研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
新井勝大	小児の消化性潰瘍	金澤一郎・永井良三（総編集）、浅利靖・有賀徹・石川三衛・石橋俊・伊藤雅章・太田伸生・尾崎紀夫・小澤敬也・門田淳一・古森公浩・高山忠利・巽浩一郎・玉井和哉・筒井裕之・冨永悌二・根木昭・原寿郎・深川雅史・堀江重郎・三浦総一郎・水澤英洋・水沼英樹・持田智・山本一彦・吉原俊雄（責任編集）	今日の診断指針	医学書院	東京	2015	1933-1935

雑誌

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Ⅳ. 研究成果の刊行物・別刷

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CONCISE COMMUNICATION

Pathological characterization of pachydermia in pachydermoperiostosis

Keiji TANESE,[1] Hironori NIIZEKI,[2] Atsuhito SEKI,[3] Atsushi OTSUKA,[4] Kenji KABASHIMA,[4] Keisuke KOSAKI,[5] Masamitsu KUWAHARA,[6] Shun-ichi MIYAKAWA,[7] Mikiko MIYASAKA,[8] Kentaro MATSUOKA,[9] Torayuki OKUYAMA,[10] Aiko SHIOHAMA,[11] Takashi SASAKI,[12] Jun KUDOH,[11] Masayuki AMAGAI,[1] Akira ISHIKO[13]

[1]*Department of Dermatology, Keio University School of Medicine,* [2]*Departments of Dermatology,* [3]*Orthopedics, National Center for Child Health and Development, Tokyo,* [4]*Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto,* [5]*Department of Orthopaedic Surgery, University of Tokyo, Tokyo,* [6]*Department of Plastic Surgery, Nara Medical University Hospital, Kashihara Nara,* [7]*Division of Dermatology, Kawasaki Municipal Hospital, Kanagawa,* [8]*Departments of Radiology,* [9]*Pathology, National Center for Child Health and Development,* [10]*Clinical Laboratory Medicine, National Center for Child Health and Development,* [11]*Laboratory of Gene Medicine, Keio University School of Medicine,* [12]*Center for Integrated Medical Research, Keio University School of Medicine,* [13]*Department of Dermatology, Toho University School of Medicine, Tokyo, Japan*

ABSTRACT

Pachydermoperiostosis is a rare hereditary disease, which presents with the cutaneous manifestations of pachydermia and cutis verticis gyrata. Histological findings in pachydermia frequently include dermal edema, mucin deposition, elastic fiber degeneration, dermal fibrosis and adnexal hyperplasia. However, the severity of these findings varies between clinical reports, and a systematic multiple-case clinicopathological correlative analysis has not been performed to date. In the present study, we reviewed the skin biopsy specimens obtained from the pachydermia of six pachydermoperiostosis patients. The severity of the characteristic histological features was semiquantitatively evaluated and correlated with the grade of pachydermia. Dermal edema, mucin deposition and elastic fiber degeneration were observed in all cases. Patients with severe pachydermia had sebaceous gland hyperplasia and fibrosis. These results suggest that the triad of mucin deposition, dermal edema and elastic fiber degeneration are found from very early stage pachydermia, and could be considered diagnostic findings. To ensure an earlier diagnosis of pachydermoperiostosis, a biopsy should be taken when a patient has grade 1 pachydermia to determine the presence of this histological triad.

Key words: **dermal edema, elastic fiber degeneration, fibrosis, mucin deposition, pachydermoperiostosis, sebaceous hyperplasia.**

INTRODUCTION

Pachydermoperiostosis (PDP, Online Mendelian Inheritance in Man no. 614441) is a rare hereditary disease diagnosed by the presence of digital clubbing, periostosis and pachydermia, including cutis verticis gyrata (CVG).[1] Recent genetic analysis revealed that homozygous or compound heterozygous mutations in the solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) gene, which is associated with prostaglandin (PG) metabolism, are significantly associated with PDP.[2,3] Clinically, three distinct forms of this syndrome have been proposed in accordance with the intensity of symptoms: the complete form, characterized by prominent furrowing of the face, CVG, digital clubbing, and primary hypertrophic osteoarthropathy; the incomplete form, in which CVG is absent; and the fruste form, characterized by one or more main skin changes and minimal skeletal involvement.[1]

Several studies have reported the following histopathological findings of pachydermia: sebaceous gland hyperplasia, dermal edema, mucin deposition in the dermis, elastic fiber loss and dermal fibrosis.[4–6] However, the severity of these findings varies among clinical reports, and a multiple-case clinicopathological correlative analysis of pachydermia has not been performed to date. To gain insight into the pathogenesis of pachydermia and CVG development, we histologically examined skin biopsy specimens of six PDP patients with known clinical information. We evaluated the degree of each of the histological findings semiquantitatively, and correlated these data with the severity of pachydermia.

PATIENTS AND TECHNIQUES

This study was approved by the ethics committee of the National Center for Child Health and Development and Keio University School of Medicine, and conformed to the provisions of

Correspondence: Hironori Niizeki, M.D., Ph.D., Department of Dermatology, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan. Email: niizeki-h@ncchd.go.jp
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the Declaration of Helsinki. Six patients who were diagnosed with PDP were included. All samples were collected after obtaining written informed consent. Although these patients' clinical features had been previously reported, none of the histological findings had been evaluated precisely.[2,4–7] All patients had the complete form of PDP by the end of the study, although two patients had initially been diagnosed with the incomplete form and gradually developed CVG during the observation period (patients 1 and 2). All samples were obtained from the forehead and stained with hematoxylin–eosin, Alcian blue and elastica van Gieson. Normal skin from the forehead of a healthy individual, which was obtained from the area surrounding benign tumors, was used as a control. The slides were independently interpreted by two investigators (K. T. and A. I.) without any knowledge of the clinical data. Any discrepancies in the findings were subsequently reconciled by a third investigator.

The clinical and histological findings in each case are provided in Figures S1 and S2.

Patient 1

This 24-year-old male[2] initially had no CVG on his scalp and was diagnosed with incomplete PDP. CVG gradually developed, changing the diagnosis to complete PDP.[7] The biopsy we studied had been taken at the age of 19 years when he was diagnosed with incomplete PDP, although he already had slight pachydermia on his forehead. Histologically, focal edema and weak but diffuse mucin deposition were observed. Elastic fiber degeneration affected approximately 40% of the entire dermis. However, sebaceous gland hyperplasia and dermal fibrosis were not observed.

Patient 2

This 19-year-old male[7] initially had no CVG on his scalp and was diagnosed with incomplete PDP. CVG gradually developed, changing the diagnosis to complete PDP. The biopsy we studied was taken when he was diagnosed with complete PDP, and had mild pachydermia on his forehead. Histologically, dermal edema affected approximately 50% of the entire dermis, and diffuse and strong mucin deposition was observed. Elastic fiber degeneration affected approximately 10% of the entire dermis. In the upper dermis, slight fibrosis around the folliculosebaceous unit and mild sebaceous gland hyperplasia were observed.

Patient 3

This 53-year-old male[4] had CVG on his scalp as well as moderate pachydermia on his forehead. Histologically, focal edema and weak but diffuse mucin deposition were observed. Elastic fiber degeneration affected approximately 10% of the entire dermis. Moderate sebaceous gland hyperplasia and slight fibrosis around the sebaceous glands were also observed.

Patient 4

This 21-year-old male[7] had CVG on his scalp and moderate pachydermia on his forehead. Histologically, dermal edema affected approximately 50% of the entire dermis, and diffuse and strong mucin deposition was observed. Elastic fiber degeneration affected approximately 10% of the entire dermis. Moderate sebaceous gland hyperplasia and slight fibrosis around the sebaceous glands were also observed.

Patient 5

This 45-year-old male[5] had severe CVG and pachydermia. Histologically, dermal edema affected the entire dermis, and focal mucin deposition was noted. Elastic fiber degeneration affected the entire dermis. Moderate sebaceous gland hyperplasia was observed, and fibrosis surrounding the folliculosebaceous unit and in parts of the dermis was noted.

Table 1. Scoring criteria of the clinical and histological findings used in this study

	Grading			
Features	0	1	2	3
Clinical features				
Pachydermia of the forehead	Not furrowed	Not furrowed but shallow ditch between slight swellings is seen	Furrowed but the bottom of furrow is visible	Deeply furrowed so that the bottom of furrow is invisible
Histological features				
Dermal edema	Absent	Limited to part of the upper dermis or lower dermis	Limited in the entire upper dermis or lower dermis	Extended to the entire upper and lower dermis
Mucin deposition in the dermis	Absent	Focal deposition	Weak deposition in the entire dermis	Strong deposition in the entire dermis
Elastic fiber degeneration	Absent	<20% of entire dermis	20–50% of entire dermis	>50% of entire dermis
Fibrosis	Absent	Restricted around the folliculosebaceous unit	Extended around folliculosebaceous unit and part of the dermis	Extended to entire dermis
Sebaceous hyperplasia (sebaceous gland occupation rate*)	<10%	10–25%	26–40%	>40%

*For each specimen, the total sebaceous gland area was divided by the area of dermis and the sebaceous gland occupation rate was calculated.

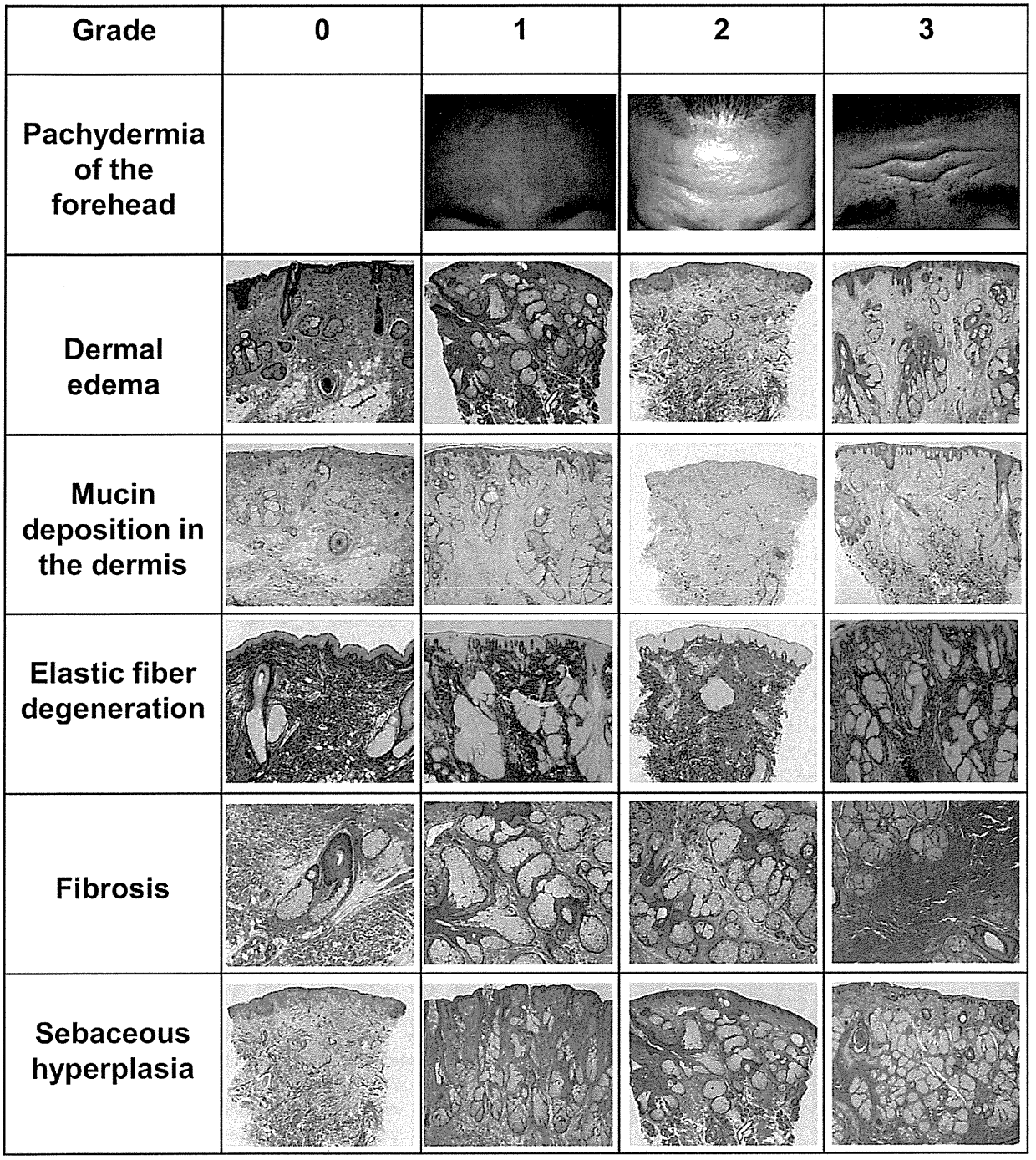

Figure 1. Representative clinical and histological manifestations of pachydermia. Representative pictures of each clinical and histological grading. Pachydermia of the forehead: grade 1 (patient 1), grade 2 (patient 2) and grade 3 (patient 5). Dermal edema (hematoxylin–eosin [HE], whole image): grade 0 (control), grade 1 (patient 3), grade 2 (patient 1) and grade 3 (patient 5). Mucin deposition in the dermis (Alcian blue, whole image): grade 0 (control), grade 1 (patient 5), grade 2 (patient 1) and grade 3 (patient 4). Elastic fiber degeneration (elastica van Gieson, whole image): grade 0 (control), grade 1 (patient 4), grade 2 (patient 1) and grade 3 (patient 5). Fibrosis (HE, original magnification ×20): grade 0 (control), grade 1 (patient 3), grade 2 (patient 5) and grade 3 (patient 6). Sebaceous gland hyperplasia (HE, ×40): grade 0 (patient 1), grade 1 (patient 2), grade 2 (patient 3) and grade 3 (patient 6).

Table 2. Summary of the clinical and histological findings of pachydermia

Patient	Current age	Onset age	Sex	*SLCO2A1* mutation	Clinical subtype when a biopsy was taken	Pachydermia of the forehead	Histological findings					
							Dermal edema	Mucin deposition in the dermis	Elastic fiber degeneration	Fibrosis	Sebaceous hyperplasia
Control	40	N/A	M	N/A	N/A	0	0	0	0	0	0
1[7]	24	13	M	p.R288Gfs*7 p.E427_P430del	Incomplete	1	2	2	2	0	0 (7.50%)
2[7]	19	15	M	p.R288Gfs*7 p.E427_P430del	Complete	2	2	3	1	1	1 (19.64%)
3[4]	53	20	M	p.R288Gfs*7 p.Q556H	Complete	2	1	2	1	1	2 (38.33%)
4[7]	21	16	M	p.R603* p.R252*	Complete	2	2	3	1	1	2 (28.57%)
5[5]	45	17	M	p.R288Gfs*7 p.R288Gfs*7	Complete	3	3	1	3	2	2 (27.67%)
6[2]	25	10	M	Not performed	Complete	3	1	2	3	3	3 (71.2%)

Clinical and histological manifestations shown in Figs S1,S2 are scored according to the grading criteria described in Table 1. A number in each column is a grading score of each manifestation. A percentage in parenthesis in column of sebaceous hyperplasia indicates sebaceous gland occupation rate. M, male; N/A, not available/not applicable.

Patient 6

This 25-year-old male[2] had severe CVG and pachydermia. Histologically, focal dermal edema and weak but diffuse mucin deposition were noted. Elastic fiber degeneration affected the entire dermis. Sebaceous gland hyperplasia was prominent, and fibrosis affected the entire dermis.

RESULTS AND DISCUSSION

In the present study, we semiquantitatively scored the severity of the pachydermia and characteristic histological findings (dermal edema, mucin deposition, elastic fiber degeneration, sebaceous gland hyperplasia and dermal fibrosis) according to the criteria described in Table 1. Representative pictures of each clinical and histological finding are shown in Figure 1. Histological features of normal skin, which was used as a control, are shown in Figure S3. Thereafter, we correlated the scores with the severity of pachydermia, as summarized in Table 2.

In the five samples taken from the pachydermia of complete PDP patients (patients 2–6), histological analysis frequently showed fibrosis and sebaceous gland hyperplasia, which tended to become more prominent as the severity of the pachydermia increased. Mucin deposition, dermal edema and elastic fiber degeneration were also noted. In contrast, the sample obtained from the pachydermia of incomplete PDP (patient 1) showed milder histological changes compared with the samples obtained from other patients. Only mucin deposition, focal edema and partial elastic fiber degeneration were observed (Table 2, Figs S1,S2). This sample was obtained from the forehead when slight pachydermia was present, but before CVG became prominent, suggesting that these three findings are the initial histological features of pachydermia. Patients 1 and 2 included in this study had the same *SLCO2A1* genotype, and had similar clinical courses with the gradual development of CVG. The biopsy samples of these two patients were taken at different points in the clinical course: one was taken before CVG had developed (patient 1); the other was taken after CVG had developed (patient 2). The sample obtained from patient 2 had mild fibrosis and sebaceous gland hyperplasia in addition to the triad of mucin deposition, dermal edema and elastic fiber degeneration (Table 2, Figs S1,S2). The difference between these two samples implies that fibrosis and sebaceous gland hyperplasia will appear later than the other three findings, in accordance with the development of pachydermia and CVG. Correlation between the severity of pachydermia and *SLCO2A1* mutational status needs to be confirmed with a greater number of cases. However, the homozygous or compound heterozygous mutations underlie loss of function or would be degraded by nonsense-mediated mRNA decay. Such a genetic background may give some insights into severity of the disease as shown in our patients 4 and 5.

We speculate that the incomplete and complete clinical subtypes occur sequentially in the same PDP patient. Pachydermia development is already initiated even in the early incomplete form. The histological triad of mucin deposition, dermal edema

and elastic fiber degeneration are found from very early stage pachydermia, and may reflect the pathogenesis of PDP. To ensure an earlier diagnosis of PDP, a biopsy should be taken when a patient has grade 1 pachydermia, and has clubbing and periostosis, to determine the presence of this histological triad.

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CONFLICT OF INTEREST: Nothing to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Clinical and histological manifestations of dermal edema and fibrosis. Left column, clinical manifestations of the forehead. Middle column, hematoxylin–eosin (HE) staining, low-power magnification. Right column, HE staining, high-power magnification.

Figure S2. Histological manifestations of mucin deposition and elastic fiber degeneration. Left column, Alcian blue staining. Middle column, elastica van Gieson (EVG) staining, low-power magnification. Right column, EVG staining, high-power magnification. The histological features in the biopsy from patient 1 are milder than those of the other patients. Only mucin deposition, focal edema and partial elastic fiber loss were observed. These three histological findings were also present in the samples obtained from all other patients. The histological features in the biopsies of patients 2–6 showed fibrosis and sebaceous gland hyperplasia, which tended to become more prominent as the severity of pachydermia increased.

Figure S3. Representative histological findings of the control used in this study. The sections were stained as indicated. The histological scores were as follows: dermal edema (0), mucin deposition (0), elastic fiber degeneration (0), sebaceous gland hyperplasia (0; occupation rate of 3.33%) and dermal fibrosis (0).

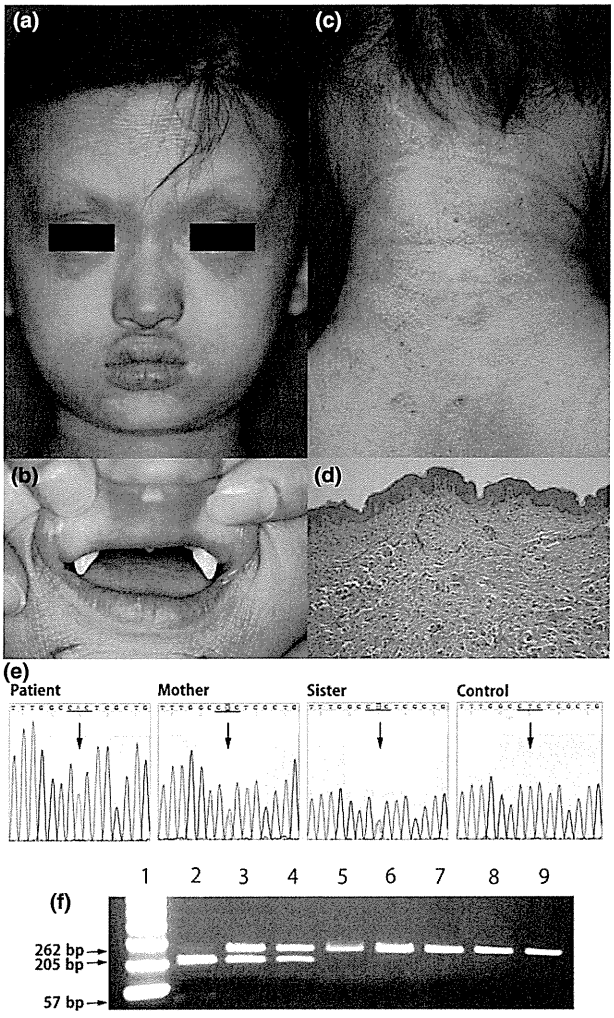

Figure 1. Patient clinical and histological findings. Physical examination revealed (a) sparse, thin hair and eyebrows, a prominent forehead, periorbital pigmentation, a saddle nose, (b) hypodontia and (c) lichenificated erythema on the nuchal region. (d) A biopsy specimen showed the absence of hair follicles and sweat glands (hematoxylin–eosin, original magnification ×100). Detection and segregation of the EDA gene mutation. (e) The patient has a missense mutation at nucleotide 146 (c.146T>A) resulting in p.L49H. His mother and sister are heterozygosis for the same mutation. (f) The Mse I digestion patterns of the polymerase chain reaction (PCR) products for the patient (lane 2), mother (lane 3), sister (lane 4) and normal controls (lanes 5–9); lane 1 shows the molecular weight markers. The 262-bp band indicates a normal allele, whereas the 205- and 57-bp bands indicate mutant alleles. PCR products from 30 healthy controls were analyzed.

CONFLICT OF INTEREST: None.

Masahito YASUDA, Chikako KISHI, Yoko YOKOYAMA, Hiroo AMANO, Osamu ISHIKAWA
Department of Dermatology, Gunma University Graduate School of Medicine, Maebashi, Japan

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Case of pachydermoperiostosis with solute carrier organic anion transporter family, member 2A1 (*SLCO2A1*) mutations

Dear Editor,

The major diagnostic criteria for pachydermoperiostosis (PDP), or primary hypertrophic osteoarthropathy (Mendelian Inheritance in Man no. 167100), are finger clubbing, periostosis, pachydermia and cutis verticis gyrata.[1,2] Additional reported symptoms include sebaceous hyperplasia, hyperhidrosis and arthropathy.[1,2] A diagnosis of PDP is usually made in patients aged older than 20 years. Here, we report a case of PDP diagnosed at puberty.

A 15-year-old Japanese boy was referred to Hirosaki University School of Medicine and Hospital. His symptoms included clubbing of the fingers and toes, and greasiness of the facial skin, although only faint pachydermia was noted (Fig. 1a,b). His sibling and parents did not display associated symptoms. He started to notice enlargement of his fingers and toes at the age of 12 years. Subsequently, he experienced pain in his shoulder and knee joints. Endocrinological examinations showed no notable evidence of acromegaly. Radiological

Correspondence: Satoko Minakawa, M.D., Ph.D., and Daisuke Sawamura, M.D., Ph.D., Department of Dermatology, Hirosaki University Graduate School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562, Japan. Emails: minakawas@yahoo.co.jp and smartdai@hirosaki-u.ac.jp

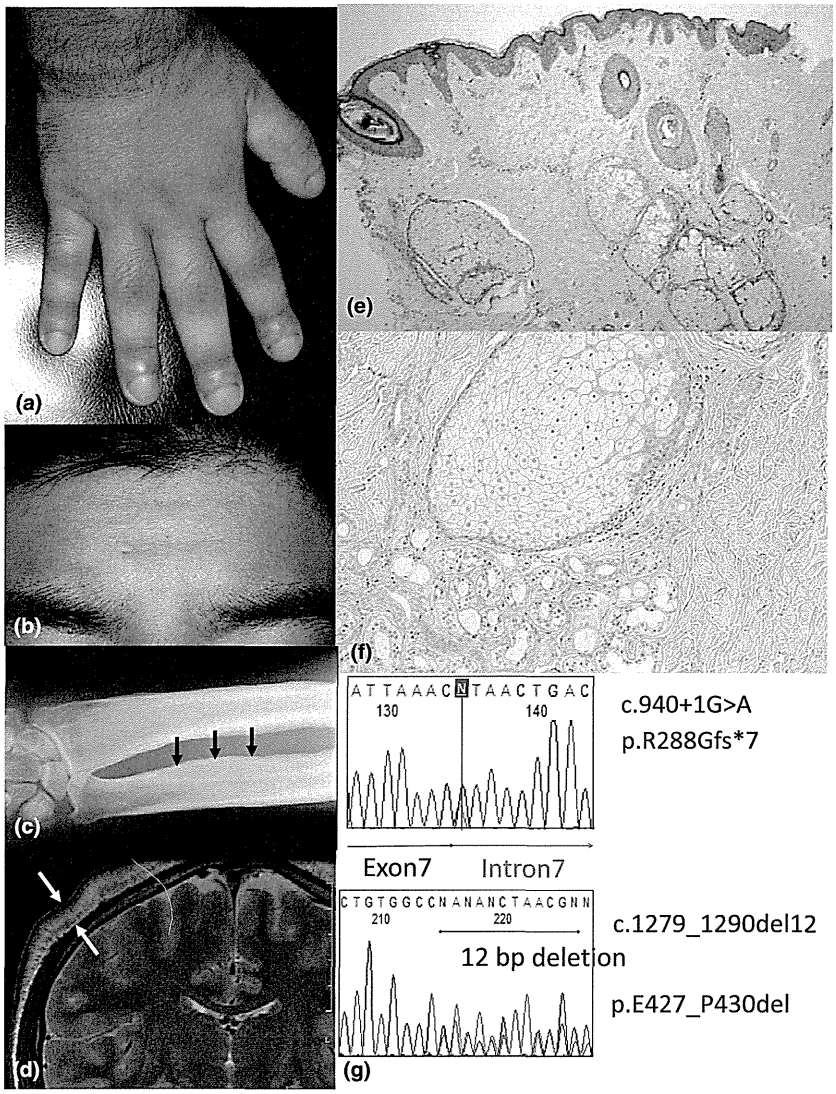

Figure 1. Clinical features from radiographic and laboratory findings. (a) Digital clubbing. (b) Furrows in the forehead and greasiness of the facial skin. (c) Periostosis of the diaphysis in the ulna. (d) Magnetic resonance imaging showed marked thickening of the scalp (between arrows). (e,f) A skin biopsy specimen from the forehead skin showed thickening of the dermis. Interwoven collagen bundles, hypertrophic sebaceous glands and increased density of sweat glands were also evident (hematoxylin–eosin, original magnification [e] ×20; Alcian blue, [f] ×40). (g) A chromatogram demonstrated the mutations (c.940+1G>A p.R288Gfs*7, c.1279_1290del12 p.E427_P430del) in a family of solute carrier organic anion transporters, member 2A1 (*SLCO2A1*) gene, that encodes the prostaglandin transporter.

examination showed periostosis of the diaphysis in the radius, ulna, tibia and fibula (Fig. 1c). Marked thickening of the scalp was also evident (Fig. 1d).

Biopsy of the skin from the forehead showed the dermis was thickened. Interwoven collagen bundles, hypertrophic sebaceous glands and increased density of sweat glands were detected in the dermis (Fig. 1e,f). These observations are common pathological features of PDP.[1]

The clinical findings indicated the manifestation of some types of PDP. Therefore, we performed a mutational analysis for *HPDG* and *SLCO2A1*, which have been previously described to be the genes responsible for PDP.[2] This study was approved by the ethics committee of the National Center for Child Health. We identified compound heterozygous mutations at c.940+1G>A and c.1279_1290del12 in the *SLCO2A1* gene (Fig. 1g). We measured serum and urinary prostaglandin E2 levels, which were 940.99 pg/mL and 139 ng/mmol creatinine, respectively. These observations confirmed the PDP diagnosis; moreover, both mutations have been reported in Japanese patients with PDP.[1,2]

The c.940+1G>A splice site mutation is located in the splice donor site on intron 7 and results in the loss of exon 7 along with truncation of the prostaglandin transporter protein.[1] This mutation has been identified in six Japanese,[1,2] two Chinese[3,4] and one African[5] patient, all of whom were unrelated cases.

The amino acid sequence containing the p.E427_P430del mutation is located in the extracellular region between the 9th and 10th transmembrane domains.[1] This mutation could have a less severe effect on PG transport activity, which may be consistent with the faint pachydermia in the present case. The initial diagnosis of the other two cases with an identical *SLCO2A1* genotype was an incomplete form of PDP.[1,2]

Phenotypes of PDP are not simply determined by *SLCO2A1* genotypes because PDP with *SLCO2A1* mutations is a sex-dependent autosomal recessive disease.[2] Because the expla-

nation of mild- and low-frequency PDP in women remains unclear, further analyses are needed to clarify correlations among *SLCO2A1* genotypes and accompanying phenotypes.

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Satoko MINAKAWA,[1] Takahide KANEKO,[1] Hironori NIIZEKI,[2] Hiroki MIZUKAMI,[3] Yoko SAITO,[4] Takeshi NIGAWARA,[5] Rie KUROSE,[6] Kazuhiko NAKABAYASHI,[7] Kenji KABASHIMA,[8] Daisuke SAWAMURA[1]

[1]Department of Dermatology, Hirosaki University Graduate School of Medicine, Hirosaki, [2]Department of Dermatology, National Center for Child Health and Development, Tokyo, [3] Departments of Pathology and Molecular Medicine, [4]Radiological Life Sciences, [5]Endocrinology and Metabolism, [6]Orthopaedic Surgery, Hirosaki University Graduate School of Medicine, Hirosaki, [7]Department of Maternal-Fetal Biology, National Research Institute for Child Health and Development, Tokyo, and [8]Department of Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

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Accelerated nail elongation speed in psoriasis patients during treatment

Dear Editor,

Psoriasis is characterized by scaly erythematous plaques, particularly on the body areas subjected to repeated minor trauma, such as extensor sites of extremities. Symptoms involving the nails are important lesions associated with arthritis. While nail lesions are commonly resistant to treatment before biologics,[1] it is not clear whether sustained nail lesions are mainly due to insufficient therapeutic effect or impaired nail elongation. Here, we compared nail elongation speed (NES) of psoriasis patients with that of healthy individuals.

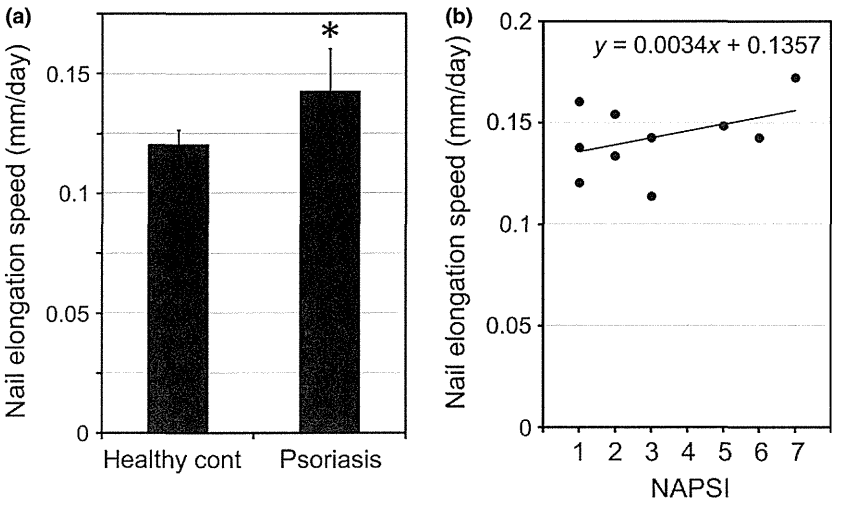

Figure 1. (a) Nail elongation speed (NES) on psoriasis compared with healthy individuals. *P = 0.0032, unpaired Student's t-test. (b) Scatter diagram of NES and Nail Psoriasis Severity Index (NAPSI) score in 10 psoriasis patients (R = 0.422).

Correspondence: Masaru Honma, M.D., Ph.D., Department of Dermatology, Asahikawa Medical University, 2-1-1-1 Midorigaoka-Higashi, Asahikawa, Hokkaido 078-8510, Japan. Email: wanwan@asahikawa-med.ac.jp