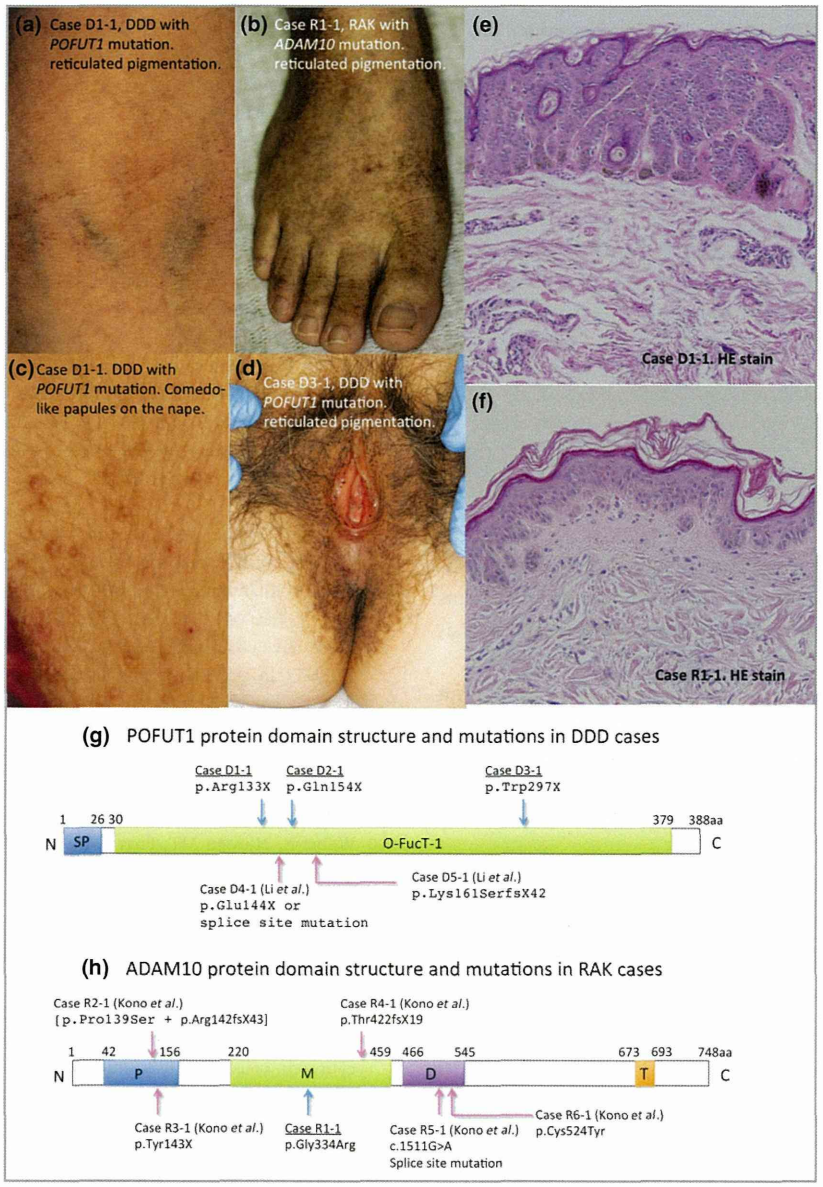

Fig 1. Clinicopathological features of the patients with Dowling–Degos disease (DDD) and reticulate acropigmentation of Kitamura (RAK) and a summary of the novel POFUT1 and ADAM10 mutations in these patients. (a) Dot-like pigmentation on the cubital fossae of a patient with DDD. (b) Reticulate pigmentation on the foot in a patient with RAK. (c) Comedo-like papules on the nape of the neck in a patient with DDD. (d) Reticulated pigmentation of the genital skin in case D3-1. Small, soft, dark-brown papules had developed in all of these areas. (e) Acanthosis, tight digitiform rete ridges with hyperpigmentation at the tip, and small cornified cysts are shown in a patient with DDD with a *POFUT1* mutation (case D1-1). We histopathologically investigated the three cases D1-1, D2-1 and D3-1,[14] and obtained similar findings in both D1-1 and D2-1, although D3-1 showed milder features than those in D1-1. HE, haematoxylin and eosin. (f) Skin biopsy of the brown macules in case R1-1 shows pigmentation in the tip of the rete ridges with thinning of the epidermis, thinning of the rete ridges with slight hyperpigmentation at the tips, and slight hyperkeratosis without parakeratosis or pigmentary incontinence. We histopathologically investigated the four cases R1-1, R1-2, R2-1 and R4-1,[7] and confirmed similar findings in all four cases. (g) Schematic of the domain structure of the protein O-fucosyltransferase (POFUT)-1 (NP_056167.1) and mutations in the patients with DDD. SP, signal peptide (amino acids 1–26); O-FucT-1, GDP-fucose protein O-fucosyltransferase 1 (amino acids 30–379). The cases in the present study are underlined. (h) Schematic of the domain structure of the metallopeptidase ADAM10 (NP_001101.1) and mutations in the patients with RAK. P, propeptide domain (amino acids 42–156); M, metalloproteinase domain (amino acids 220–459); D, disintegrin domain (amino acids 466–545); T, transmembrane domain (amino acids 673–693). The present case is underlined.

the abolishment of only the C-terminal 92 amino acids of the POFUT-1 protein. The phenotypic differences might be associated with the truncation sites of the mutations. None of the present cases of DDD (families D1–D3) showed hypopigmentation. However, the Chinese patients with DDD (families D4 and D5) had hypopigmentation. It remains unclear why similar truncation mutations in the identical gene lead to different phenotypes.

Table 1 Five important points in clinically differentiating between Dowling–Degos disease (DDD) and reticulate acropigmentation of Kitamura (RAK)

Onset age: RAK develops at 9·2 ± 2·2 years, whereas DDD develops at 28·8 ± 13·9 years
Sites of the initial skin lesions: RAK appears initially on the dorsa of the hands, whereas DDD appears on the flexure regions and the neck
Comedo-like follicular papules suggest DDD
Skin lesions on the genital regions suggest DDD
A mixture of small hypopigmented and hyperpigmented macules in the affected skin areas suggests DDD. In addition, histopathologically, acanthosis with tight digitiform rete ridges is seen in the skin lesions of DDD, and thinning of the epidermis and narrowing of the rete ridges characterize the skin lesions of RAK

This is the first report to compare the clinical and histopathological features of patients with DDD with those of patients with RAK, with the respective diagnoses confirmed by analysis of the causative gene mutations in *POFUT1* and *ADAM10*.

Summarizing the present data, there are five important points that help in the clinical differentiation between DDD and RAK; these are described in Table 1. These distinguishing features and our mutation analysis data clearly indicate that DDD is clinicopathologically distinct from RAK.

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan
[2]Takama Dermatology Clinic, Kasugai 486-0844, Japan
[3]Department of Dermatology, Hospital Vall d'Hebrón, Barcelona 08035, Spain
[4]Department of Dermatology, Sri Manakula Vinayagar Medical College & Hospital, Madagadipet 605107, India
[5]Department of Dermatology, Yamagata University Faculty of Medicine, Yamagata 990-9585, Japan
Correspondence: Michihiro Kono and Masashi Akiyama.
E-mails: miro@med.nagoya-u.ac.jp; makiyama@med.nagoya-u.ac.jp

M. Kono[1]
M. Suganuma[1]
H. Takama[2]
I. Zarzoso[3]
M. Saritha[4]
D. Bodet[3]
S. Aboobacker[4]
K. Kaliaperumal[4]
T. Suzuki[5]
Y. Tomita[1]
K. Sugiura[1]
M. Akiyama[1]

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1. Details of the patients and their causative mutations.

Fig S1. Pedigrees of families D1 and R1.

Fig S2. Sequence analysis of the novel POFUT1 and *ADAM10* mutations

[1]Ueo Dermatology Clinic, Saiki, Oita 876-0831, Japan
[2]Department of Dermatology, Kurume University School of Medicine, and Kurume University Institute of Cutaneous Cell Biology, Kurume, Fukuoka 830-0011, Japan
[3]Department of Dermatology, Faculty of Medicine, Oita University, Hasama, Yufu, Oita 879-5593, Japan
Correspondence: Sakuhei Fujiwara.
E-mail: fujiwara@oita-u.ac.jp

D. Ueo[1]
N. Ishii[2]
T. Hamada[2]
K. Teye[2]
T. Hashimoto[2]
Y. Hatano[3]
S. Fujiwara[3]

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The novel *GJB3* mutation p.Thr202Asn in the M4 transmembrane domain underlies erythrokeratodermia variabilis

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Dear Editor, Erythrokeratodermia variabilis (EKV; OMIM 133200) is a rare autosomal dominant disorder characterized by migratory erythematous areas and fixed keratotic plaques. *GJB3* and *GJB4*, which encode connexin (Cx)31 and Cx30.3, respectively, are causative genes for EKV and nonsyndromic hearing loss.[1,2] Here, we report a single novel mutation of *GJB3*, p.Thr202Asn, in the M4 transmembrane domain in a Japanese family suffering from EKV. In addition, we review the literature and characterize the possible genotype–phenotype correlations for *GJB3* mutations. Specifically, missense mutations, other than those in the second extracellular loop (E2) domain, are associated with EKV and those in the E2 domain underlie autosomal dominant nonsyndromic hearing loss (ADNSHL).

A 17-year-old girl presented with palmoplantar keratoderma (PPK), which had been noted since infancy. Physical examination showed variably sized and irregularly shaped erythema, with scaling on the trunk and the extremities (Fig. 1a). These lesions were transient, but reappeared repeatedly. Notable PPK was also observed (Fig. 1b). She had no hearing loss and refused to undergo hearing tests. Histological examination showed hyperkeratosis with intact granular layers. Her paternal grandfather, father and sister showed similar clinical features (Fig. 1c). Clinical and histological features supported the diagnosis of EKV.

After ethical approval was granted, written informed consent was obtained from the participants, in compliance with the Declaration of Helsinki. The coding regions, including the exon–intron boundaries of *GJB3* and *GJB4*, were amplified by polymerase chain reaction from genomic DNA obtained from the participants, as described previously.[1,2] The mutation analysis revealed that the proband, her father and her sister harboured the heterozygous mutation p.Thr202Asn

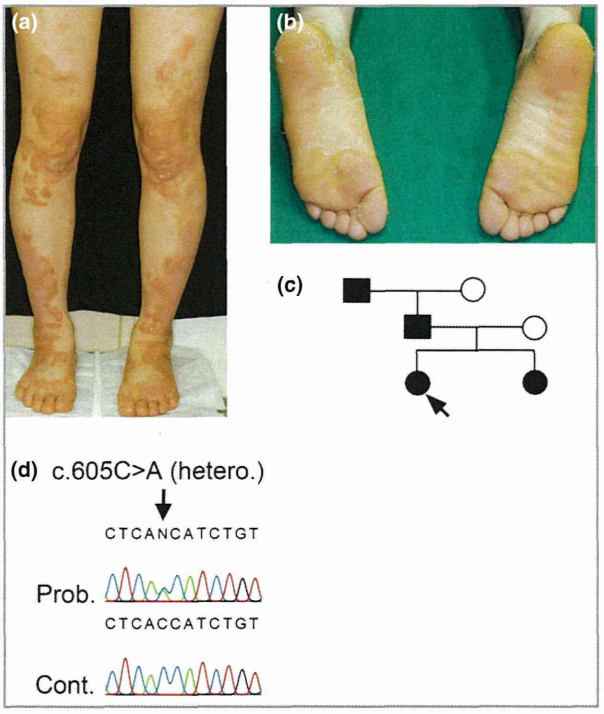

Fig 1. Clinical features of the proband (Prob.), family pedigree and sequence data for GJB3. (a) Persistent indurated erythematous plaques on the lower limbs. (b) Hyperkeratotic skin on the soles. (c) Pedigree of the proband's family. (d) Sequence of *GJB3* for the proband and control (Cont.).

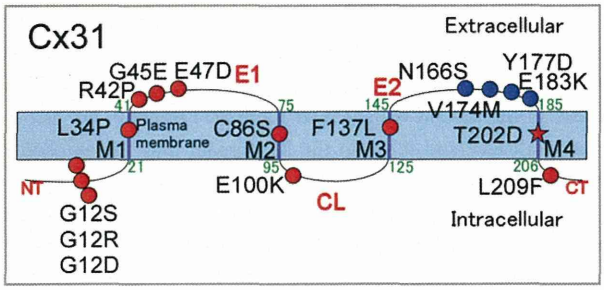

Fig 2. Reported causative dominant pathogenic missense mutations for erythrokeratodermia variabilis (EKV) and autosomal dominant nonsyndromic hearing loss (ADNSHL) in connexin (Cx)31. Only dominant missense mutations in the E2 domain underlie ADNSHL (blue circles), and all dominant pathogenic missense mutations outside the E2 domain cause EKV (red circles and asterisk). Residues at the boundaries between the functional domains are indicated by green numbers. M1–M4, transmembrane domains 1–4; E1, extracellular domain 1; E2, extracellular domains 2; CL, cytoplasmic loop; NT, N terminus; CT, C terminus.

(c.605C>A) in *GJB3*, while her mother did not (Fig. 1d). MutationTaster (http://www.mutationtaster.org/) predicted that p.Thr202Asn was a disease-causing allele. p.Thr202Asn is not reported in the Exome Sequencing Project of the Human Genetic Variation Browser (http://www.genome.med.kyoto-u.ac.jp/SnpDB/), which is a database of genetic variants in > 1400 Japanese individuals. Thus, the proband and her affected family members were diagnosed as having EKV with the heterozygous *GJB3* mutation.

Cxs are highly homologous and comprise a large gene family encoding plasma membrane proteins.[3] Cxs contain four transmembrane domains linked by one cytoplasmic and two extracellular loops; N and C termini are located on the cytoplasmic side (Fig. 2). The transmembrane domains bear conserved amino acids, whereas the cytoplasmic loop and the C-terminal region are highly variable among Cxs. Cxs are assembled in groups of six to form hemichannels in the plasma membrane, and two hemichannels of adjacent cells then combine to form a gap junction. Various Cxs combine into homomeric and heteromeric gap junctions.

Cx31 is expressed in the upper differentiating epidermal layers.[4] In addition to the epidermis, it is expressed in the cochlea, and some mutations are involved in hearing loss without obvious cutaneous phenotypes.[5] Figure 2 summarizes the *GJB3* missense mutant alleles reported thus far, including that of the present case, and their associations with EKV or ADNSHL, according to the Human Gene Mutation Database of the Institute of Medical Genetics, Cardiff, U.K. (http://www.hgmd.cf.ac.uk/ac/index.php). p.Thr202Asn is the first autosomal dominant missense mutation reported in the M4 domain; it was the only remaining domain of Cx31 for which no pathogenic autosomal dominant mutations were reported (Fig. 2). Interestingly, all missense mutations in any domain other than E2 were associated with EKV. In contrast, all missense mutations in the E2 domain were associated with ADNSHL. Figure S1 (see Supporting Information) shows the sequence alignment of the E2 domain for diverse vertebrate species. p.174Val, p.177Tyr and p.183Glu are conserved among vertebrate species, but p.166Asn is not. Based on a review of *GJB3*-associated autosomal recessive nonsyndromic hearing loss, *GJB3* missense mutations have been reported that are not located in the E2 domain (http://www.hgmd.cf.ac.uk/ac/index.php).

We assume different pathogenic mechanisms determine the phenotypes associated with *GJB3* dominant missense mutations in the E2 domain and those outside the E2 domain. The E1 domain is important for the formation of the gap junction channel, and the E2 domain is important for docking compatibility in heterotypic channels in many members of the Cx family.[3] Indeed, one of the missense mutations in the E2 domain of Cx31 reportedly has no effect on the function of wild-type Cx31 but interferes with Cx26 function.[6] Of all the Cxs, malfunction of Cx26 most frequently results in hearing loss.[7] In this context, we suspect that dominant missense mutations in the E2 domain of *GJB3* might cause hearing loss via dysfunction of Cx26.

In summary, to our knowledge, we have identified the first dominant pathogenic missense mutation in the M4 transmembrane domain of *GJB3*. As was the case for other *GJB3* dominant pathogenic missense mutations outside the E2 domain, the mutation led to the EKV phenotype in the patient's family. Our results, combined with a literature review, suggest that dominant missense mutations outside the E2 domain in *GJB3* are associated with EKV, and those within the E2 domain cause ADNSHL.

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[1]*Department of Dermatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan*
[2]*Department of Dermatology, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan*
Correspondence: Masashi Akiyama.
E-mail: makiyama@med.nagoya-u.ac.jp

K. Sugiura[1]
M. Arima[2]
K. Matsunaga[2]
M. Akiyama[1]

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Conflicts of interest: none declared.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig S1. Sequence alignment of the E2 domain of Cx31 in diverse vertebrate species.

Dermatitis induced by first-generation hepatitis C virus protease inhibitors

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Dear Editor, We read with great interest the U.K. experience of the cutaneous side-effects of first-generation hepatitis C virus (HCV) protease inhibitors.[1] The majority of the side-effects are mild-to-moderate and are generally similar to those observed with peginterferon-α (PEG-IFN)/ribavirin, including xerosis, pruritus and eczema.[1,2] The authors stated that these adverse reactions had a class effect but they did not discuss the pathophysiology.

It is remarkable that these dermatological manifestations were already known in patients with untreated chronic hepatitis C. However, their frequency increased with the use of IFN and became more frequent with the development of a PEG-IFN/ribavirin schedule. We previously studied the prevalence of skin manifestations in patients with chronic hepatitis C at the Department of Hepatology, Beaujon Hospital, Clichy, France, in 2003.[3] Xerosis, pruritus and eczema were observed in 14%, 6% and 7% of the patients not receiving any treatment (n = 98) and in 49%, 48% and 19% in patients treated with PEG-IFN/ribavirin (n = 108 patients), respectively. Recent data have demonstrated that the use of telaprevir and boceprevir dramatically increased their frequency.

Antiproteases may have a direct effect on keratinocytes and stratum corneum but we propose that these antiproteases may favour immune reconstitution. These adverse reactions may be related to the IFN pathway. Telaprevir and boceprevir are targeted to the NS3/NS4 proteases. These nonstructural proteins are not only necessary for virus replication, but are also responsible for the 'immune evasion' of HCV.[4] The NS3/NS4 complex has been described to suppress activation of IFN regulatory factor 3 (IRF-3), a central antiviral transcription factor.[5] IRF-3 promotes the production of IFN and regulates many of the IFN-stimulated genes in response to viral infection. We assume that in addition to antiviral specific action, protease inhibitors such as telaprevir may increase IFN efficacy (produced by, and administrated to, the patient), and may also increase the adverse skin reactions associated with IFN. In this regard, new direct acting antiviral agents against HCV do not target NS3/NS4 and have fewer cutaneous side-effects (Table 1).[6–10]

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We are indebted to Patrick Marcellin (Beaujon Hospital, Clichy, France).

Table 1 Prevalence of adverse skin reactions in some pivotal studies with telaprevir, boceprevir, sofosbuvir and ledipasvir

Previous treatment	Telaprevir (previously treated)[6]		Boceprevir (previously treated)[7]		Ledipasvir–sofosbuvir (untreated)[8]		Ledipasvir–sofosbuvir (previously treated)[9]		Sofosbuvir (untreated)[10]		
Regimen	PEG-IFN/ ribavirin (48 weeks)	PEG-IFN/ ribavirin/ telaprevir (48/24 weeks)	PEG-IFN/ ribavirin (44 weeks)	PEG-IFN/ ribavirin/ boceprevir (44 weeks)[a]	Ribavirin/ ledipasvir/ sofosbivir (24 weeks)[b]	Ledipasvir/ sofosbivir (24 weeks)	Ribavirin/ ledipasvir/ sofosbivir (24 weeks)	Ledipasvir/ sofosbivir (24 weeks)	PEG-IFN/ ribavirin (24 weeks)	PEG-IFN/ ribavirin/ sofosbivir (12 weeks)	Ribavirin/ sofosbivir (12 weeks)
Dry skin (%)	ND	ND	8	22	ND	ND	10	3	ND	ND	ND
Pruritus (%)	15	44	ND	ND	12	7	ND	ND	17	17	7
Rash (%)	20	60	5	14	12	7	14	6	18	18	9

PEG-IFN, peginterferon-α; ND, no data. [a]Ledipasvir is hepatitis C virus NS5A inhibitor; [b]Sofosbivir is a nucleotide analogue of the hepatitis C virus NS5B polymerase inhibitor.

Case Reports in Dermatology

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Elderly-Onset Generalized Pustular Psoriasis without a Previous History of Psoriasis Vulgaris

Takayuki Aizu[a] Akinobu Matsui[a] Noriko Takiyoshi[a] Eijiro Akasaka[a] Takahide Kaneko[a] Hajime Nakano[a] Kazumitsu Sugiura[b] Masashi Akiyama[b] Daisuke Sawamura[a]

[a]Department of Dermatology, Hirosaki University Graduate School of Medicine, Hirosaki, and [b]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Key Words
IL36RN · CARD14 · Pustulosis · Aging

Abstract
Generalized pustular psoriasis (GPP) is characterized by sudden fever and extensive erythema with pustules and occurs in patients with or without preceding psoriasis vulgaris. We report an 83-year-old man showing irregularly shaped erythema with pustules on the trunk and extremities. He initially had no fever and came to our clinic a few days after the onset of the skin lesions because of high fever and general malaise. We found an extension and new development of erythema and pustules on the whole body. The patient also manifested night delirium. Histological examination revealed neutrophil infiltration into the upper epidermis, which formed a spongiform pustule of Kogoj. Pustular fluid cultures were negative for bacteria. We diagnosed GPP without preceding psoriasis vulgaris. Mutation analysis revealed no significant mutations in *IL36RN* and *CARD14*. Previous reports indicated that onset of GPP at the age of 83 years is definitely rare. In older individuals, general disease characteristics include an atypical clinical course, an especially slow appearance and cure, and mental disorder. Our case also revealed such characteristics. Thus, it is necessary to be aware of the clinical course and mental problems in elderly patients with GPP.

Takayuki Aizu, MD, PhD
Department of Dermatology
Hirosaki University Graduate School of Medicine
5 Zaifu-cho, Hirosaki, Aomori 036-8562 (Japan)
E-Mail derma@hirosaki-u.ac.jp

Case Reports in Dermatology

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Introduction

Generalized pustular psoriasis (GPP) is a rare severe psoriasis characterized by the presence of variable numbers of sterile pustules appearing in erythematous and scaly lesions. It can be lethal without proper treatment, especially in the elderly population. Mutations in *IL36RN* have been identified in familial GPP and in sporadic cases of GPP [1, 2]. Cases with *IL36RN* mutations have been delineated as psoriasis with a deficiency of IL36RN (DITRA) [1]. Recently, the gene *CARD14* has also been found to be responsible for GPP [3]. Herein, we report our recent experience with an 83-year-old man with GPP without a previous history of psoriasis vulgaris in whom we examined mutations in *IL36RN* and *CARD14*.

Case Presentation

An 83-year-old man with a 7-day history of erythematous eruption on the trunk and extremities was referred to our clinic. His history showed bronchial asthma, hypertension, atrial fibrillation, and postoperative colon carcinoma. He had never been previously diagnosed with psoriasis vulgaris. Physical examination revealed irregularly shaped erythema with scales and small pustules on the trunk and extremities (fig. 1). He had no fever. The blood test revealed a white blood cell count of 12,530/μl (segment 87.8%, lymphocytes 6.7%, monocytes 4.9%, eosinophils 0.5%, and basophils 0.1%) and a C-reactive protein level of 2.2 mg/dl.

We suspected pustular psoriasis and took a skin biopsy from an abdominal lesion. Since the patient had no fever, we started to treat him with oral antihistamine and topical steroid.

However, after 4 days, the patient came to our clinic because of high fever and general malaise. We found an extension and new development of erythema and pustules on the whole body (fig. 2). Coalescence of pustules resulted in lakes of pus. The blood test showed a white blood cell count of 18.920/μl (segment 88.4%, lymphocytes 65.0%, monocytes 6.3%, eosinophils 0.2%, and basophils 0.1%) and a C-reactive protein level of 20.171 mg/dl.

The patient was immediately admitted to our hospital ward. Although the results of pustular fluid culture and histopathology were not yet submitted, we started 60 mg/day of oral etretinate, and pustule formation decreased (fig. 3). However, erythema continued to expand, and consequently the lesions became erythrodermic. In addition, a decrease in serum albumin caused general edema, and night delirium appeared. Afterwards, erythema gradually decreased, and we tapered the dose of etretinate. Administration of diuretic furosemide was effective for general edema. The delirium gradually disappeared.

Later, histological examination revealed neutrophil infiltration into the upper epidermis, which formed a spongiform pustule of Kogoj (fig. 4). Direct immunofluorescence showed no significant deposits of immunoglobulins. Pustular fluid cultures were negative for bacteria. We performed mutation analysis, which detected no significant mutations in *IL36RN and CARD14*.

Discussion

GPP is characterized by sudden fever and extensive erythema with pustules and occurs in patients with or without psoriasis vulgaris. Since this case showed pustule formation on the whole body and no history of psoriasis vulgaris, the differential diagnosis initially included GPP, subcorneal pustular dermatosis, acute generalized exanthematous pustulosis,

and intercellular immunoglobulin IgA dermatosis. However, clinical, histological, and immunofluorescence findings, in conjunction with a lack of recent administration of causative drugs, resulted in a final diagnosis of GPP.

Recently, mutations in *IL36RN* and *CARD14* have been found to be responsible for GPP [1, 2]. The IL36RN protein is primarily expressed in the skin and is an antagonist of three cytokines that belong to the interleukin-1 family: interleukin-36α, interleukin-36β, and interleukin-36γ, which are also known as interleukin-1F6, interleukin-1F8, and interleukin-1F9, respectively [4]. These cytokines activate several proinflammatory signaling pathways, such as the nuclear factor-κB and mitogen-activated protein kinase pathways [4]. Therefore, loss of function of IL36RN may cause GPP. Tominaga et al. [5] reported that a 78-year-old woman with GPP and a previous history of psoriasis vulgaris had causative mutations in the *IL36RN* gene. Since it was possible that our patient might have had mutations in *IL36RN* or *CARD14*, we performed mutation analysis. However, we were unable to find any of the known mutations.

An interesting point of this case is that the onset of GPP occurred at an older age. The age of onset in Japanese patients recently reported in reliable English-language papers was 2–78 years in 31 cases [6], 36–71 years in 3 cases [7], 16–74 years in 14 cases [8], and 21–64 years in 3 cases [9]. In addition, the age of onset in a recent report from Malaysia was 21–81 years in 102 cases [10]. These reports suggest that the age of onset in the present case (at 83 years) is definitely rare. In older individuals, general disease characteristics include an atypical clinical course, an especially slow appearance, a slow cure, and mental disorder. In our case, we were initially unable to recognize the severity of the disease because of the lack of fever and a low C-reactive protein level. Three days after his first visit, however, sudden fever and extension of the skin lesions were detected, and he reported night delirium. This illustrates the need to be aware of the clinical course and mental problems in elderly patients with GPP.

Statement of Ethics

The authors state that the patient gave his informed consent, and the informed consent was in accordance with the guidelines approved by Hirosaki University Graduate School of Medicine.

Disclosure Statement

The authors declare that there are no conflicts of interest.

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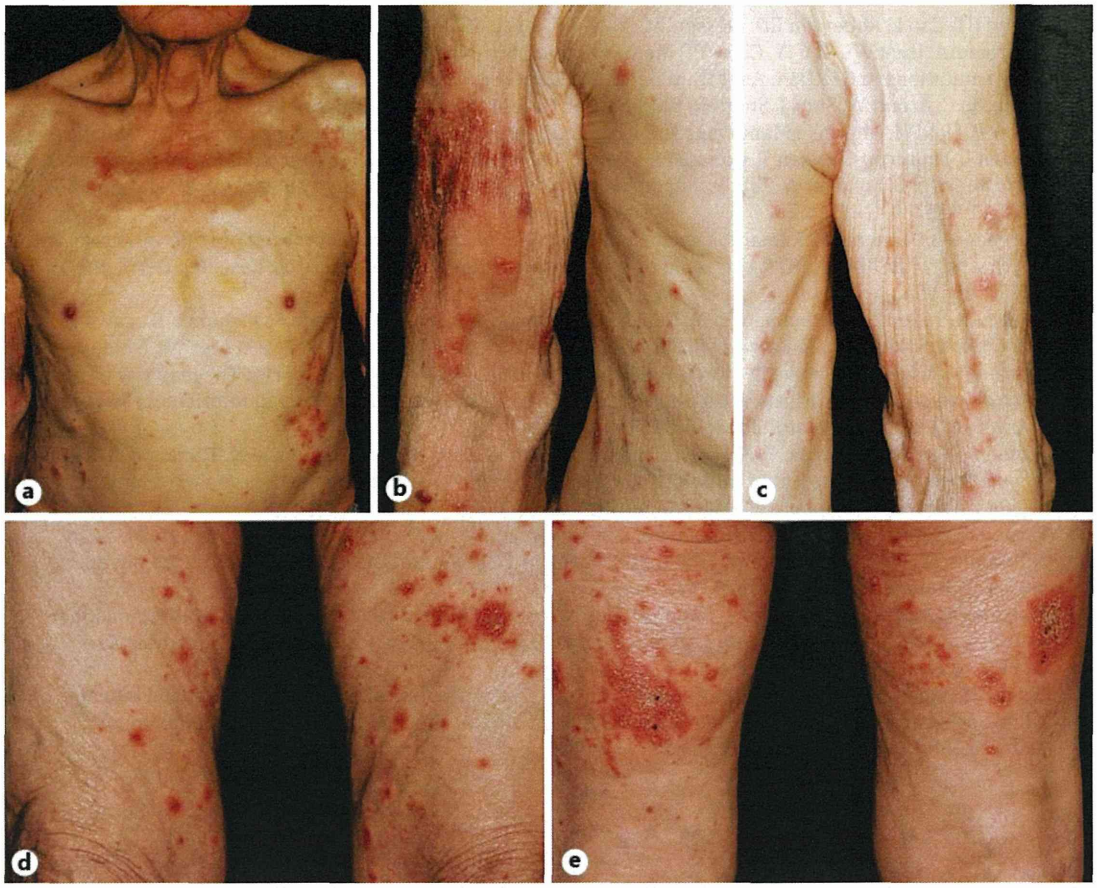

Fig. 1. Clinical findings at his first visit. Irregularly shaped erythema with scales and small pustules on the trunk and extremities. The patient had no fever. **a** Trunk. **b**, **c** Upper extremities. **d**, **e** Thighs.