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diet and medication (nateglinide, candesartan cilexetil, and allopurinol). Cutaneous examination revealed ring-like yellowish tumors on his periorbital regions (fig. 1a), rope necklace-like tumors on his neck (fig. 1b, c), and spindle-shaped tumors on his right preauricular region and cubital fossas (fig. 1d). Histological examination of his right neck tumor showed foamy macrophages and touton-type giant cells (fig. 2a). Immunohistochemical staining revealed that the cells were positive for CD68 (fig. 2b) and CD163 (fig. 2c) and negative for S-100 and CD1a. X-rays of the long bones of the upper and lower extremities showed no apparent osteosclerotic or osteolytic changes. Exophthalmos, diabetes insipidus, and the pathological findings confirmed the diagnosis of Erdheim-Chester disease (ECD; table 1). The patient had also been diagnosed with atopic dermatitis in childhood. He demonstrated diffuse facial erythema, pruritic chronic eczematous lesions on the trunk and flexor aspect of the extremities (fig. 1d), and multiple prurigo of the extremities. Laboratory findings related to atopic dermatitis were white blood cells: 12,640/μl, eosinophils: 19%, immunoglobulin E-radioimmunosorbent test (IgE-RIST) score: 38,500 IU/ml, IgE radioallergosorbent test (IgE-RAST) score of *Dermatophagoides farinae*: 99.9 IU, and thymus- and activation-regulated chemokine (TARC): 47,980 pg/ml. Therefore, our patient was diagnosed with ECD complicated by atopic dermatitis.

Discussion

ECD is a rare non-Langerhans form of histiocytosis with multiple organ involvement. Involvement of the long bones is observed in 86% of patients, and a typical manifestation is bilateral symmetric sclerosis of the metaphyseal region of the long bones of the lower extremities [1, 2]. Approximately one half of all cases have extraskeletal manifestations, including effects on the hypothalamus-pituitary axis, lungs, heart, retroperitoneum, skin, liver, kidneys, spleen, and orbit. Skin involvement is seen in approximately 20% of patients, who frequently present with xanthoma-like lesions that usually manifest on the eyelids and occasionally on the trunk and submammary area [3].

Here, we report a case of ECD with a peculiar distribution of tumorous xanthomas and without bone involvement. The patient was initially diagnosed in childhood with HSCD, one of the syndromes of Langerhans cell histiocytosis (LCH), based on the histological findings of his left retro-orbital mass. It is sometimes difficult to distinguish ECD from HSCD because they have certain clinical findings in common such as exophthalmos, diabetes insipidus, and radiological findings of osseous lesions. Osteolysis of the scalp bones is typical in HSCD, whereas osteosclerosis of the long bones is the characteristic presentation of ECD. However, osteosclerosis in ECD is sometimes difficult to identify, and osteolytic lesions are found in approximately one third of patients with ECD [4]. ECD commonly occurs in adulthood, whereas HSCD occurs in infancy. The mortality rate for ECD is 57% and for HSCD it is 30% [5] (table 1).

Immunohistochemical analyses are useful for distinguishing between these two diseases. The histiocytes in the skin involve two major cell lineages, macrophages and Langerhans cells, which are derived from monocytes [6]. Pathogenic macrophages are observed in ECD. In contrast, Langerhans cells are characteristic of HSCD. The histiocytes in ECD are immunoreactive for CD68 and CD163, but not for S-100 or CD1a. The pattern is reversed in histiocytes in HSCD (table 1). Because we were not able to obtain detailed histological information on the left retro-orbital mass removed in childhood, we could not conclude that this was a case of HSCD in childhood that converted to ECD in adulthood, or a case of ECD that showed an HSCD-like manifestation in childhood. Previously, it was suggested but not definitively established that ECD may represent a spectrum of LCH [7, 8]. However, it was recently suggested

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that ECD is a unique disease entity and LCH-like findings may be within the spectrum of ECD [9, 10]. Further examination of cases and research are needed to explore this issue.

It is interesting that tumorous xanthomas were present mainly in sites predisposed to atopic dermatitis such as the neck skin and flexor aspect of the extremities. Although some cases show nodular xanthomatous masses of the neck [11], rope necklace-like xanthomas and bulging xanthomas on the flexor aspect of the extremities as observed in the present case are rare. We suggest that the complication of atopic dermatitis modified the clinical presentation in this case. Activation of fibroblasts due to scratching behavior evoked by itching due to atopic dermatitis [12] may have resulted in tumorous xanthomas.

In conclusion, we reported a case of ECD with a peculiar distribution of tumorous xanthomas. We suggested that the complication of atopic dermatitis played a role in the development of the uncommon clinical features of our case.

Table 1. Hand-Schüller-Christian disease and Erdheim-Chester disease

	Onset	Clinical sign	Mortality	Proliferated histiocyte	S-100	CD1a	CD68	CD163
HSCD	Infant	DI, exophthalmos, osteolysis of the scalp bone	30%	Langerhans cell	+	+	–	–
ECD	Adult	DI, exophthalmos, osteosclerosis of long bones (sometimes osteolysis)	57%	Macrophage	–	–	+	+

DI = Diabetes insipidus; HSCD = Hand-Schüller-Christian disease; ECD = Erdheim-Chester disease.

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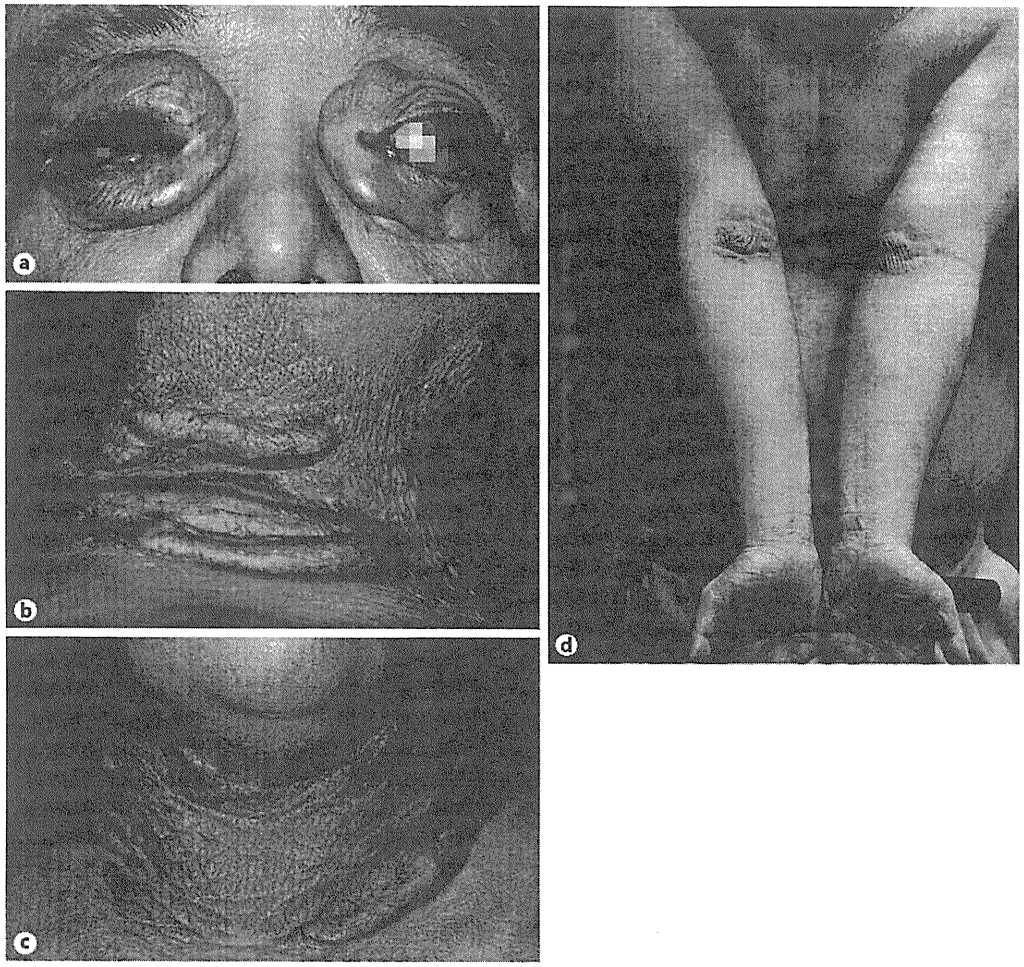

Fig. 1. **a** Ring-like yellowish tumors in the periorbital regions. **b**, **c** Rope necklace-like yellowish tumors on the patient's neck. **d** Spindle-shaped yellowish tumors on the patient's cubital fossas and diffuse erythema and pigmentation on the patient's forearm.

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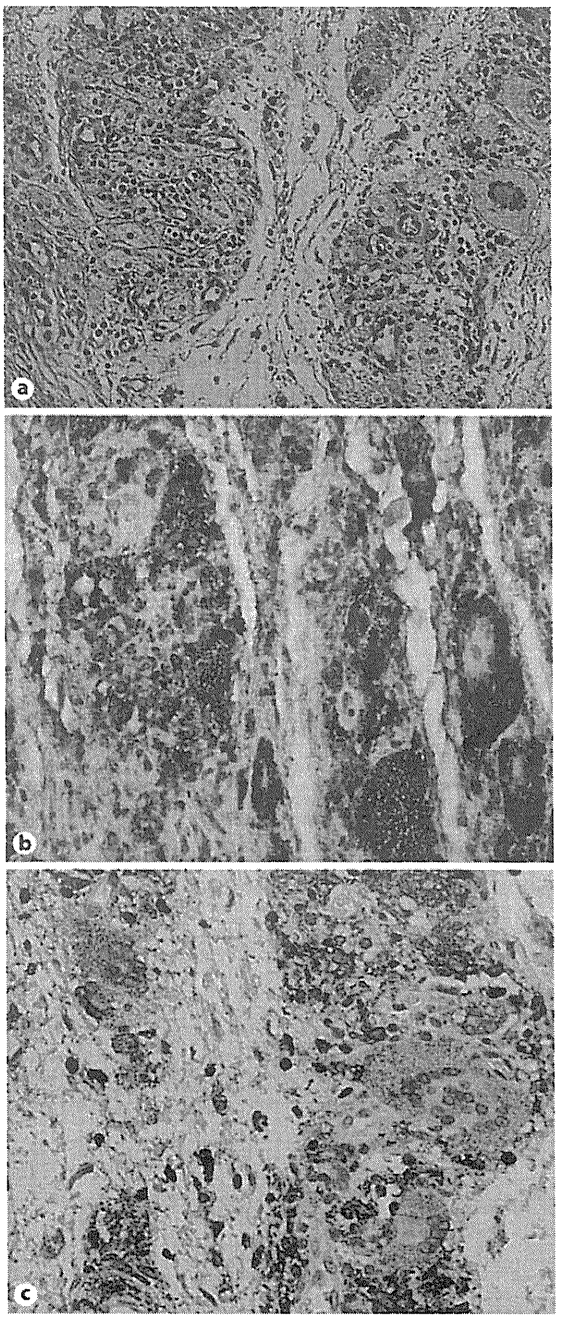

Fig. 2. Histopathological images from hematoxylin-eosin (**a**), original magnification, 100×, and immunohistochemical analyses showing the expression of CD68 (**b**) and CD163 (**c**), original magnification, 200×.

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CASE REPORT

Cedar Pollen Aggravates Atopic Dermatitis in Childhood Monozygotic Twin Patients with Allergic Rhino Conjunctivitis

Yukako Murakami[1], Saki Matsui[1], Akiko Kijima[1], Shun Kitaba[1], Hiroyuki Murota[1] and Ichiro Katayama[1]

ABSTRACT

We report a case of 7-year-old monozygotic twin patients with atopic dermatitis. The HLA haplotypes were HLA A2, A11, B27, B61, DR1, and DR4. Both serum IgE levels and cedar pollen radioallergosorbent test (RAST) scores were high in the twins (elder/younger sister: IgE: 5170/3980 IU/ml and Japansese cedar pollen: >100/64.0) in contrast to low mite and food RAST scores (Dermatophagoides Pterygonium; 0.59/0.4 and egg white 9.24/4.6). The patients showed positive immediate (20 min in both sisters) and delayed (24 hours in elder sister, 24, 48, 72 hours in younger sister) reactions to a scratch test with Japanese cedar pollen. Skin lesions on the face were aggravated and extended to the trunk and extremities during the Japanese cedar pollen season and gradually subsided in summer. Oral provocation with egg white or cow milk showed no exacerbations, and topical corticosteroid did not improve the eczema. In contrast, successful protection from severe scratching behaviors was achieved by use of topical anti-allergic eye drops and wearing nightgowns made by the mother.

KEY WORDS

atopic dermatitis, cedar pollen, childhood, monozygotic twins, scratching behavior

INTRODUCTION

Since Besnier's first description in 1892, atopic dermatitis has been recognized as a representative, multi-factorial allergic disease influenced by genetic factors.[1] When both parents show atopic eczema, the children have a high risk (-70%) of developing eczema.[2] Monozygotic twins run a risk of 0.86 of having atopic dermatitis if either twin has the disease, whereas the disease risk of 0.21 by dizygotic twins does not differ from the frequency seen in ordinary brothers and sisters.[3] Dry skin, immunological dysfunction, increased IgE production, or an autonomous nervous system imbalance are frequently observed in patients with atopic dermatitis, along with bronchial asthma or pollenosis, which have closely related genetic factors.

In 2006, Palmer *et al.* reported that common loss-of-function variants of the epidermal barrier protein filaggrin are major genetic factors for the risk of atopic dermatitis. Subsequently, these mutations have also been linked to atopic dermatitis,[4-6] asthma,[7-9] and allergy.[10] Environmental factors initiate allergic diseases by penetrating barrier-disrupted skin. Our current monozygotic twin case shows aggravation of facial skin lesions during the cedar pollenosis season, followed by severe scratching behavior resulting in eczema. In contrast to the high IgE-RAST scores of various pollen allergens with aggravation of eczema, RAST scores for mites and food antigens were low, and a challenge test of several foods with positive RAST scores did not affect eczema. Successful protection from severe scratching behaviors was achieved with use of topical anti-allergic eye drops and wearing nightgowns hand-made by their mother.

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CLINICAL SUMMARY

Seven-year-old monozygotic twin sisters visited our outpatient clinic with severe eczema. Both patients suffered from neonatal melena, mental retardation, and atopic dermatitis, and had been treated for atopic dermatitis. Their mother had suffered from atopic dermatitis since childhood.

The twins were delivered by normal birth, but were given a whole blood transfusion due to newborn melena of unknown origin. Soon after birth, they developed skin lesions, which gradually worsened during the cedar pollenosis season. Severe uncontrolled scratching behaviors were observed in both patients, and skin lesions extended over their whole body in a similar distribution. Their scratching behaviors were uncontrolled due to mental retardation, possibly related to newborn melena. Several food intake tests did not affect the exacerbation of the eczema.

At the first visit, crusted and lichenified eczematous lesions were observed, especially around the periorbital region and the trunk skin (Fig. 1A-D). A diagnosis of atopic dermatitis was made according to the diagnostic criteria proposed by the Japanese Dermatological Association.[11] Monozygosity was confirmed by the patients' similarity and birth record, and their HLA haplotypes were HLA A2, A11, B27, B61, DR1, and DR4. Both serum IgE levels and Japanese cedar pollen RAST scores were high in the twins (elder/younger sister; IgE: 5170/3980 IU/ml and cedar pollen: >100/64.0) in contrast to low mite and food RAST scores (Dermatophagoides Pterygonium: 0.59/0.4, egg white: 9.24/4.6, egg yolk: 1.76/0.77, soybean: 35.5/4.3, cow milk: 5.63/0.44, rice: 14.3/5.0, and wheat 12.7/4.4). Information obtained by questioning the patients raised the possible involvement of mugwort, benzalconium chloride, and ε-aminocapronic acid in developing facial eczema. Although these compounds are tested by patch test which was difficult for them to complete for 48 hours due to mental retardation, we adopted prick test method. The patients showed positive immediate (20 min in both sisters) and delayed (24 hours in elder sister, 24, 48, 72 hours) reactions to a skin prick test with Japanese cedar pollen (Fig. 2A-C).

During the pollen season, both patients showed pollenosis symptoms including sneezing and eye congestion with elevated lacrymal flow and uncontrolled scratching on the face, followed by aggravation of the atopic dermatitis.

Topical glucocorticoid or antihistamines failed to suppress the scratching behaviors or exacerbation of eczema. However, after using overall -type nightgowns made by their mother (Fig. 3) and anti-allergic eye drops, worsening of the skin lesions during the cedar pollen season was prevented, and laboratory scores improved. IgE titer (elder: 5170 to 1749 IU/l, younger 3980 to 656 IU/l) was improved after the therapy and protection.

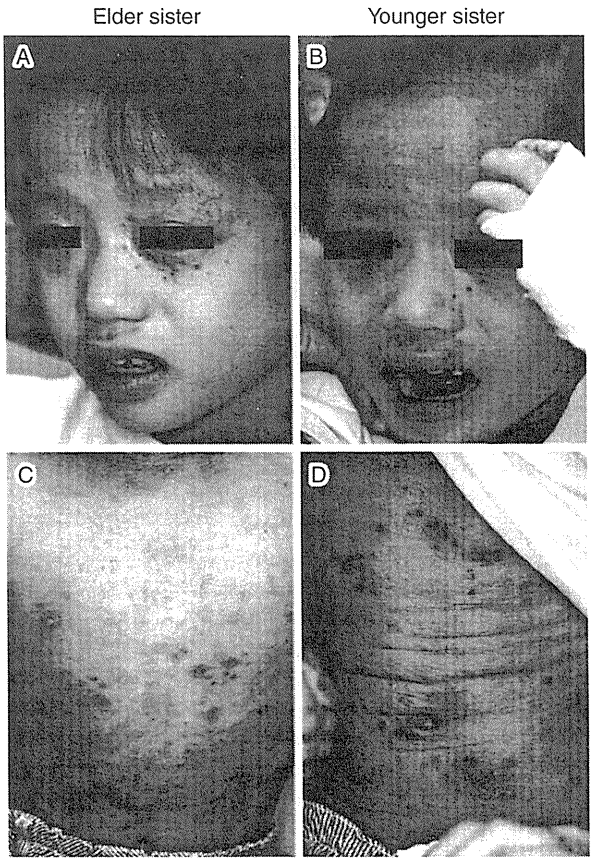

Fig. 1 Clinical features of identical twin sisters with atopic dermatitis. Note the result of severe scratching dermatitis around in the periorbital regions. **A, B.** Periorbital lesions (left; elder sister, right; younger sister). **C, D.** Trunkal lesions (left: elder sister, right: younger sister).

DISCUSSION

In 2006, Palmer *et al.* reported that common loss-of-function variants of the epidermal barrier protein filaggrin are major genetic factors for the risk of atopic dermatitis.[5] Subsequently, these mutations have also been linked to atopic dermatitis,[4-6] asthma,[7-9] and allergy.[10] Environmental factors initiate allergic diseases by penetrating barrier-disrupted skin. Our current twin cases of atopic dermatitis showed similar clinical manifestations, including aggravation of facial skin lesions during the cedar pollen season, followed by severe scratching behavior resulting in generalization of eczema and hyposensitivity to food allergens. In the recent literature, the prevalence rate of pollenosis in childhood has been increasing,[12] especially in children bearing filaggrin mutations.[7] Masuda *et al.* recently reported that the ratio of cedar pollenosis sensitization gradually increases from infancy to adolescence. In their survey,

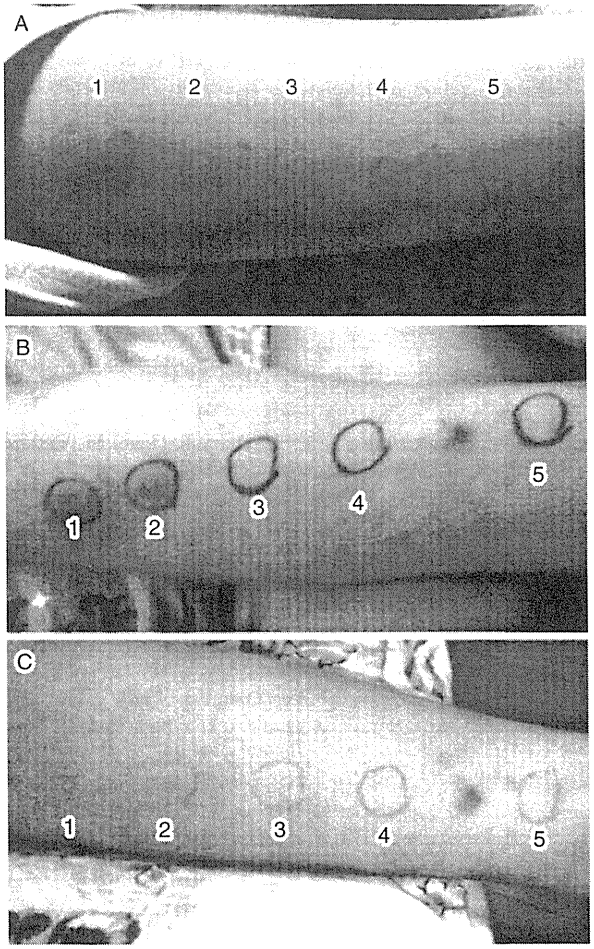

Fig. 2 Positive skin reaction to Japanese cedar pollen prick test. **A.** Skin reaction at 72 hours (younger sister) after positive immediate reaction. Note indurated erythematous reaction. **B.** Skin reactions at 15 minutes (elder sister). **C.** Skin reaction at 24 hours (elder sister). 1, Japanese cedar pollen. 2, Mugwort. 3, Benzalconium chloride. 4, εAminocapronic acid. 5, Control.

the youngest child sensitized to Japanese cedar pollen was a 23-month-old boy with atopic dermatitis.[13] Kusunoki *et al.* reported that the prevalence of cedar pollenosis is 5.2% in school-age children and higher in older children. Kusunoki *et al.* also demonstrated that among children with atopic dermatitis, there was a statistically significant correlation between the severity of atopic dermatitis and the presence of cedar pollenosis, and children with cedar pollenosis tended to have more severe atopic dermatitis symptoms. On the other hand, the severity of bronchial asthma was not affected by the presence of cedar pollenosis, which suggests a possible contribution of cedar pollen to atopic dermatitis but not to bronchial asthma symptoms.[14] In contrast to high IgE-RAST scores of various pollen allergens with aggravation of eczema,

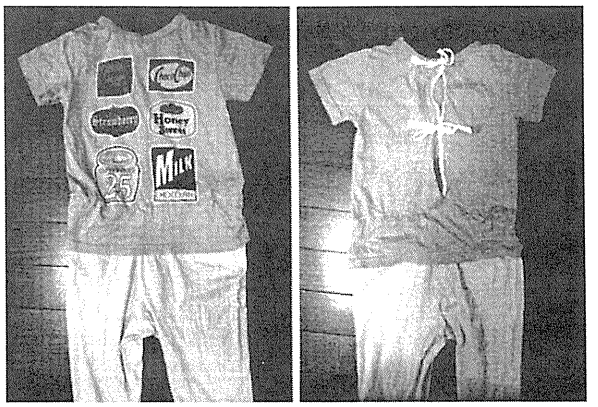

Fig. 3 Hand-made overall nightgown that directly prevents scratching.

RAST scores for mites and food antigens were low, and challenge tests of several foods with positive RAST scores did not affect eczema.

We previously reported that exposure to Japanese cedar pollen induces airborne contact dermatitis in Japanese individuals.[15-17] Exacerbation of atopic dermatitis lesions is occasionally observed after contact with airborne antigens during the pollen season.[15,16] The clinical features of airborne contact dermatitis related to cedar pollenosis usually include a characteristic appearance affecting the face and hands. The eruption frequently has a sharp demarcation at the mid-bicep level and the upper sternal V line.[16,17] Although cedar pollen dermatitis is not currently well recognized, our report and the reports of others suggest that cedar pollen is responsible for aggravation of atopic dermatitis in adult patients. However, no childhood cases have been reported in Japan.

Our current twin cases showed both high RAST score of cedar pollen and gave positive reactions to a scratch test with cedar pollen in younger sister. During the cedar pollenosis season, both twins showed pollenosis symptoms, including sneezing and eye congestion with elevated lacrymal flow and uncontrolled scratching on the face followed by aggravation of the atopic dermatitis. At present, it is very difficult to conclude whether cedar pollen directly or indirectly related to trunk lesions. Both mechanisms might be worked in the present cases.

Anti-allergic eye drops were very effective at preventing the scratching behavior along with the daily use of hand-made nightgowns, which restrains scratching directly. In addition to protective effect of cotton made-night wear from scratching, it is conceivable that it also prevent the contact with environmental factors.

It is now well recognized that barrier dysfunction and food sensitivity are the major aggravating factors in childhood atopic dermatitis.[7] However, even in childhood, appropriate diagnosis and management of

pollenosis are required to control and prevent the progression of atopic dermatitis.

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CASE REPORT

Four Cases of Atopic Dermatitis Complicated by Sjögren's Syndrome: Link between Dry Skin and Autoimmune Anhidrosis

Shun Kitaba[1], Saki Matsui[1], Eriko Iimuro[1], Megumi Nishioka[1], Akiko Kijima[1], Noriko Umegaki[1], Hiroyuki Murota[1] and Ichiro Katayama[1]

ABSTRACT

We report four adult cases of atopic dermatitis (AD) complicated by Sjögren's syndrome (SS). The patients fulfilled diagnostic criteria for AD and SS. All cases showed persistent itchy dry skin and eczematous lesions complicated by sicca symptoms including dry eyes and dry mouth with moderate joint pain. One case manifested annular erythema and another manifested widespread discoid erythema. To investigate the underlying cause of dry skin in these cases, sweating function was evaluated using a quantitative sudomotor axon reflex test (QSART) in which the axon reflex is stimulated by acetylcholine iontophoresis. The sweating latency time was significantly prolonged in eczematous skin of AD and AD/SS compared to normal controls. Axon reflex (AXR) sweat volume was also significantly reduced in AD (normal and eczematous skin) and AD/SS (normal and eczema) compared to normal control. In contrast, the direct sweat volume of lesional or non-lesional AD skin induced by direct stimulation with acetylcholine was only slightly reduced compared to that in normal controls, but not in SS and lesional skin of AD/SS patients. These results suggest that the impaired sweat response in AD is attributable to an abnormal sudomotor axon reflex, which is accelerated and modulated when complicated by SS resulting in dry skin in the present cases.

KEY WORDS

atopic dermatitis, dry skin, hypohidrosis, QSART, Sjögren's syndrome

INTRODUCTION

Dry skin, immunological dysfunction, increased IgE production, and an autonomic nervous system imbalance are frequently observed in patients with atopic dermatitis (AD), along with bronchial asthma or pollenosis, which have closely related genetic risk factors. Recent reports suggest that common loss-of-function variants of the epidermal barrier protein filaggrin are major genetic risk factors for AD.[1-3] Sjögren's syndrome (SS), another representative autoimmune disease with hypohidorosis, also manifests dry skin and might exacerbate dry skin in the setting of AD. Although the prevalence of AD and SS in the general population is not low, complication of these diseases has been rarely documented. We report sweat function in four cases of AD associated with SS (AD/SS).

CLINICAL SUMMARY

All patients fulfilled the diagnostic criteria for AD[4] and SS,[5] including moderate to severe, persistent itchy skin lesions and sicca symptoms of dry eyes and dry mouth with moderate joint pain. One case manifested annular erythema and another manifested widespread discoid erythema. Clinical profiles of the four patients are described in Table 1, 2, and clinical features are shown in Figure 1. The profile of Case 3 was described elsewhere.[6]

With the Institutional Review Board approval, a

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Table 1 Clinical data related to atopic dermatitis

Case No.	Age	Gender	SCORAD	TARC (pg/ml)	IgE-RIST (IU/L)	Eosinophil (%)	Eosinophil (mm^3)
1	29	female	35.2	497	298	3.7	192
2	32	female	49.5	1,596	6,790	14.1	1,112
3	32	female	60.3	2,363	15,300	6.3	306
4	17	male	25.3	224	124	7.3	392

SCORAD, severity scoring of atopic dermatitis; TARC, Thymus and activation regulated chemokine/CCL17 (pg/ml: normal < 400).

Table 2 Clinical data related to Sjögren's syndrome

Case No.	Schirmer's test	Conjunc-tivitis	Lip biopsy (grade)	Gum test (ml/10 minutes)	Positive findings of salivary gland scintigram	Anti-S SA ab (U/ml)	Anti-S SB ab (U/ml)	IgG (mg/dl)	ANA	Anti DNA ab (IU/ml)
1	+	+	ND	5	-	-	62.1	1,633	-	-
2	+	+	ND	8	+	101	41.7	2,178	×80	-
3	+	+	3	8	+	68	-	4,478	×80	-
4	-	-	3	9	ND	122	183	1,727	×1280	-

ND, not done; ab, antibody.

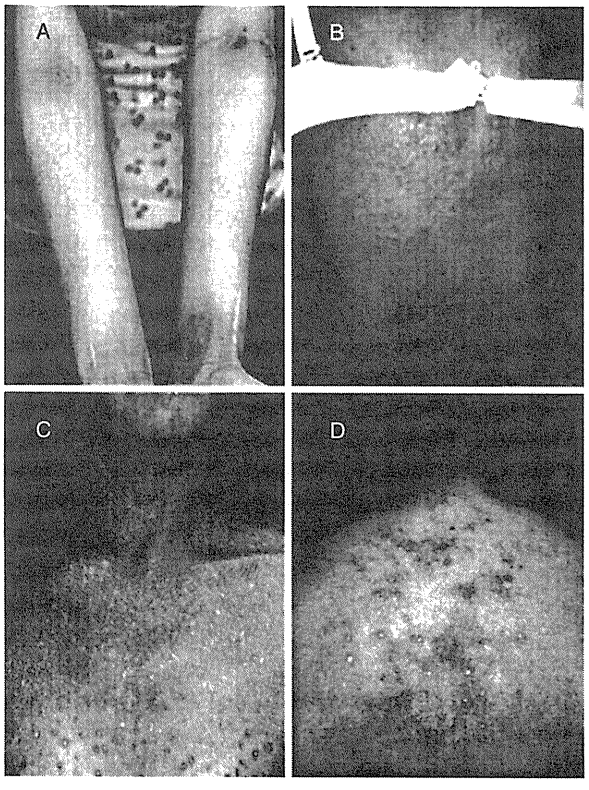

Fig. 1 Clinical appearance of the patients. (**A**) Patient 1: Lichenified and crusted lesions are present on the cubital fossa and wrist, (**B**) Patient 2: Diffuse erythema and lichenified eczematous lesions are observed on the trunk skin, (**C**) Patient 3: Diffuse erythematous scaly patches with crusted and papular eruptions were observed on her face, scalp, and dorsal aspect of the hands, and (**D**) Patient 4: Pruriginous crusted papules are present on the back.

quantitative sudomotor axon reflex test (QSART) in which the axon reflex is stimulated by acetylcholine iontophoresis was performed as described previously.[7] Briefly, the subjects were asked to remain quiet in the measurement room before undergoing QSART. The two-channel type perspirometer (POS-02, Skinos, Co. Ltd., Nagoya, Japan) was used for the measurement of sweat volume. Acetylcholine induced-QSART (AXR sweating) was measured after iontophoretical application of acetylcholine (100 mg/ml) to the skin from the outer capsule using CI-5.0 (Skinos, Co.Ltd.). AXR sweat volume in the inner capsule separated by plastic wall from outer capsule was measured during 5 min of iontophoresis. Data for DIR sweating were obtained over the subsequent 5 min. Sweat onset time, i.e., the latency period from current loading to sweating (latency time), and sweat volume over 5 min were measured, and the area under the sweating curve was calculated during 0-5 min for AXR sweating and 6-11 min for DIR sweating (Table 3).

The latency time was significantly prolonged in AD (eczema) and AD/SS (eczema) compared to normal controls (N, Fig. 2) and AXR sweat volume was also significantly reduced in AD (normal and eczema) and AD/SS (normal and eczema) compared to normal controls (N, Fig. 3). In contrast, the DIR sweat volume of lesional or non-lesional AD skin was only slightly reduced compared to that in non-atopic controls, but that of lesional skin of AD/SS was apparently decreased without statistical significance (Fig. 4). These results suggest that the impaired sweat response in AD is attributable to an abnormal sudomotor axon reflex, which is accelerated and modulated when complicated by SS.

Table 3 Measured values in quantitative sweat tests

Case No.	Latency (NL) seconds	Latency (L) seconds	AXR (NL) mg/5 minutes	AXR (L) mg/5 minutes	DIR (NL) mg/5 minutes	DIR (L) mg/5 minutes
1	107	143	0.145	0.354	1.224	0.735
2	143	155	0.314	0.367	1.775	2.801
3	170	161	0.353	0.388	2.455	0.975
4	120	300	0.785	0.040	6.839	0.543

NL, non-lesional skin; L, lesional skin.

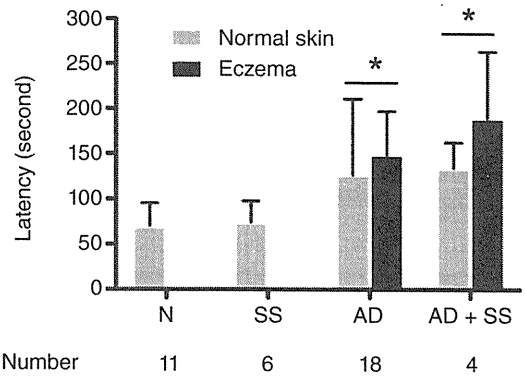

Fig. 2 Quantitative sweating test. Quantitative sweating test was performed as previously described.[7] Latency period (seconds) in normal skin (normal control, SS, AD, and AD/SS) and lesional eczematous skin (AD and AD/SS). One-way ANOVA was used for the statistical analysis. *$p < 0.05$. AD (eczema) to normal control (N), AD/SS (eczema) to normal control (N), AD (eczema) to SS, and AD/SS (eczema) to SS. Number: case number.

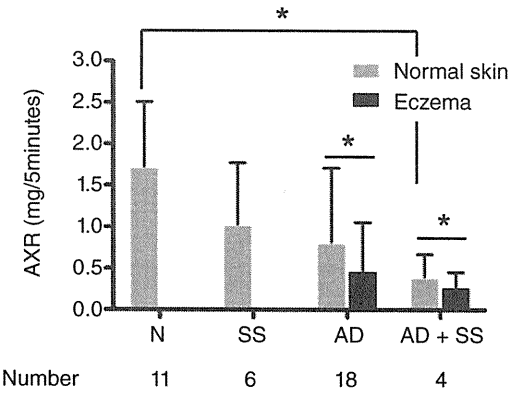

Fig. 3 Sweat volume of AXR in normal skin (normal control, SS, AD, and AD/SS) and lesional eczematous skin (AD and AD/SS). One-way ANOVA was used for the statistical analysis. *$p < 0.05$ AD to normal control (N) and AD/SS to normal control (N). Number: case number.

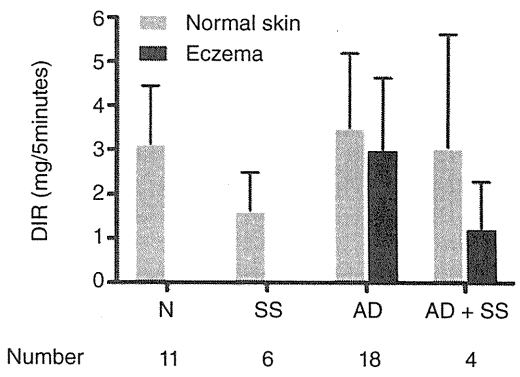

Fig. 4 Sweat volume of DIR in normal skin (normal control, SS, AD, and AD/SS) and lesional eczematous skin (AD and AD/SS). Number: case number.

DISCUSSION

Although the prevalence of adult atopic dermatitis in Japan is 6.9%,[8] complication of AD by SS is relatively rare and few case reports are available in the literature except in the setting of SLE.[9,10] The involvement of Th17 cells in both SS[11] and AD,[12] as well as the Th1 and Th2 balance theory are thought to be responsible for the rare complication of these allergic and systemic autoimmune diseases. Although it is conceivable that complication of two diseases is coincident, recent reports suggest ANA positivity in atopic dermatitis.[13] Therefore Sjögren's syndrome might exist in this populations of atopic dermatitis.

We previously reported that sweating function is impaired in patients with AD and primary SS compared to normal controls.[7,14] In SS, sweating induced by both the direct action of acetylcholine and the axon reflex is impaired, possibly due to eccrine gland dysfunction resulting from autoimmune mechanisms mediated by CD8 T cells[15] or M3 receptor-specific autoantibodies[16] as previously described. In contrast to SS, the reduced sweating function seen in AD is restricted only to axon reflex-induced indirect sweating, which is usually restored to normal levels after improvement of the dermatitis.[7] Therefore, xerotic skin lesions seen in the present cases might be due to additive AD- and SS-related hypohidrosis with accelerated dry skin. It is well known that dry skin is occa-

sionally seen in SS and clinical use of muscarinic M3 receptor agonists occasionally improves this condition through recovery of sweating function.[17]

In regard to the sweating function in AD, it is well known that sweating may cause itching and secondary eczema; however, the results of previous studies on sweat-gland function in AD are controversial. Sweat secretion has been reported to be decreased,[18,19] increased,[20,21] or normal[22] in various experimental studies of AD. Our previous observation on sweating function using QSART clearly demonstrated that reversible impairment of sweating function is present in AD. Most previous investigations assessed sweating function using a direct stimulation sweating test in which intradermal acetylcholine injection resulted in direct sweat responses.[17-19] To clarify sweat function in AD, we evaluated the postganglionic sweat output, which reflects axon reflex-mediated sweating function, using QSART. In the present cases, AXR sweat volumes were reduced and latency time prolonged in both non-lesional and lesional skin of AD/SS patients compared to those in non-atopic controls, and the reduction was greater in AD/SS. In contrast to patients with AD, the DIR response characterized by exocrine gland dysfunction in patients with SS,[14,23,24] was significantly reduced compared to that in normal AD skin or healthy controls. The reason for normal DIR in normal skin of AD/SS patient is unclear at present. The presence of atopic skin lesions may modulate sweating function in normal skin of AD/SS by possible compensatory mechanisms.

Recent reports have suggested that the barrier function, including TEWL, recovers or that ceramide content in the stratum corneum return to normal levels when eczematous changes resolve.[25,26] Possible tolerance to cholinergic stimulation, manifesting as a higher sudomotor nerve excitation threshold or negative feedback, may be controlled in patients with severe AD by psychosomatic or unknown factors that could be therapeutic targets in adults with refractory disease. Although complication of AD by SS disease has been rarely documented, it might be underestimated or overlooked in daily practice. For the skin care in AD, the complication of SS should be monitored, especially in adult AD patients.

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Lichen aureus responding to topical tacrolimus treatment

Dear Editor,

Lichen aureus (LA) was originally reported in 1958,[1] and is characterized by persistent, grouped lichenoid papules or plaques having a distinctive rust, copper, or burnt orange color, and is generally localized in a circumscribed area. While the capillary fragility,[2] perforator vein incompetence,[3] and adverse effects of certain drugs were thought to be possible causes of this skin disorder, the underlying cause remains unknown. Therefore, a definitive cure for LA has not been established.

A 34-year-old man presented with rust colored macules on the dorsal surface of both feet, which had persisted for 10 years and were not preceded by trauma. He had received a certain oral anti-platelet treatment continually after the diagnosis of pigmented purpura; however, this treatment had offered no benefit.

The patient visited our outpatient clinic with intractable macules but with no other subjective symptoms. Examination indicated lesions up to about 1 cm in diameter, rust-colored, sharply defined, and slightly elevated. Some macules had fused with induration and were distributed over the whole dorsal surface of the feet and malleoli (Fig. 1a). The biopsy specimen from lesional skin on the right dorsal foot showed thinning of the epidermis without spongiosis or epidermal exocytosis; a lymphohistiocytic band was present in the upper dermis with interspersed extravasated erythrocytes and an increased number of siderophores in the mid-dermis (Fig. 2). Analysis of the T-cell receptor gene rearrangement to rule out mycosis fungoides[4] yielded a negative result. From these clinical and histopathological manifestations, this case was diagnosed as LA. Oral administration of 100 mg/day minocycline for 6 months, prescribed

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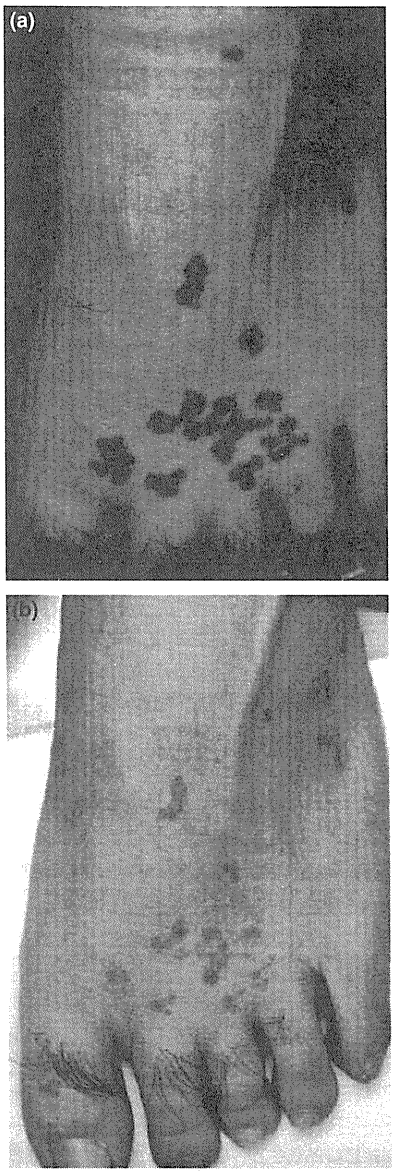

Figure 1. Clinical manifestation of skin lesion on left dorsal foot. (a) Before treatment. (b) After 1 year of topical tacrolimus application.

due to its anti-inflammatory action, had no effect; therefore, topical 0.05% clobetasol propionate ointment was added. After 3 months of this combination therapy, depigmentation around the individual macules was observed but the macules themselves were not affected. Thus, topical 0.1% tacrolimus ointment was applied to the skin lesion after cessation of minocycline and 0.05% clobetasol ointment.

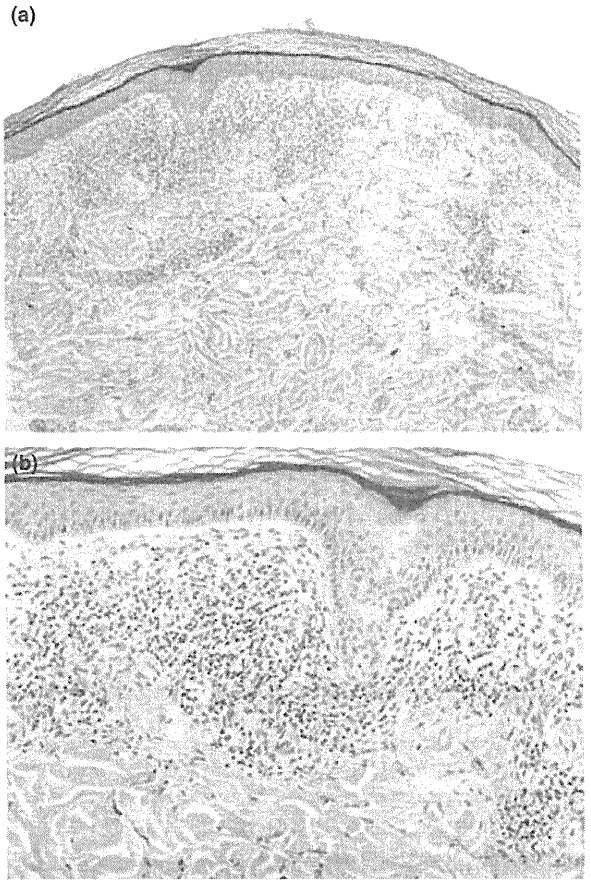

Figure 2. Histologic features of a biopsy specimen from a skin lesion on right dorsal foot. (a) magnification, ×80; (b) magnification, ×200.

Improvement in the color of the skin lesion was observed after 3 months of tacrolimus ointment application. One year of continual topical application of tacrolimus ointment improved the rust-colored macules to almost healthy skin color, and caused the induration to disappear (Fig. 1b). At the 6-month follow-up after completion of therapy, exacerbation of LA has not been observed.

Lichen aureus is a chronic, persistent pigmented intractable purpuric dermatitis. Historically, topical immunosuppressive agents, oral administration of vasodilators (e.g. pentoxifylline or prostacyclin), and phototherapy have been used to treat LA, and have been reported to achieve symptomatic improvement. However, regarding the topical immunosuppressive agents, the effect of topical corticosteroids

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for LA is controversial.[5,6] Böhm *et al.*[5] reported one case of a responder to topical pimecrolimus. Such topical treatment may be patient-friendly, but topical pimecrolimus is not approved in Japan. Together with our report, it is assumed that treatment strategy targeting calcineurin might be effective for topical corticosteroid-resistant cases of LA. Psoralen-ultraviolet A (PUVA) therapy also has been reported to improve LA, possibly via its immunosuppressive action.[7] Thus, the immune system might be a therapeutic target for LA, and our case suggests that topical tacrolimus might be a candidate therapeutic agent.

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Rare presentation of human orf as multiple lesions

Dear Editor,

Although the clinical picture of orf is usually characterized by a solitary lesion, we report a case with four lesions on their fingers. A 34-year-old man was referred with a 10-day history of mildly painful lesions on the tip and the dorsa of fingers. The lesions consisted of a raised granulomatous mass with a violaceous center, a white middle ring, and a red periphery (Fig. 1). The lesions measured 5–10 mm in diameter, initially in the right hand with subsequent spread to the left hand. Regional lymphadenopathy was present. No pathology was found in systemic examination. Complete blood count (CBC) and plain X-rays were within normal limits. With the characteristic lesion after history of contact with sheep, orf was diagnosed. The lesions were managed conservatively (adequate analgesia, wound care with povidone-iodine and mupirocin cream). The lesions resolved in 33 days without residual scarring or any complications. This clinical course also verified the diagnosis of orf.

Orf, which is caused by a Parapox virus, is acquired through direct contact with the virus via infected animals or fomites, including fences, barn doors and feeding troughs.[1] Instead of being reported simply as

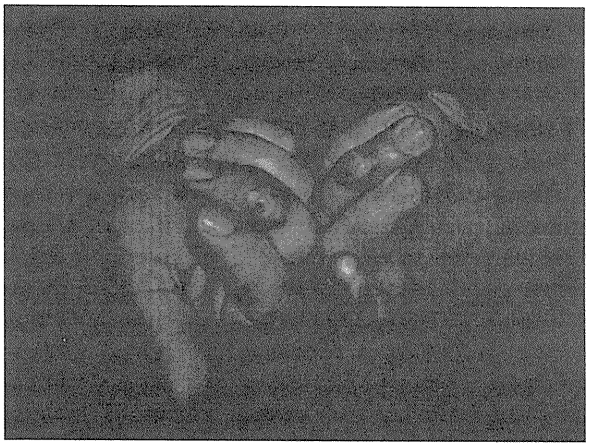

Figure 1. Multiple orf lesions on the hands of our case.

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CASE REPORT

Clinical effect of tocoretinate on lichen and macular amyloidosis

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ABSTRACT

Lichen amyloidosis and macular amyloidosis are commonly therapy-resistant. Tocoretinate is a hybrid compound of retinoic acid and tocopherol that is commonly used for the treatment of skin ulcers. Although beneficial effect of oral retinoic acid on lichen amyloidosis is reported, tocoretinate has not been reported to be useful for the treatment of lichen amyloidosis or macular amyloidosis. We evaluated the effects of topical tocoretinate on lichen amyloidosis and macular amyloidosis lesions. Tocoretinate was topically applied daily to the lesions and clinical improvement and histological changes were evaluated. The outcome was very good for four, good for two, moderate for two and poor for two of 10 treated patients. Epidermal hypertrophy was reduced and expression of involucrin, keratin 1 and keratin 10 was decreased by tocoretinate treatment, suggesting the normalization of epidermal differentiation. Amyloid deposits remained histologically detectable, even in clinically responsive patients. Together, topical application of tocoretinate reduced the clinical symptoms of lichen amyloidosis and macular amyloidosis, and normalized disturbed epidermal differentiation.

Key words: lichen amyloidosis, macular amyloidosis, retinoic acid, tocoretinate.

INTRODUCTION

Lichen amyloidosis (LA) and macular amyloidosis (MA) are primary localized cutaneous amyloidosis characterized by chronic hyperkeratotic hyperpigmented itchy papules and macules.[1,2] Histologically, amyloid deposits which are thought to be composed of degenerated keratin peptides are observed in the papillary dermis.[3] LA and MA commonly co-occur with other skin disorders such as atopic dermatitis (AD).[4]

Although topical corticosteroid is an effective treatment for milder cases of LA and MA, treatment of the majority of cases is unsatisfactory. Alternative treatments include topical dimethylsulfoxide (DMSO),[5] tacrolimus,[6] calcipotriol,[7] oral acitretin,[2,8] cyclosporine,[4] cyclophosphamide,[9] cepharanthine,[10] phototherapy (ultraviolet B, psoralen and ultraviolet A therapy),[8] laser therapy,[11,12] surgical therapy[13] and hydrocolloid dressings.[14] Herein, we evaluate the effects of topical tocoretinate, a synthetic esterified compound of tocopherol and retinoic acid, on the LA and MA lesions of 10 patients.

METHODS

Patients

Ten patients (seven men and three women) diagnosed with LA or MA by biopsy were included in this study (Table 1). Written informed consents were taken from every patient. Amyloid deposits were confirmed by thioflavin T staining. The mean age was 43 years (range 23–66), and the mean disease duration was 7.5 years (range 3–30). Nine patients had received previous treatment with topical corticosteroid. Five patients also had atopic dermatitis, and one

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Table 1. Characteristic features and outcome of lichen amyloidosis and macular amyloidosis patients treated with tocoretinate

Patient	Sex	Age (years)	Disease duration (year)	Type	Localization	Complication	Previous treatment	Improvement (month)	Outcome
1	M	28	3	LA and MA	Forearm, chest, upper back	AD	Topical steroid	2	Very good
2	M	35	30	LA	Forearm	AD	Topical steroid	1	Very good
3	M	47	15	LA	Upper arm	–	Topical steroid	1	Very good
4	M	66	3	MA	Upper back	–	Topical steroid	1	Very good
5	F	23	2	MA	Leg, upper back	AD	Topical steroid	1	Good
6	M	60	10	LA	Upper arm	–	Topical steroid	4	Good
7	F	36	3	LA	Leg	AD	–	3	Moderate
8	F	52	3	LA	Leg	–	Topical steroid	4	Moderate
9	M	33	3	LA and MA	Upper back	AD	Topical steroid	–	Poor
10	M	50	3	LA	Leg	RA	Topical steroid	–	Poor

AD, atopic dermatitis; LA, lichen amyloidosis; MA, macular amyloidosis; RA, rheumatoid arthritis.

had rheumatoid arthritis. Tocoretinate was topically applied to the LA or MA lesion of each patient twice a day and the outcome was evaluated every month.

Measurement of involucrin (IVL) and nerve growth factor (NGF) levels

Normal human epidermal keratinocytes (NHEK) were purchased from DS Pharma Biomedical (Osaka, Japan) and cultured in Human Keratinocyte Serum Free Medium (DS Pharma Biomedical) at 37°C with 5% CO_2. Culture dishes precoated with type 1 collagen (Asahi Techno Glass, Funabashi, Japan) were used to plate cells. Tocoretinate was provided by Kayaku (Saitama, Japan) and diluted in acetone. Tocoretinate at the concentration of 10 μmol/L or 100 nmol/L was added to the medium and the same concentration of acetone was added to the control sample. Cells were collected 6 h later. RNA was isolated using the SV Total RNA Isolation System (Promega, Madison, WI, USA). The product was reverse-transcribed into first-strand complementary DNA (cDNA). Thereafter, the expressions of IVL and NGF were measured using the Power SYBR green PCR Master Mix (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used to normalize the mRNA levels. Sequence-specific primers were designed as follows: IVL sense 5′-tctgcctcagccttactgtg-3′ and antisense 5′-ggaggaggaacagtcttgagg-3′; NGF sense 5′-cagttttaccaaagggagcagctt -3′ and antisense 5′-caacatggacattacgctatgca-3′; and GAPDH sense 5′-tgtcatcatacttggcaggtttct-3′ and antisense 5′-catggccttccgtgttccta-3′. Real-time PCR (40 cycles of 92°C for 15 s and 60°C for 60 s) was run on an ABI 7000 Prism (Applied Biosystems).

Immunohistochemical staining

Lichen amyloidosis lesions were biopsied before and 3 months after applying tocoretinate. The sections were fixed in formalin and embedded in paraffin. After deparaffinization and rehydration, the sections were incubated in 3% H_2O_2 for 5 min to block endogenous peroxidase activity, and the rinsed sections were boiled in 10 mmol/L citrate buffer pH 6.0 for antigen retrieval. After blocking non-specific protein binding with 2% bovine serum albumin for 10 min, the sections were stained with primary antibody: anti-filaggrin antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA), anti-involucrin antibody (Santa Cruz Biotechnology), anti-cytokeratin 1 antibody (Covance, Emiryville, CA, USA) anti-cytokeratin 10 antibody (Covance), anti-cytokeratin 14 antibody (Covance), or anti-protein gene product (PGP) 9.5 (DAKO Cytomation, Carpentaria, CA, USA) for 60 min. After washing with Tris-buffered saline (TBS) containing 0.05% Triton-X (TBST), samples were developed using the DAKO ChemMate Envision Kit/HRP (Dako Cytomation) for cytokeratins, involucrin, filaggrin statins or LSAB + System-AP (Dako Cytomation) for PGP 9.5 stain. Finally, they were counterstained with hematoxylin.

RESULTS

Three patients (30%) exhibited very good responses, two patients (20%) had good responses and three patients (30%) had moderate responses. Two

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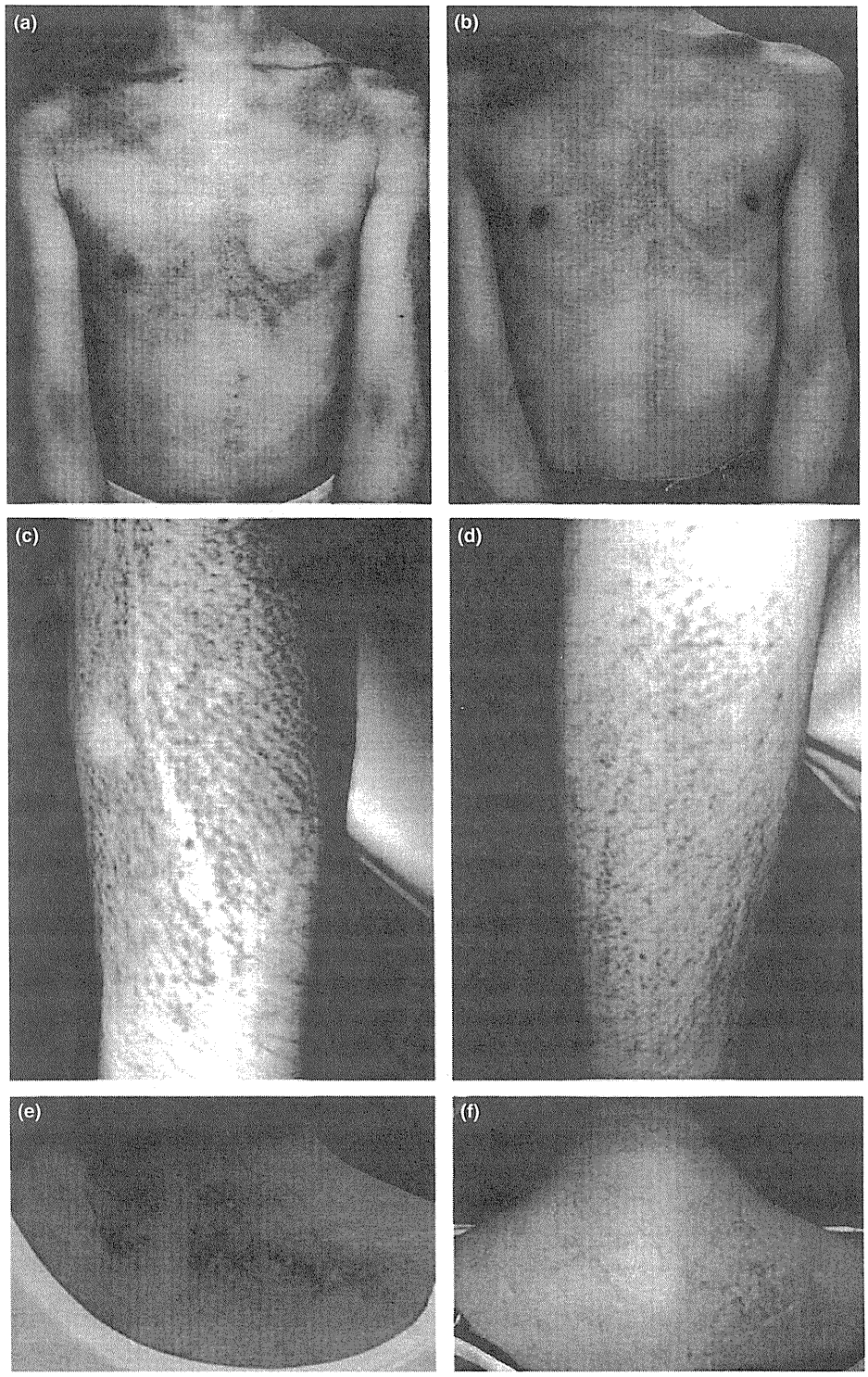

Figure 1. Clinical features of patients. Papules and macules of the chest of patient 1 before (a) and after (b) tocoretinate treatment. Papules of the forearm of patient 1 before (c) and after (d) tocoretinate treatment. Macules of the upper back of patient 4 before (e) and after (f) tocoretinate treatment.

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