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Narita T, Oiso N, Fukai K, Motokawa T, Hayashi M, Yokoyama K, Hozumi Y, Kawada A, Suzuki T	Two children with a mild or moderate piebaldism phenotype and a father with no leukoderma in a family with the same recurrent missense mutation in the kinase domain of *KIT*	**Euro J Dermatol**	21	446-447	2011
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Oiso N, Suzuki T, Fukai K, Katayama I, Kawada A	Nonsegmental Vitiligo and Autoimmune Mechanism.	**Dermatology Research and Practice**	—	Article ID 518090, doi:10.1155/2011/518090	2011

Ⅴ．研究成果の刊行物・別刷

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A novel *IL36RN/IL1F5* homozygous nonsense mutation, p.Arg10X, in a Japanese patient with adult-onset generalized pustular psoriasis

K. Sugiura[1], T. Takeichi[1,2], M. Kono[1], Y. Ogawa[1], Y. Shimoyama.[3], Y. Muro[1], M. Akiyama[1]

Department of Dermatology[1], Department of Laboratory Medicine[3], Nagoya University Graduate School of Medicine
65 Tsurumai-cho, Showa-ku, Nagoya, Japan, 466-8550
Department of Dermatology, Inazawa City Hospital[2],
1-1 Gokusho-cho, Inazawa, Japan 492-8510

Corresponding Author: Kazumitsu Sugiura M.D., Ph.D.
Tel: +81-52-744-2318, Fax: +81-52-744-2318
E-mail: kazusugi@med.nagoya-u.ac.jp

Abbreviations: C-reactive protein (CRP), generalized pustular psoriasis (GPP), interleukin 36 receptor antagonist (IL36RN), palmoplantar pustulosis (PPP), psoriasis vulgaris (PV)

Keywords: adult onset, generalized pustular psoriasis, *IL36RN*, immunohistochemistry, nonsense mutation

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Conflicts of interest: The authors have no conflicts of interest to declare.

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(M.A.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Sir, Generalized pustular psoriasis (GPP) is a rare but severe form of psoriasis that is sometimes life threatening. It is characterized by sudden, repeated episodes of high-grade fever, generalized rash and disseminated pustules. The pathogenesis is unclear except for familial GPP, whose cause was recently identified as homozygous or compound heterozygous mutations in the *IL36RN* gene, also known as *IL1F5*, encoding the interleukin 36 receptor antagonist (IL36RN)[1, 2].

IL36RN is primarily expressed in the skin[3], 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, 5]. These cytokines activate several proinflammatory signaling pathways, such as the nuclear factor-κB and mitogen-activated protein kinase pathways[6, 7].

We have followed a Japanese male patient with GPP, and *IL36RN* mutation analysis revealed the previously unreported homozygote nonsense mutation p.Arg10X.

A 68-year-old man presented with recurrent episodes of localized sterile pustules with erythema but without scaly erythematous plaques, on the extremities (Figure 1a, b) and the trunk, but not on the palmoplantar areas. He had been suffering from similar eruptions since the age of 34. He

once showed widespread generalized pustules accompanied by high fever and elevation of circulating CRP to 30 mg/dl, which were triggered by infection, and he was hospitalized. A skin biopsy from a pustular eruption on the trunk revealed a spongiform pustule of Kogoj in the epidermis (Figure 1c), which is consistent with GPP. He was diagnosed as GPP unassociated with psoriasis vulgaris (PV) or palmoplantar pustulosis (PPP). There was no apparent family history of skin disorders, although his parents are first cousins (Figure 1d).

The ethics committee of Nagoya University approved studies described below. The study was conducted according to the Declaration of Helsinki Principles. The participants gave written informed consent. The coding region of *IL36RN* (Gene bank accession No. 26525) was amplified from genomic DNA by PCR, as described previously[1]. Direct sequencing of the patient's PCR products revealed that the patient was homozygous for the previously unreported nonsense mutation of p.Arg10X (c.28C>T) in *IL36RN* (Figure 2a). C at nucleotide position 28 is 2 bases upstream from the C' end of exon 2 (the exon 2-intron 2 boundary) of *IL36RN*. *In silico* analysis by splicing donor score algorithm[8] was conducted to predict whether this mutation would lead to aberrant or normal splicing, and the results suggest that this mutation results in normal splicing (data not shown).

Immunohistochemistry with rabbit polyclonal anti-IL1F5 antibody (R&D Systems Inc. Minneapolis, MN) showed almost no expression of IL36RN in the patient's epidermal lesion but strong IL36RN expression in a positive control of psoriatic epidermis (Figure 2b,c), as reported previously[9]. Thus, it was apparent that the IL36RN protein was almost absent in the patient.

Very recently, *IL36RN* mutations were reported as causative genetic defects in GPP cases in Tunisian and European populations[1, 2]. In these reports, only three missense mutation were identified: *IL36RN,* i.e., IL36RN pLeu27Pro in the Tunisian population[1], and p.Arg48Trp and p.Ser113Leu in the European population[2]. pLeu27Pro and p.Ser113Leu were thought to be very prevalent mutations in the respective (Tunisian and European) populations.

We report for the first time a GPP patient with an *IL36RN* mutation in an Asian population, and we note that the mutation differs from those prevalent in the Tunisian and European populations. In addition, the present mutation is the first documented nonsense mutation of *IL36RN.* It is nearly a null mutation of IL36RN, and its abolition or extreme reduction of the protein expression of IL36RN was confirmed in the patient's skin. Thus, the present case bolsters the argument that IL36RN functional deficiency really contributes to GPP.

It is interesting that the disease onset of the present case was the rather late age of 34, although the present case was homozygous for *IL36RN* loss-of-function mutation and had no apparent IL36RN protein. In previous reports, most GPP cases with *IL36RN* mutations have been children, though they included three young adults (disease onset in the twenties). The only exceptional case in previous reports was a patient whose age of onset was 51[2]. The present case suggests that even when onset is not until middle age, we cannot exclude the possibility of underlying *IL36RN* mutations as causative genetic defects.

In addition, it is noteworthy that no GPP cases with *IL36RN* mutations, including the present case, have been associated with PV or PPP[1, 2], and the absence of PV and PPP is a clue in identifying GPP patients with *IL36RN* mutations.

We believe it is very important to discriminate familial GPP cases with *IL36RN* mutations from the other GPP cases, not only for genetic counseling but also because we expect familial GPP will be treatable with customized therapy that targets IL-36 signaling in the near future.

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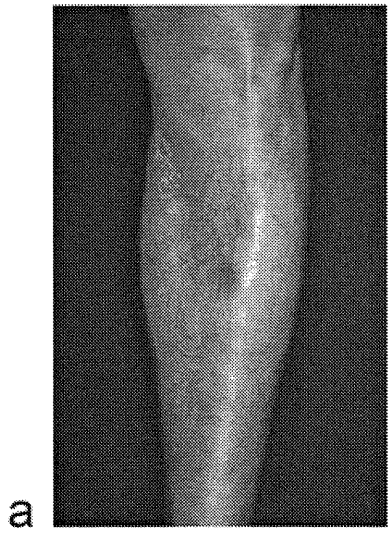
Figure Legends

Figure 1. Skin manifestation, histopathology of the skin lesion and pedigree of the patient

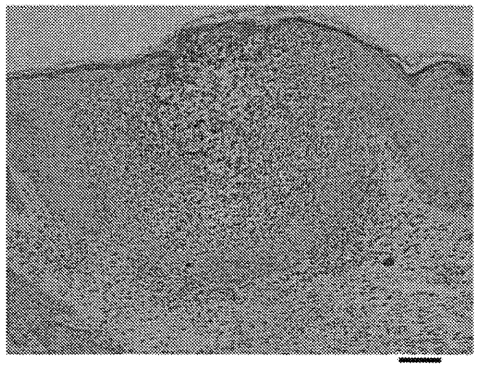
Pustular erythema on internal left knee of the patient (a, b). Spongiosis of Kogoj and acanthosis are observed in the epidermis of the pustular erythema lesion in the trunk upon the patient's admission to hospital (c). Bar: 100 μm. Pedigree of the patient (d).

Figure 2. Sequence data of *IL36RN* and expression of IL36RN on the lesion of the GPP

Sequence data of *IL36RN* in the patient and control (a). Arrow shows heterozygous mutation of c. 28C>T (p.Arg10Ter). C at nucleotide position 28 is 2 bases upstream from the C' end of exon 2 (the exon 2-intron 2 boundary) of *IL36RN*. Immunohistochemistry of GPP lesion by anti-IL1F5 (IL36RN) (b). Staining was almost negative. Immunohistochemistry of skin lesion of a patient with psoriasis vulgaris by anti-IL1F5 (IL36RN) (c). Staining was strong in keratinocytes in the upper layers. Bar: 100 μm.



a



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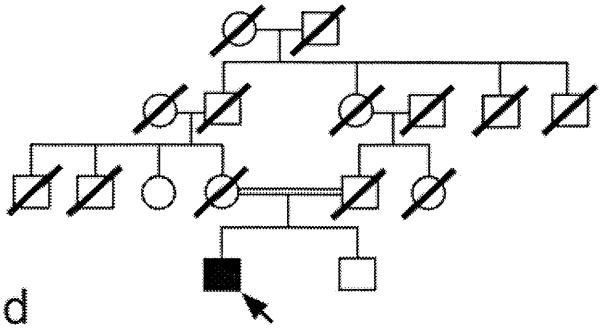
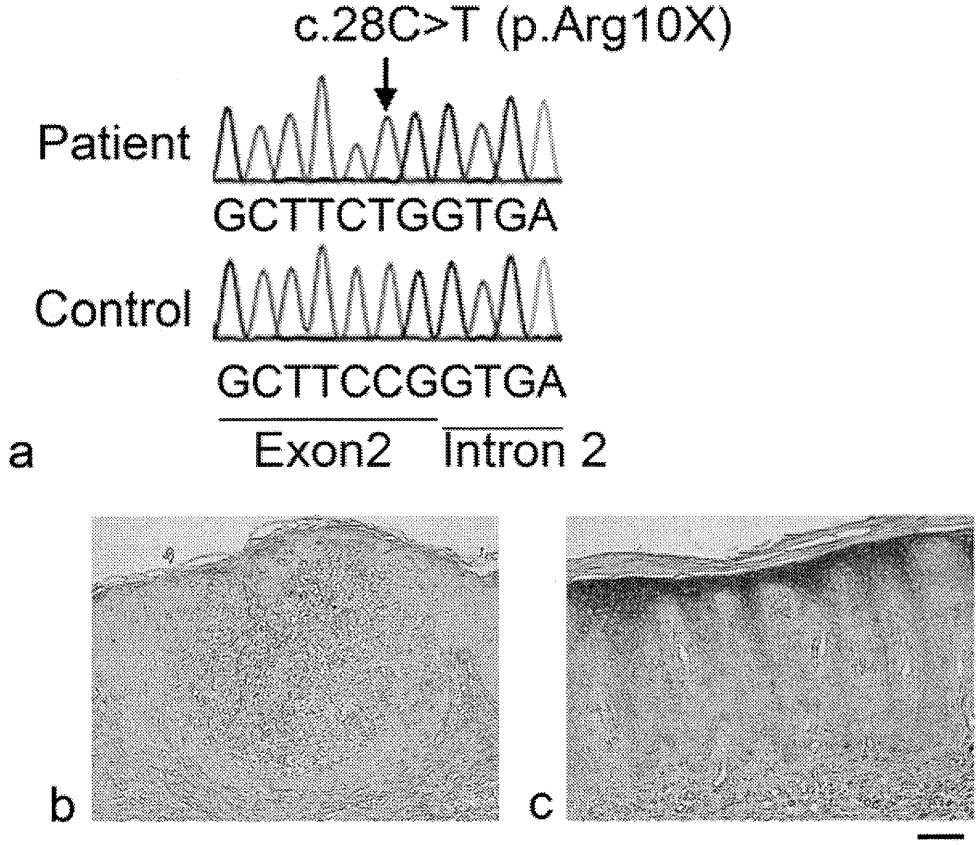
b



d


c.28C>T (p.Arg10X)
Patient
GCTTCTGGTGA
Control
GCTTCCGGTGA
a
Exon2
Intron 2
b
c

SHORT REPORT

Prevalent founder mutation c.736T>A of *LIPH* in autosomal recessive woolly hair of Japanese leads to variable severity of hypotrichosis in adulthood

K. Tanahashi,[†] K. Sugiura,[†] T. Takeichi,[†,‡] H. Takama,[§] S. Shinkuma,[¶] H. Shimizu,[¶] M. Akiyama[†,*]

[†]Department of Dermatology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Japan
[‡]Department of Dermatology, Inazawa City Hospital, Inazawa, Japan
[§]Takama Dermatology Clinic, Kasugai, Japan
[¶]Department of Dermatology, Hokkaido University Graduate School of Medicine, Sapporo, Japan
*Correspondence: M. Akiyama. E-mail: makiyama@med.nagoya-u.ac.jp

Abstract

Background Mutations in *LIPH* are a cause of autosomal recessive woolly hair (ARWH). Homozygous c.736T>A (p.Cys246Ser), and compound heterozygous c.736T>A and c.742C>A (p.His248Asn) have been reported in 5 and 7 Japanese children with ARWH respectively. The severity of hypotrichosis is known to be able to change in the clinical course, and the mutation patterns of *LIPH* do not always correlate with the severity of hypotrichosis in ARWH caused by other mutation sites of *LIPH*. However, all 12 Japanese children previously reported to have ARWH have shown similar severity of hypotrichosis.

Objective In this study, we investigated the clinical features and molecular basis of ARWH in patients including three adults (three adults and two children) from five non-related Japanese families.

Methods Five families of Japanese origin that presented with woolly hair were studied. The phenotype was confirmed by clinical examination. Direct automated DNA sequencing of the *LIPH* gene was performed to identify the mutations in our probands.

Results All patients had had woolly hair since birth. Homozygous c.736T>A mutations were found in four patients, including three adult cases, and compound heterozygous c.736T>A and c.742C>A mutations were found in one child patient. The two adults and two children had only sparse scalp hair, although one adult woman had mild hypotrichosis with long hairs.

Conclusion Some patients with homozygous c.736T>A can have a mild hypotrichosis phenotype with long hairs in adulthood.

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Conflicts of interest

None to declare.

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Introduction

Autosomal recessive woolly hair/hypotrichosis (ARWH: OMIM #278150/604379/611452) is a rare hereditary hair disease characterized by tightly curled hair at birth. It can lead to sparse hair later in life. The disease was shown to be caused by mutations in either the *LIPH* or the *LPAR6* gene.[1,2] The *LIPH* gene encodes a membrane-associated phosphatidic acid-preferring phospholipase $A_1\alpha$ (PA-PLA$_1\alpha$), which produces lysophosphatidic acid (LPA) from phosphatidic acid.[3] LPA is an extracellular mediator, which possesses many biological functions. The *LPAR6* gene encodes the G protein-coupled receptor LPA receptor 6 (LPAR6).[2] Both PA-PLA$_1\alpha$ and LPAR6 are abundantly expressed in human hair follicles, where their expression overlaps in the inner root sheath.[1,2] Thus, it has been postulated that PA-PLA$_1\alpha$ and LPAR6 are components of a common signalling pathway, which plays a crucial role in hair growth in humans.[2,4]

In Japanese, only two patterns of mutations have been reported: homozygous c.736T>A, and compound heterozygous c.736T>A

and c.742C>A of *LIPH*, in 12 children from 4 and 6 ARWH families respectively.[5–8] The *LIPH* mutations c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn) were proven to be dysfunctional by *in vitro* studies.[6] Both missense mutations are considered extremely prevalent founder mutations for ARWH in the Japanese population.[6] The frequencies of the c.736T>A and c.742C>A alleles in healthy Japanese control individuals are 1.5% (3/200) and 0.5% (1/200) respectively, which implies the existence of many carriers for each mutation in the Japanese population.[6] Thus, it can be estimated that there are approximately 10 000 Japanese patients with ARWH carrying the *LIPH* mutations.

The mutation patterns of *LIPH* do not always correlate with the severity of hypotrichosis in ARWH. For example, affected individuals with homozygous mutation c.659–660delTA of *LIPH* showed significant differences in the severity of the hypotrichosis.[9] However, in the previous reports, all patients carrying homozygous mutations c.682delT or c.322T>C of *LIPH* have mild hypotrichosis,[9] and all patients harbouring homozygous mutations Ex4 deletion or c.346–350del of *LIPH* have severe hypotrichosis.[1,10] Therefore, some mutations of *LIPH* are thought to have genotype–phenotype correlation on severity of hypotrichosis in ARWH. As for c.736T>A, the prevalent *LIPH* mutation in the Japanese population, five Japanese children were reported to be homozygous for this mutation and all the children showed severe hypotrichosis, as we mentioned above.[5,6,8] Thus, all the patients homozyogous for c.736T>A were thought to have severe phenotype. However, the present study revealed that patients with this prevalent mutation possibly show mild hypotrichosis at least in the adulthood.

Materials and methods

Subjects

Five unrelated non-consanguineous Japanese families A, B, C, D and E (Fig. 1) with ARWH were seen in our hospital or referred to us in the previous 6 months. Family A was from Tokyo. Families B, C, D, and E were from Aichi Prefecture, in central Japan. The patients' ages and sexes are summarized in Table 1. The medical ethics committee of Nagoya University approved all the described studies. The study was conducted according to the Declaration of Helsinki Principles. The patients and families gave written informed consent.

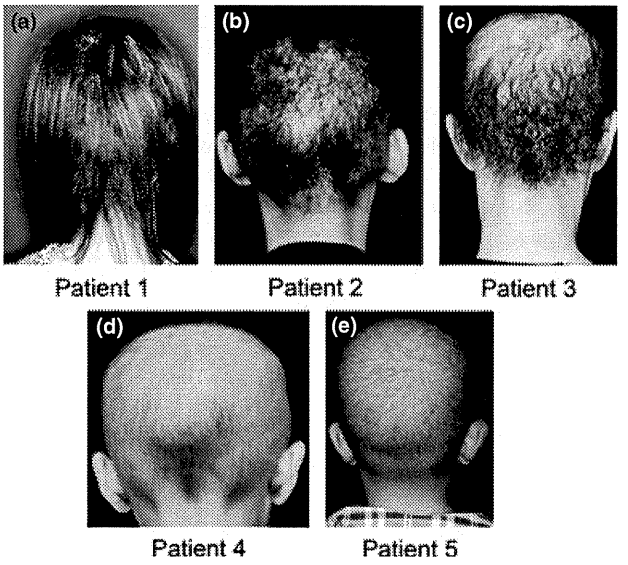

Figure 1 Clinical features of five Japanese families with ARWH. (a) Patient 1. (b) Patient 2. (c) Patient 3. (d) Patient 4. (e) Patient 5. All the affected individuals have features of ARWH, which is characterized by woolly hair on the scalp. In Patient 1, the hypotrichosis is notably mild and the hair is longer than in Patients 2 to 5. Scalp hairs of Patient 1 were treated with straight permanent wave.

Mutation detection

LIPH mutation search was performed as previously reported.[6] Briefly, genomic DNA (gDNA) isolated from peripheral blood was subjected to polymerase chain reaction (PCR) amplification, followed by direct automated sequencing using an ABI PRISM 3100 Genetic Analyzer (Advanced Biotechnologies, Columbia, MD, USA). The entire coding regions of *LIPH* including the exon/intron boundaries were sequenced using gDNA samples from patients and their family members.

Results

Clinical findings

All 5 affected individuals in the five unrelated Japanese families showed features of ARWH (Fig. 1). Eyebrows and eyelashes were slightly sparse to absent, although nails, teeth, sweating and

Table 1 Mutations in the *LIPH* gene in five families

Patient	Age	Sex	Family	*LIPH* mutation	Father	Mother	Sibling
1	25	F	A	c.736 T>A, homo	N.A.	c.736 T>A, hetero	
2	27	F	B	c.736 T>A, homo	N.A.	N.A.	
3	35	F	C	c.736 T>A, homo	N.A.	N.A.	
4	3	M	D	c.736 T>A, homo	c.736 T>A, hetero	c.736 T>A, hetero	c.736 T>A, hetero
5	4	M	E	c.736 T>A, c.742C>A, compound hetero	c.736 T>A, hetero	c.742 C>A, hetero	

N.A., not analysed.

hearing were normal in all the affected individuals. The hypotrichosis of one adult patient, Patient 1, was relatively less severe. Patient 1 had woolly hair and hypotrichosis at birth. According to the Patient 1, the hypotrichosis improved after treatment by herself with commercially available 1% minoxidil solution. She did not remember how long it took to improve the hypotrichosis. At the first visit to our hospitals, the scalp hairs were treated with straight permanent wave. Her hair was long enough without any cosmetic problem. She showed a much milder phenotype of the scalp hair than the other two adult patients, Patients 2 and 3. The two child patients had woolly hair with severe hypotrichosis. The heterozygous carriers of the *LIPH* mutations had normal hair.

Mutation detection

Direct sequencing analysis of exons and intron–exon boundaries of *LIPH* revealed that affected members of families A, B, C and D were homozygous for c.736T>A (p.Cys246Ser) (Table 1). The affected individual in Family E was compound heterozygous for the two missense mutations c.736T>A (p.Cys246Ser) and c.742C>A (p.His248Asn). All the patients' parents whose DNA was available for mutation search were heterozygous carriers of one of the two mutations (Table 1).

Discussion

In this study, we analysed five cases including three adults from five unrelated families with ARWH. All five cases had one or two of the two prevalent *LIPH* mutations in the Japanese population.[5–8] One 25-year-old woman had long hair with mild hypotrichosis, features that were extremely different from other adult cases.

ARWH caused by homozygous c.736T>A mutations, and compound heterozygous c.736T>A and c.742C>A mutations of *LIPH* are specific and common in the Japanese population. However, affected individuals who were previously reported have been under 10 years of age, and all the affected individuals have had sparse, curled hair that grew slowly from birth and then stopped growing after reaching a few inches. There have been no significant differences in clinical features between families and patients so far.[5–8] As ARWH patients with these mutations are estimated to be rather prevalent in Japan, it is important to know the clinical course of hypotrichosis of ARWH caused by these mutations. Patient 1 is a distinct example of an ARWH patient with hypotrichosis in childhood whose hypotrichosis phenotype improved in adulthood.

Patient 1 was administrated commercially available 1% minoxidil solution by herself before the first visit to our hospital. It was not certain whether the minoxidil solution really worked on the hypotrichosis of this case. Future large clinical studies might reveal whether the solution actually improves sparse scalp hairs of ARWH.

In conclusion, we presented the clinical features of three adult ARWH cases caused by the most prevalent mutation patterns of *LIPH* in Japan. This study suggests that the severity of hypotrichosis can decrease in adulthood.

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Correspondence

Extraordinarily large, giant spider angioma in an alcoholic cirrhotic patient

Spider angioma/nevus, or nevus araneus, is a common cutaneous vascular anomaly, and is present in 10–15% of normal adults and children.[1] A spider angioma is typically a central, elevated, red punctum, from which blood vessels radiate 1–2 cm in diameter. We report here an extremely large spider angioma in a patient with liver cirrhosis.

A 68-year-old man with an 8-year history of alcoholic liver cirrhosis consulted our outpatient clinic complaining of a large reddish-purple soft tumor with radiating telangiectasia on the back. He had had the lesion for more than 1 year. The lesion had expanded and elevated gradually, and radiating telangiectasia appeared surrounding it. Subsequently, 10 or more small telangiectatic lesions appeared on his upper trunk and arms. He had been drinking about 50 g of alcohol per day until being diagnosed with liver cirrhosis. He had esophageal varices and was treated with endoscopic therapy. Physical examination revealed a reddish-purple, soft, dome-shaped node with a diameter of 2.3 × 1.3 cm, and telangiectasia radiating from the center to a diameter of 10 cm (Fig. 1).

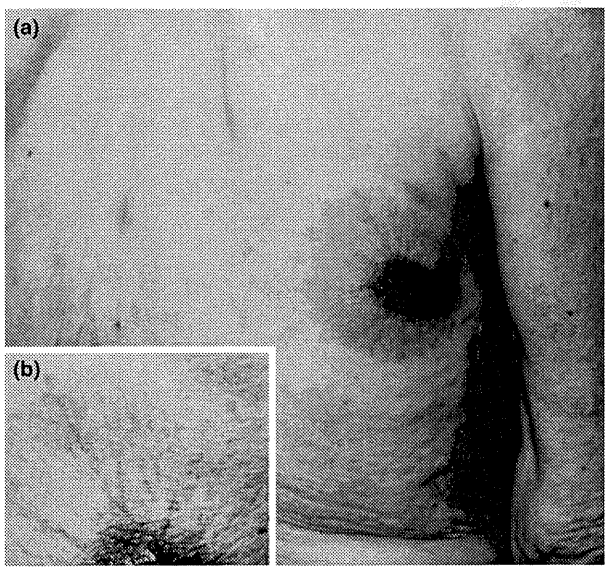

Figure 1 (a) A large reddish-purple soft tumor with radiating telangiectasia on the patient's back. (b) Close-up of the radiating telangiectasia. The clinical features of the present case are similar to those of a case reported previously[5]

Multiple, typical spider angiomas of ordinary size (<2 cm in diameter) were scattered on his upper trunk and upper extremities. Laboratory studies showed liver dysfunction and decreased platelet count. A skin biopsy was taken from the central reddish-purple node. Histopathologically, dilated vessels of various sizes were observed to have proliferated in the superficial and mid dermis. Inflammatory cells, mainly lymphocytes and histiocytes, were infiltrated around the dilated vessels, and erythrocyte extravasation was also seen. Endothelial cells of the vessels were round and protruding into the lumen, although no atypism was observed (Fig. 2). From these clinical and histopathological features, the diagnosis of spider angioma was made. During the 6-month follow-up period, no remarkable changes were seen in either the liver cirrhosis or the spider angioma. The patient did not want any treatment for the angioma.

Spider angioma is seen in patients with pregnancy, thyrotoxicosis, oral contraceptive use and, most commonly, liver cirrhosis. Spider angiomas are known to be more common in patients with alcoholic cirrhosis than in those with viral or idiopathic cirrhosis. The pathogenesis of spider angioma is still unclear. Li *et al.*[2] reported an association between elevated plasma levels of vascular endothelial growth factor and spider angiomas. In patients with non-alcoholic cirrhosis, the plasma level of substance P is elevated, and this may play an important

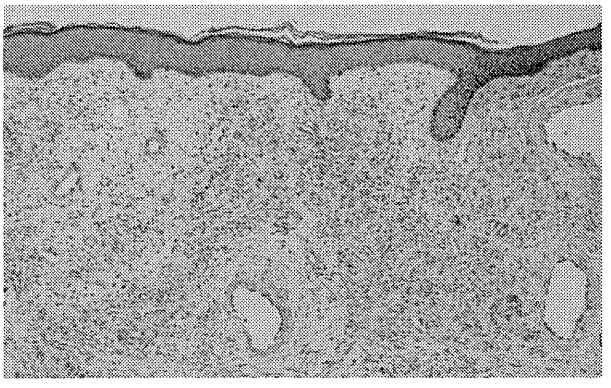

Figure 2 Photomicrograph of a skin biopsy specimen from the central node. Dilated vessels of various sizes are proliferated in the superficial and mid dermis. No atypism is observed in the endothelial cells. Low-density inflammatory cell infiltrate is observed around the dilated vessels (hematoxylin-eosin, original magnification ×100)

role in the pathogenesis of spider angioma.[3] Estrogen also is suspected of playing a role.[4] Spider angiomas are usually <2 cm in diameter. Okada reported a giant spider angioma 6 cm in diameter.[5] As far as we know, the present spider angioma is the biggest ever reported. Generally, the central feeding vessel of spider angiomas can be destroyed with electrolysis or hyfrecation. Spider angiomas are also well treated by various types of lasers.[6,7] Giant spider angiomas can be treated by surgical excision.

The differential diagnosis for giant spider angioma includes several tumors of vascular origin, among them angiosarcoma, Kaposi's sarcoma and malignant hemangiopericytoma. Histopathological examination is often necessary to exclude these malignant tumors. Typical spider angiomas of ordinary size on the upper trunk and extremities were helpful in diagnosing the present case. Although giant spider angioma is rare, we have to keep it in mind in the differential diagnosis of large tumors of vascular origin, especially in patients with chronic liver diseases.

Hiroaki Hane, MD
Kenji Yokota, MD
Michihiro Kono, MD, PhD
Yoshinao Muro, MD, PhD
Masashi Akiyama, MD, PhD
Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan
E-mail: makiyama@med.nagoya-u.ac.jp

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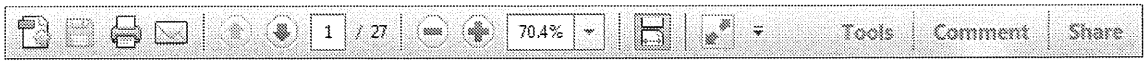

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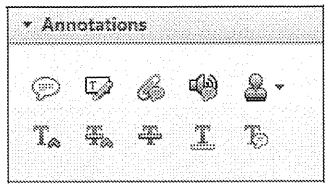

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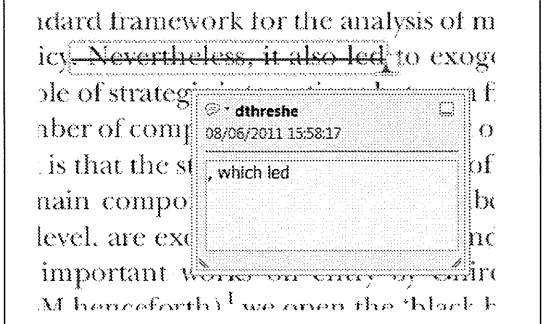

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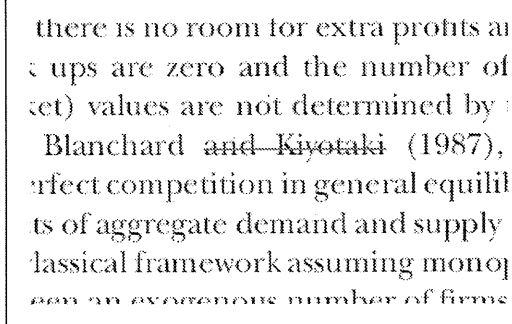

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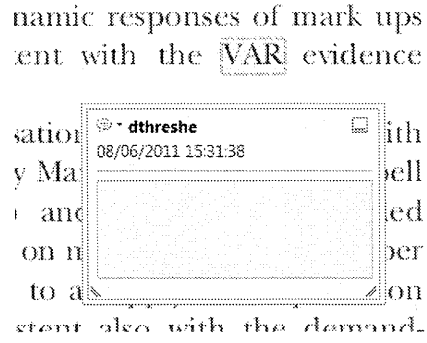

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