).

General framework for the revised classification system

At present, molecular diagnosis is not available for all forms of ichthyosis, and access to genetic diagnostics may be impeded by the high cost of analysis. Similarly, ultrastructural techniques are not in common clinical use by pathologists and are not widely available to clinicians. Other laboratory techniques, including light microscopy, narrow the differential diagnoses in some cases (see "Diagnostic Aspects" section), but decisions regarding further testing, ie, molecular diagnostics, rest on an initial, rigorous clinical evaluation. Therefore, the result of the consensus discussion process is a clinically based classification, in which the diseases are referenced with the causative gene or genes. Two principal groups are recognized: nonsyndromic forms (Table II) and syndromic forms (Table III). This algorithm is in the tradition of previous concepts[3,12-14] and based on the following question:

- Is the phenotypic expression of the disorder only seen in the skin (prototypes: lamellar ichthyosis (LI) and epidermolytic ichthyosis [EI]), or is it seen in the skin and in other organs (prototypes: Sjögren-Larsson syndrome and trichothiodystrophy [TTD])?

Noteworthy, recessive X-linked ichthyosis (RXLI) is regarded as syndromic when accompanied by associated manifestations such as testicular maldescent, and nonsyndromic when ichthyosis occurs as an isolated type[3] without extracutaneous signs. To facilitate the readability and understanding of the long list of autosomal ichthyosis syndromes, subheadings have been introduced that point to the prominent associated signs, eg, hair abnormalities or neurologic signs (Table III).

Another question distinguishes between congenital ichthyosis and ichthyoses of delayed onset. This criterion is important for common ichthyoses (Table IV), namely ichthyosis vulgaris (IV) and RXLI, which often have a delayed onset (Fig 1). However, early subtle skin changes may be overlooked, eg, RXLI may present with fine superficial scaling shortly after birth, which may fade within weeks and recur as a clear ichthyosis in later life. Therefore, considering the high variability of the initial disease presentation of some ichthyoses, eg, TTD, the age of onset has not been chosen as a major classification criterion.

Table I. Main definitions, and recommended new terms and disease names

Recommended terms	Definition
General terminology	
Disorder of cornification (DOC)	Disease with abnormal terminal keratinocytic differentiation
MEDOC	Mendelian disorders of cornification
Inherited ichthyosis	MEDOC affecting all or most of integument characterized by hyperkeratosis and/or scaling
Common ichthyoses	Ichthyoses with high prevalence: IV (1:250-1000) and RXLI (1:2000-6000)
Acquired ichthyosis	Noninherited ichthyosis associated with malignancy; autoimmune, inflammatory, nutritional, metabolic, infectious, and neurologic diseases; or medications
Autosomal recessive congenital ichthyosis (ARCI)*	Modified umbrella term for nonsyndromic congenital ichthyoses referring to HI and spectrum of LI and CIE (Tables II and V)
Keratinopathic ichthyosis (KPI)†	New umbrella term for ichthyoses caused by keratin mutations, namely EI, SEI, and other minor variants (Tables II and VI)
Epidermolytic ichthyosis (EI)	New disease name for bullous ichthyosis, bullous CIE, epidermolytic hyperkeratosis, ichthyosis exfoliativa
Superficial epidermolytic ichthyosis (SEI)	New disease name for ichthyosis bullosa Siemens
Diagnostic main criteria for classification	
Nonsyndromic ichthyosis	Phenotypic expression of underlying genetic defect is only seen in skin
Syndromic ichthyosis	Phenotypic expression of underlying genetic defect is seen in skin and other organs
Clinical and dermatologic terms	
Collodion membrane	Tight shiny cast encasing newborn that cracks after some time, resulting in irregularly branched fissures
Congenital	Disorder is evident at birth or soon after birth (<1 wk)
Delayed onset	Disorder becomes evident after weeks, months, or years
Hyperkeratosis	Histopathological: increased thickness of SC Clinical descriptive: thick and horny skin; it is not necessarily accompanied by visible scaling
Hystrix	Massive hyperkeratosis, cobblestone-like or spiky
Keratoderma	Localized form of hyperkeratosis
Lamellar scaling	Phenotype in which scales tend to be coarse and large (platelike scales)
Scaling	Visible flakes of SC of variable size, color, and thickness

CIE, Congenital ichthyosiform erythroderma; *HI*, harlequin ichthyosis; *IV*, ichthyosis vulgaris; *LI*, lamellar ichthyosis; *MEDOC*, mendelian disorders of cornification; *RXLI*, recessive X-linked ichthyosis; *SC*, stratum corneum.

*Previously termed LI/nonbullous ichthyosiform erythroderma.

†Previously used umbrella term: bullous ichthyosis, epidermolytic hyperkeratosis, or exfoliative ichthyosis.

Classification of ARCI

The acronym "ARCI" has been used as an umbrella term for nonsyndromic disorders, eg, LI and CIE, and for syndromic types of ichthyosis, such as Netherton syndrome (NS). We propose that "ARCI" should be used to refer to harlequin ichthyosis (HI) and disorders of the LI/CIE phenotypic spectrum (Table V) exclusively. HI (Fig 2, *A*) was included, because functional null mutations in the *ABCA12* gene cause the disease,[15,16] whereas missense mutations in the same gene may result in a milder phenotype that shows collodion membrane at birth and develops into LI[17,18] or CIE,[19,20] often with palmoplantar keratoderma (PPK). Those infants with HI who survive the perinatal period go on to express a severe and very scaling erythroderma[21] (Fig 2, *B* and *C*).

One difficulty of the ARCI classification is the limited genotype-phenotype correlation within the LI/CIE spectrum. Mutations in 6 genes have been described in non-HI ARCI to date, including *TGM*, the gene encoding transglutaminase (TGase)-1,[22,23] the genes *ABCA12*,[17] *NIPAL4* (also known as *ICHTHYIN*),[24] *CYP4F22*,[25] and the lipoxygenase genes *ALOX12B* and *ALOXE3*.[26] A large cohort of 520 affected families showed a mutation distribution of 32% for *TGM1*, 16% for *NIPAL4*, 12% for *ALOX12B*, 8% for *CYP4F22*, 5% for *ALOXE3*, and 5% for *ABCA12*,[27] which approximately correlated with a recent report of 250 patients.[28] At least 22% of these cases did not exhibit mutations in any of the known ARCI genes,[27] implying that further loci must exist, such as two loci on chromosome 12p11.2-q13.[29,30] A preliminary clinicogenetic correlation based on the

Table II. Clinicogenetic classification of inherited ichthyoses, part A: nonsyndromic forms

Inherited ichthyoses Part A: nonsyndromic forms		
Disease	**Mode of inheritance**	**Gene(s)**
Common ichthyoses*		
IV	Autosomal semidominant	*FLG*
RXLI		
Nonsyndromic presentation	X-linked recessive	*STS*
ARCI		
Major types		
HI	Autosomal recessive	*ABCA12*
LI†	"	*TGM1/NIPAL4‡/ALOX12B/ABCA12/*loci on 12p11.2-q13
CIE	"	*ALOXE3/ALOX12B/ABCA12/CYP4F22/NIPAL4‡/TGM1/*loci on 12p11.2-q13
Minor variants		
SHCB	Autosomal recessive	*TGM1, ALOX12B, ALOXE3*
Acral SHCB	"	*TGM1*
BSI	"	*TGM1*
Keratinopathic ichthyosis (KPI)		
Major types		
EI§	Autosomal dominant	*KRT1/KRT10*
SEI	"	*KRT2*
Minor variants		
AEI§	Autosomal dominant	*KRT1/KRT10*
ICM	"	*KRT1*
AREI	Autosomal recessive	*KRT10*
Epidermolytic nevi//	Somatic mutations	*KRT1/KRT10*)
Other forms		
LK	Autosomal dominant	*LOR*
EKV¶	"	*GJB3/GJB4*
PSD	Autosomal recessive	Locus unknown
CRIE	Autosomal dominant (?) (isolated cases)	Locus unknown
KLICK	Autosomal recessive	*POMP*

AEI, Annular epidermolytic ichthyosis; *ARCI*, autosomal recessive congenital ichthyosis; *AREI*, autosomal recessive epidermolytic ichthyosis; *BSI*, bathing suit ichthyosis; *CIE*, congenital ichthyosiform erythroderma; *CRIE*, congenital reticular ichthyosiform erythroderma; *EI*, epidermolytic ichthyosis; *EKV*, erythrokeratodermia variabilis; *HI*, harlequin ichthyosis; *ICM*, ichthyosis Curth-Macklin; *IV*, ichthyosis vulgaris; *KLICK*, keratosis linearis—ichthyosis congenita—keratoderma; *LI*, lamellar ichthyosis; *LK*, loricrin keratoderma; *PSD*, peeling skin disease; *RXLI*, recessive X-linked ichthyosis; *SEI*, superficial epidermolytic ichthyosis; *SHCB*, self-healing collodion baby.

*Often delayed onset (in RXLI mild scaling and erythroderma may be present already at birth).

†Few cases of autosomal dominant LI described in literature (locus unknown).

‡Also known as *ICHTHYIN* gene.

§*KRT1* mutations are often associated with palmoplantar involvement.

//May indicate gonadal mosaicism, which can cause generalized EI in offspring generation.

¶Whether progressive symmetric erythrokeratodermia represents distinct mendelian disorders of cornification form is debated.

recent literature[17-20,22-45] and our discussions at the consensus conference is given in Tables II and III.

LI is characterized by coarse and brown/dark scaling (Fig 2, *E* and *F*). Affected individuals are often born with collodion membrane and pronounced ectropion (Fig 2, *D*). CIE is characterized by fine, white scaling with varying degrees of erythema (Fig 2, *G* and *H*). Individuals with CIE may also be born with collodion membrane (often less severe), and then transit to generalized fine scaling and pronounced erythroderma.[31,45] The phenotypes can change over time and in response to treatment, eg, LI treated with oral retinoids can evolve into an erythrodermic ichthyosis with a finer scale pattern.[46] In a recent North American study of 104 patients with non-HI ARCI, mutations in *TGM1* were significantly associated with collodion membrane, ectropion, platelike scales, and alopecia. Patients who had at least one mutation predicted to truncate TGase-1 were more likely to have severe

Table III. Clinicogenetic classification of inherited ichthyoses, part B: syndromic forms

Inherited ichthyoses Part B: syndromic forms		
Disease	**Mode of inheritance**	**Gene(s)**
X-linked ichthyosis syndromes		
RXLI*		
- Syndromic presentation	X-linked recessive	*STS* (and others[†])
IFAP syndrome	"	*MBTPS2*
Conradi-Hünermann-Happle syndrome (CDPX2)	X-linked dominant	*EBP*
Autosomal ichthyosis syndromes (with)		
Prominent hair abnormalities		
NS	Autosomal recessive	*SPINK5*
IHS[‡]	"	*ST14*
IHSC syndrome[§]	"	*CLDN1*
TTD	"	*ERCC2/XPD ERCC3/XPB GTF2H5/TTDA*
*TTD (not associated with congenital ichthyosis)	"	*C7Orf11/TTDN1*
Prominent neurologic signs		
SLS	"	*ALDH3A2*
*Refsum syndrome (HMSN4)	"	*PHYH/PEX7*
MEDNIK syndrome	"	*AP1S1*
Fatal diseases course		
Gaucher syndrome type 2	"	*GBA*
MSD	"	*SUMF1*
CEDNIK syndrome	"	*SNAP29*
ARC syndrome	"	*VPS33B*
Other associated signs		
KID syndrome	Autosomal dominant	*GJB2 (GJB6)*
Neutral lipid storage disease with ichthyosis	Autosomal recessive	*ABHD5*
IPS	"	*SLC27A4*

ARC, Arthrogryposis–renal dysfunction–cholestasis; *CDPX2,* chondrodysplasia punctata type 2; *CEDNIK,* cerebral dysgenesis–neuropathy–ichthyosis–palmoplantar keratoderma; *HMSN4,* hereditary motor and sensory neuropathy type 4; *IFAP,* ichthyosis follicularis–atrichia–photophobia; *IHS,* ichthyosis hypotrichosis syndrome; *IHSC,* ichthyosis–hypotrichosis–sclerosing cholangitis; *IPS,* ichthyosis prematurity syndrome; *MEDNIK,* mental retardation–enteropathy–deafness–neuropathy–ichthyosis–keratodermia; *MSD,* multiple sulfatase deficiency; *NS,* Netherton syndrome; *RXLI,* recessive X-linked ichthyosis; *SLS,* Sjögren-Larsson syndrome; *TTD,* trichothiodystrophy.

*Often delayed onset (in RXLI mild scaling and erythroderma may be present already at birth).

[†]In context of contiguous gene syndrome.

[‡]Clinical variant: congenital ichthyosis, follicular atrophoderma, hypotrichosis, and hypohidrosis syndrome.

[§]Also known as neonatal ichthyosis sclerosing cholangitis syndrome.

hypohidrosis and overheating than those with *TGM1* missense mutations only.[35]

Clinically other minor ARCI variants/subtypes can be distinguished: bathing suit ichthyosis[47] has been attributed to particular *TGM1* mutations that render the enzyme sensitive to ambient temperature (Fig 2, *I*).[32,42,43,48] The self-healing collodion baby representing approximately 10% of all ARCI cases[36,49] has so far been associated with *TGM1* or *ALOX12B* mutations.[37,44] The recently described acral self-healing collodion baby, ie, at birth the collodion membrane is strictly localized to the extremities and then resolves, can also be a result of *TGM1* mutations.[41]

Classification of the keratinopathic ichthyoses

The term "epidermolytic hyperkeratosis" derives from the characteristic light microscopic observation of intracellular vacuolization, clumping of tonofilaments, and formation of small intraepidermal blisters, as commonly seen in ichthyoses as a result of keratin mutations. Therefore the term "epidermolytic hyperkeratosis" is used (by some) as synonymous with bullous ichthyosis, ichthyosis exfoliativa, bullous CIE (of Brocq), or ichthyosis bullosa of Siemens.[50-55] However, the light microscopic features of the cytoskeletal abnormalities as a result of keratin mutations may not be observed in all instances.[56-59] To replace the long list of names, which have been used for these ichthyoses—those that are all a result of keratin mutations—we propose the novel umbrella term and definition "keratinopathic ichthyosis" (KPI) (Table I). In analogy to the prevalent morphologic key features, we suggest the term "epidermolytic ichthyosis" as a novel name for the specific disease