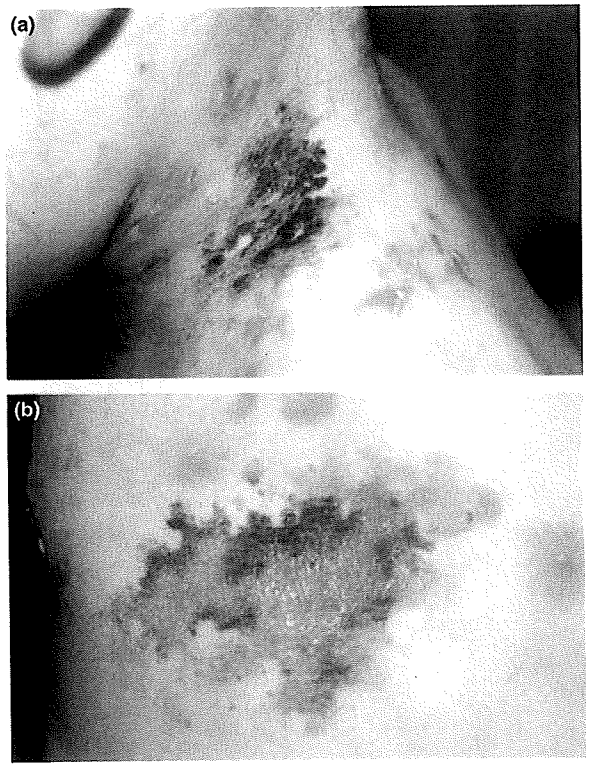

Figure 2. Irregular-shaped, asymmetrical pigmented plaques with color variegation.

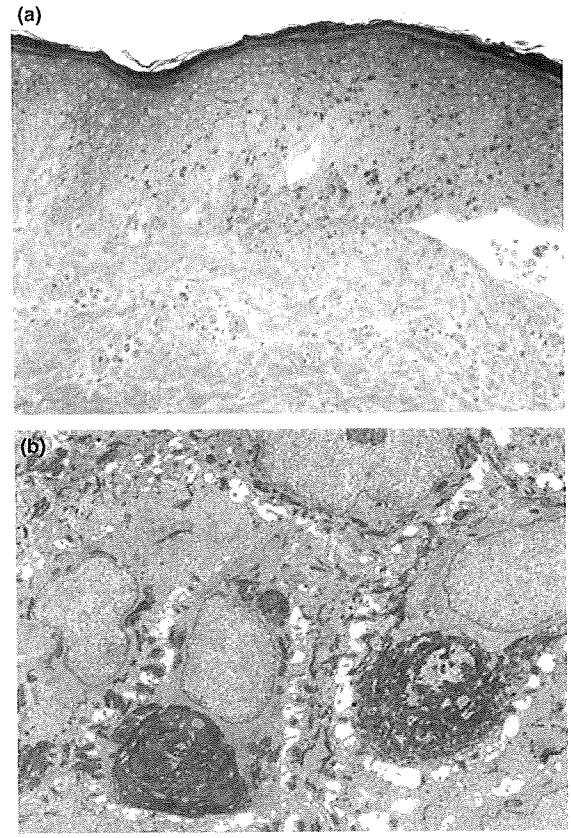

Figure 3. Intracytoplasmic inclusions in keratinocytes (a: semithin section stained with methylene blue) and aggregation of tonofilaments (b).

Histopathological observations of the pigmented lesion demonstrated the presence of small nests of nevus cells in the rete ridges of the epidermis and superficial dermis (Fig. 5a). No mitotic figures or atypical cells suggestive of malignant melanoma were found. Immunostaining revealed that the majority of nevus cells expressed MART-1, S100 and tyrosinase, and a small number of the cells expressed HMB45. Proliferating cells determined by MIB-1 staining were almost negative in the nevus cell nests (Fig. 5b–d). A considerable number of CD68-positive melanophages were present in the dermal infiltrates. The pigmented lesion was diagnosed as a compound type of EB nevus, associated with melanophage infiltration.

DISCUSSION

Twenty-two patients with EB nevus have been reported in the published work (Table 1),[1–8,11] including four patients with EB simplex, nine with junctional EB and nine with dystrophic EB. The ages

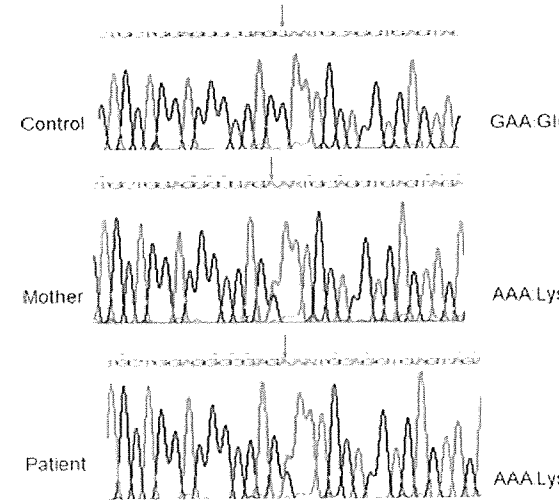

Figure 4. An E478K (Glu to Lys) mutation in exon 5 of the keratin 5 (K5) gene in the polymerase chain reaction products obtained from the mother and patients.

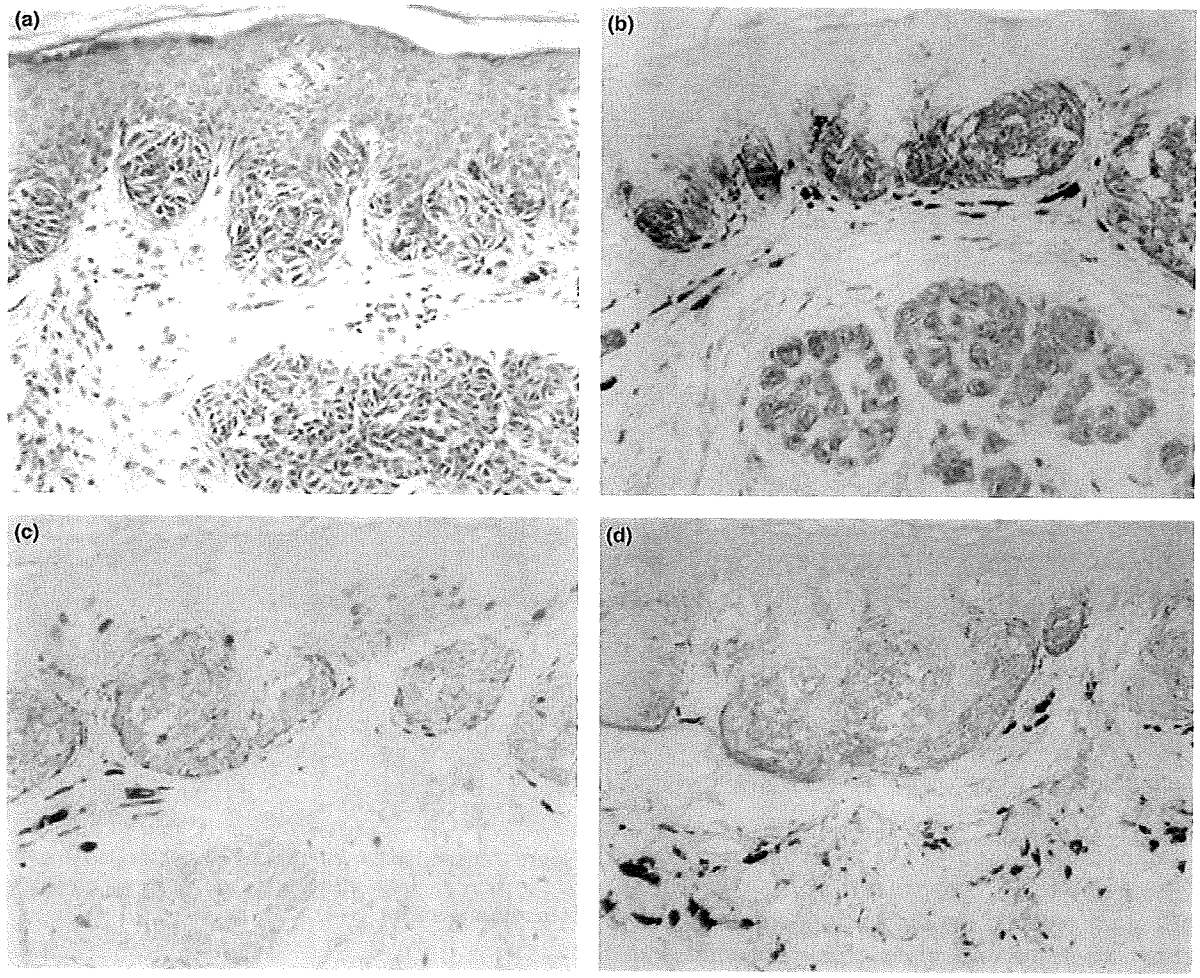

Figure 5. Small nests of nevus cells in the rete ridges of the epidermis and superficial dermis (a: hematoxylin–eosin staining). The majority of nevus cells are positive for MART-1 (b), S100 and tyrosinase, and almost negative for proliferating nuclear cell antigens (c: MIB-1 staining). Many CD68-positive melanophages are present in the dermal infiltrates (d).

of the patients ranged 1–49 years. Of the 22 patients, EB nevus occurred in the first decade in 15 patients, but there is no specific information regarding the ages of the remaining cases. No apparent difference was found in sex, anatomical regions, or histopathological types of the nevi. So far, no patient with a malignant course has been reported. In acquired blistering diseases such as pemphigus and pemphigoid, the development of EB nevus-like lesions have only been reported in an 8-year-old girl with vulvar bullous pemphigoid.[12]

Our patient had a Dowling–Meara type, epidermolysis bullosa simplex with a novel K5 mutation. Prominent palmoplantar hyperkeratosis in our patient might reflect characteristic symptoms related to the K5 mutation.[13] Her mother had had similar symptoms in childhood, but she had only a localized bulla on the arm on examination as a result of spontaneous improvements with age.

In addition to the blistering disorders, our case presented with three large, atypical, pigmented lesions associated with color variegation. The histopathological features, however, indicated a benign, compound type of pigmented nevus associated with a considerable number of melanophages in the upper dermis. It has been reported that patients with EB have asymmetrical, pigmented plaques, mimicking the clinical and dermoscopic

Table 1. Summary of the previously reported cases with epidermolysis bullosa (EB) nevus

EB major subtype	EB subtype or mode of inheritance	Age	Sex	Onset	Region	Size	Histopathological examination	Ref
EB simplex	Recessive	8	M	8 years	Forearm	12 × 5 cm	Compound nevus	5
	Dominant	25	M	Early childhood	Trunk and extremities	10 × 2 cm (leg)	Compound nevocytic nevus with junctional nests and strands of nevocytic cells in upper and mid-dermis	1
	Recessive	5		By 4 years	Left hip	egg-sized	Clark nevus, compound type	3
	With muscle dystrophy	5	M	3 years	Right thumb/thenar		Melanocytic nevus of the compound type with some features of Clark's naevus	6
Junctional EB	GABEB	10	F					11
	GABEB	21		By 10 years	Knee, axilla		Knee 1988: Compound nevus Knee 1993: Clark nevus, compound type Axilla 1994: Clark nevus, compound type Axilla 1995: Persisting nevus/pseudomelanoma	3
	GABEB	9		By 2 years	Left upper arm	palm-sized	Junctional nevus	3
	GABEB	57					Dermal nevus	3
	GABEB	60		By 49 years	Right upper inner arm		Dermal nevus	3
	GABEB	53					Dermal nevus	3
	GABEB	45		By 34 years	Left shoulder		Persisting nevus/ pseudomelanoma	3
	GABEB	22					Persisting nevus/ pseudomelanoma	3
	Recessive	9	F	9 years	Right heel		Acral naevus of compound type	6
Dystrophic EB	Hallopeau–Siemens	6	F	End of 1st year	Left hip	5.5 × 5 cm	Junctional nevus	2
	Non-Hallopeau–Siemens	1	F	End of 1st year	Left forearm	4 × 3 cm	Increased number of melanocytes in the basal layer	4
	Hallopeau–Siemens	1	F	1 year	Left forearm	4 × 4 cm	Increased number of melanocytes in the basal layer	4
	Recessive	3	M	3 years	Right lateral thigh	10 × 9 cm	Intradermal nevus	8
	Recessive	3	M	3 years	Lower back	2.6 × 1.8 cm	Compound nevus	7
	Recessive	5					Persisting nevus/ pseudomelanoma	3
	Recessive	8					Not done	3
	Recessive						Not done	3
	Recessive	16		By 14 years	Right side of the back	15 × 5 cm	1997: Persisting nevus/ pseudomelanoma 1998: Compound congenital nevus	3

features of malignant melanoma,[1–3] although they usually have a benign clinical course. There has been one reported case with recessive dystrophic EB who developed malignant melanoma and squamous cell carcinoma, but it is unclear whether the patient had a preexisting EB nevus.[14]

The occurrence of peculiar pigmented nevi associated with EB has been called EB nevus.[3,8] EB nevus might not be uncommon in patients with EB as 12 of 86 patients with EB in the Austrian EB Registry had EB nevus.[3] Of the 22 patients with EB nevus reported in the published work, two patients had the junctional

type, and eight patients had the compound type of pigmented nevus. These data suggest no association of a specific type of pigmented nevus with the development of EB nevus.

Regarding the subtypes of EB, at least eight of the 22 patients with EB nevus had a non-Herlitz type of junctional EB, and all of them had generalized atrophic benign EB (GABEB) associated with collagen type XVII (BPAG2) mutation.[3,11] Considering its rare incidence, GABEB might be more of a risk factor for the occurrence of EB nevus, although any type of EB may complicate EB nevus. In addition to junctional blistering, inherited alterations of cell–cell adherence molecules related to BPAG2 mutations might be responsible for the development of EB nevus. Unlike in our case and another reported case,[1] EB nevus seldom occurs in dominantly inherited forms of EB.[3]

Epidermolysis bullosa nevi-like eruptive melanocytic nevi have also been described in acquired blistering disorders including erythema multiforme, toxic epidermal necrolysis and Stevens–Johnson syndrome.[15–18] We have experienced a considerable number of adult patients with autoimmune blistering diseases, but we could find only one child EB nevi case associated with vulvar bullous pemphigoid in the published work.[12] These observations indicate that EB nevus may occur in conditions of repetitive blistering and remodeling in patients with inherited fragility at the dermoepidermal junction.

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A case of epidermolysis bullosa acquisita with clinical features of Brunsting-Perry pemphigoid showing an excellent response to colchicine

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Background: Brunsting-Perry pemphigoid is a rare subepidermal blistering disease characterized by scarring blisters on the head and neck. However, the identity of the responsible autoantigens is still unresolved.

Methods: We reported a patient with epidermolysis bullosa acquisita who had clinical features typical of Brunsting-Perry pemphigoid and investigated the involved type VII collagen epitopes. The patient was a 65-year-old Japanese woman with a 20-month history of recurrent subepidermal bullae on her head, face, and neck.

Results: Immunoblot studies revealed that the serum of this patient reacted with type VII collagen, specifically with the noncollagenous domain 1 and the triple-helical domain. The patient responded completely to colchicine monotherapy.

Limitations: This study was performed on only one case.

Conclusion: This study suggests that Brunsting-Perry pemphigoid may be a clinical variant of epidermolysis bullosa acquisita. (J Am Acad Dermatol 2009;61:715-9.)

Key words: Brunsting-Perry pemphigoid; epidermolysis bullosa acquisita; type VII collagen.

In 1957, Brunsting and Perry[1] described 7 patients with a localized form of cicatricial pemphigoid, characterized by pruritic chronic recurrent circumscribed vesiculobullous eruptions located on the head, face, and neck and leaving atrophic scarring. This disease is common in middle-aged and elderly populations. Skin lesions are usually confined to the head, neck, scalp, and upper aspects of the trunk. Mucous membranes are also affected in some patients.[2-5]

The identity of the responsible autoantigens in Brunsting-Perry pemphigoid is still controversial. Indirect immunofluorescence and immunoelectron microscopy has shown that some patients' sera react with a dermal antigen, suggesting that Brunsting-Perry pemphigoid is a variant of epidermolysis bullosa acquisita.[5,6] However, there has been no case report of this disease with immunoblot analyses showing reactivity with type VII collagen or bullous pemphigoid antigens, except for our reports in the Japanese literature showing reactivity of patients' sera with a recombinant protein of the 180-kd bullous pemphigoid antigen (BP180) noncollagenous (NC)16a domain.[7,8] These findings suggest that Brunsting-Perry pemphigoid is not a single disease entity but is heterogeneous.

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Conflicts of interest: None declared.

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We describe a patient who had typical clinical features of Brunsting-Perry pemphigoid, whereas the results of indirect immunofluorescence on 1-mol/L salt-split human skin sections and immunoblot analyses were consistent with a diagnosis of epidermolysis bullosa acquisita. The patient responded well to colchicine therapy. In addition, we investigated the epitopes in all the 3 structural domains of type VII collagen.

METHODS

Patient

A 65-year-old Japanese woman with diabetes mellitus showed recurrent bullous skin lesions on the head, face, and neck that had first appeared 20 months previously. According to the patient, similar bullous lesions had also appeared on the oral mucosa at the onset of the skin disease. On her first visit, there were tense blisters and crusts with erythematous and slightly atrophic scars over the face, neck, and upper aspect of back (**Fig 1**, *A* and *B*). There were no milia, and other areas and mucous membranes were unaffected. The results of laboratory tests were almost within normal limits.

Histopathologic studies

A skin biopsy specimen was taken from a spontaneously formed blister on the face. The specimen was formalin fixed and paraffin embedded. The skin sections were stained with hematoxylin and eosin in a standard protocol.

Indirect immunofluorescence on 1-mol/L salt-split skin

Normal-appearing human skin was placed for 48 hours at 4°C in 100 mL of 1-mol/L salt solution that contained 1 mmol/L of ethylenediaminetetraacetic acid, 1 mmol/L of phenylmethanesulfonyl fluoride, and 25 mmol/L of tris (hydroxymethyl)-aminomethane-hydrochloric acid (pH 7.4). The skin specimen was quickly frozen in liquid nitrogen, sectioned in a cryostat, and stained for indirect immunofluorescence with fluorescein isothiocyanate-conjugated rabbit antihuman IgG polyclonal antiserum.[4]

Immunoblot analyses

Immunoblot analyses with extracts of normal human dermis, bacterial recombinant proteins of NC1 and NC2 domains of human type VII collagen, recombinant full-length type VII collagen, and the triple-helical domain of type VII collagen were performed as described previously.[9-11] Specifically, dermal extracts containing type VII collagen were prepared using ethylenediaminetetraacetic acid-split normal-appearing skin.[9] We prepared recombinant glutathione-S-transferase fusion proteins containing the entire 1253 residues of the NC1 domain and the entire 161 residues of the NC2 domain of type VII collagen.[9] Because the two recombinant proteins of type VII collagen were not soluble in phosphate-buffered saline containing 1% Triton X-100, the pellets were further extracted by resuspending and sonicating them in 3 mL of 2-mol/L urea solution. Subsequently, the pellets were resuspended in 1 mL of Laemmli sample buffer, boiled for 5 minutes, and centrifuged. The supernatants were used for immunoblot analyses. Recombinant expression of full-length type VII collagen was performed as described previously.[10,11] The triple-helical domain of type VII collagen was prepared by pepsinization of human keratinocyte extracts.[12] In brief, full-length type VII collagen was extracted from confluent human keratinocytes cultured in the presence of ascorbic acid (50 $\mu g\ mL^{-1}$) and native triple-helical domain was generated by pepsin digestion at 4°C.

RESULTS

Histopathologic findings

A histopathologic examination showed a subepidermal blister formation that contained numerous eosinophils and neutrophils. Distinct fibrosis with loss of elastic fibrils was detected under the blister, surrounded by a sparse mixed infiltrate of lymphocytes, histiocytes, eosinophils, and neutrophils (Fig 1, *C*).

Immunopathologic findings

Indirect immunofluorescence on normal-appearing skin sections showed circulating IgG antiepidermal basement membrane zone antibodies that reacted with the dermal side of an artificial blister on 1-mol/L salt-split human skin sections (Fig 1, *D*). In immunoblotting with extracts of normal human dermis, the patient's serum reacted with a 290-kd antigen that was identical to that detected by control epidermolysis bullosa acquisita serum, showing IgG antibodies reactive with type VII collagen (Fig 2, *A*). Immunoblotting using recombinant protein confirmed the reactivity of the patient's serum with the full-length type VII collagen (Fig 2, *C*). In immunoblot analyses using recombinant proteins of NC1 and NC2 domains of type VII collagen, the IgG antibodies from the patient's serum showed a clear reactivity with the NC1 domain but not with the NC2 domain (Fig 2, *B*). In immunoblotting using pepsin-treated procollagen VII, the patient's serum reacted with the central triple-helical collagenous domain,[13] although the reactivity was relatively mild (Fig 2, *C*). The patient's serum (both IgG and IgA) did not show any positive reactivity with the recombinant proteins of

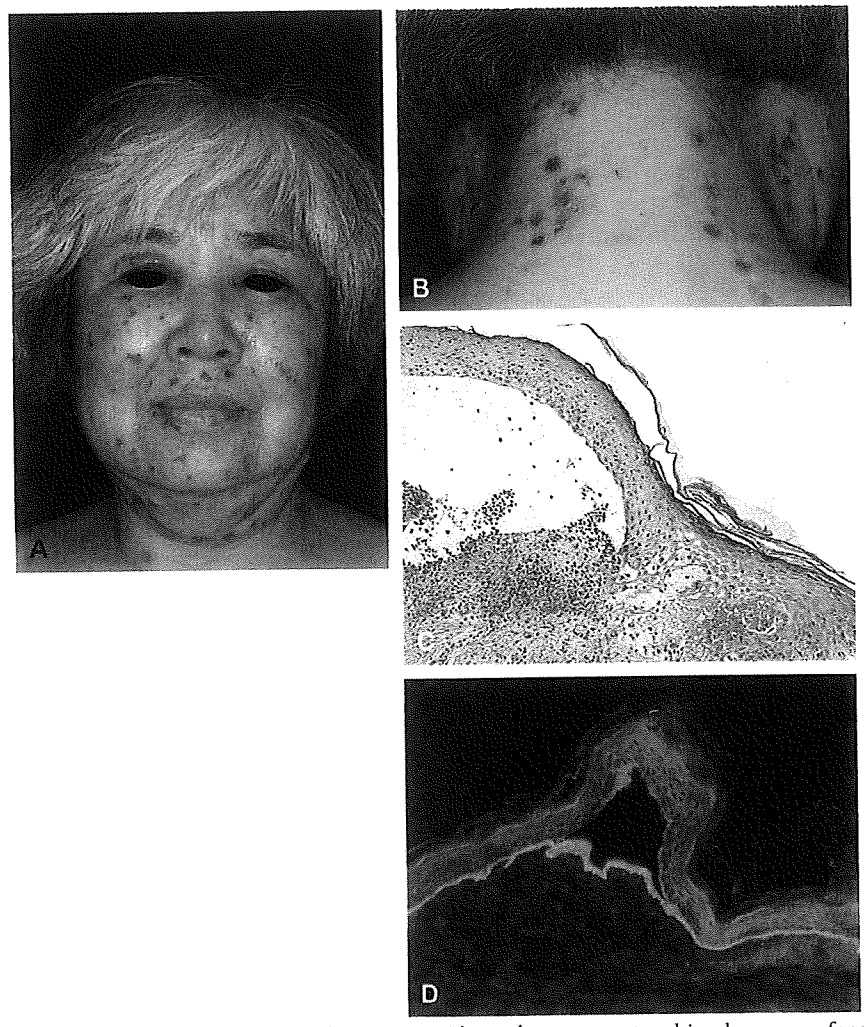

Fig 1. Clinical features: blisters and erosions with erythematous atrophic plaques on face (**A**) and neck (**B**). Histologic examination showed subepidermal blister formation with infiltration of numerous eosinophils (**C**). Indirect immunofluorescence on 1-mol/L salt-split human skin sections showed that IgG antibodies reacted with dermal side of artificial blister (**D**).

either BP180 NC16a domain or BP180 C-terminal domain (data not shown).[14,15] The IgG antibodies of the patient's serum did not react with any subunit of laminin 332 (formerly laminin 5) in immunoblotting using purified laminin 332 (data not shown).[16]

Clinical response

Systemic steroid administration was avoided because of the possible exacerbation of diabetes mellitus. Topical corticosteroids and an administration of dapsone (50 mg/d) showed no significant effect. Because of the results of the immunoblot analyses, an administration of colchicine (1 mg/d), which has been shown to be effective in epidermolysis bullosa acquisita,[17-19] was initiated. Blister formation quickly ceased, leaving mild scarring within a month, and the patient remained free from skin lesions on this regimen.

DISCUSSION

To our knowledge, this is the first reported case of epidermolysis bullosa acquisita with clinical features of Brunsting-Perry pemphigoid, in which reactivity with type VII collagen was confirmed by immunoblot analyses. Since the original description by Brunsting and Perry[1] in 1957, 57 cases have been described with vesiculobullous lesions located on the head and neck that left atrophic scarring.[4,5,12,20] Among these cases, only one previous report has confirmed reactivity with type VII collagen by immunoblotting.[5] However, clinical features of this case were not typical of

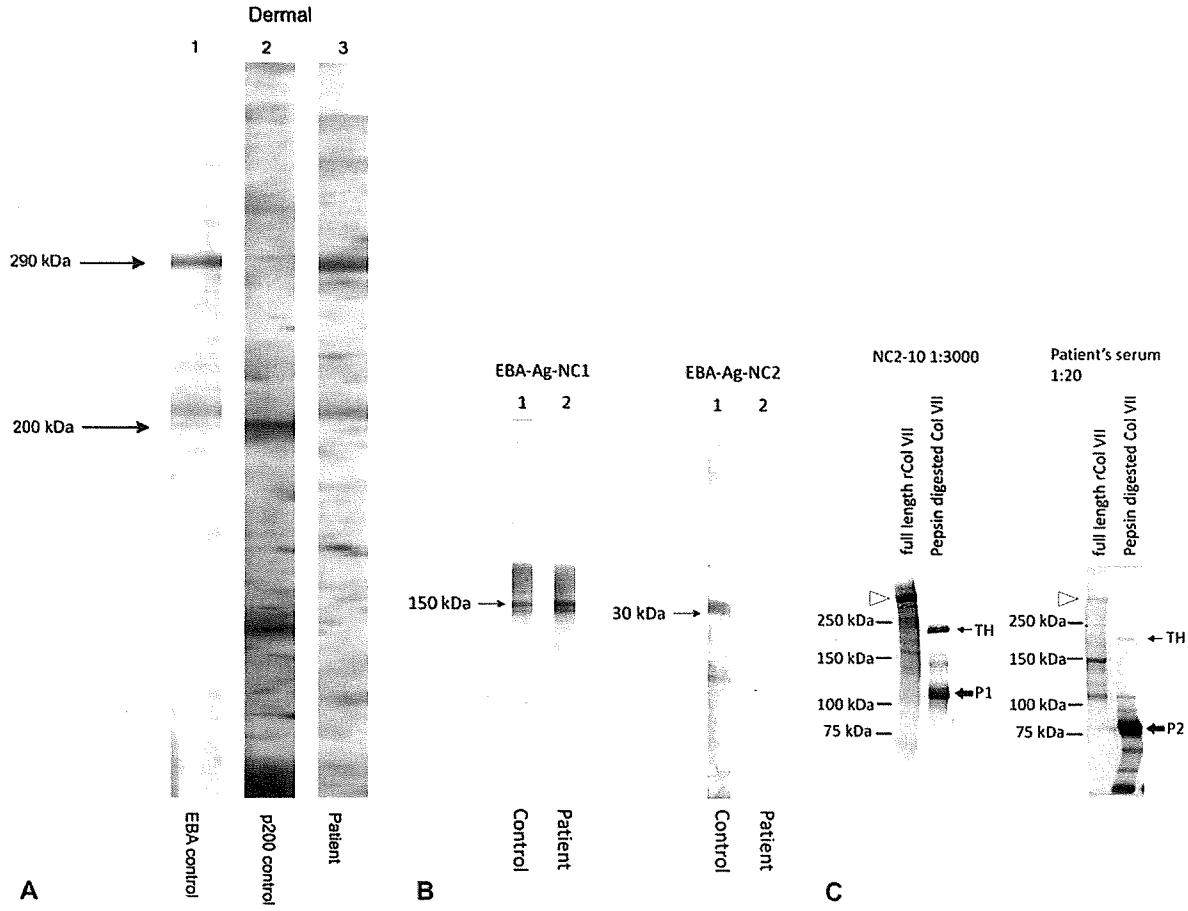

Fig 2. A, Immunoblotting using normal human dermal extracts. Both control epidermolysis bullosa acquisita (*EBA*) serum (*lane 1*) and patient serum (*lane 3*) reacted with 290-kd EBA antigen (*Ag*), ie, type VII collagen (*Col*) (*arrow*), whereas control anti-p200 pemphigoid serum reacted only with 200-kd Ag (*lane 2*). **B**, Immunoblot analyses using recombinant proteins of noncollagenous (*NC*)1 and NC2 domains. Control EBA serum (*lanes 1*) reacted with both NC1 (*left*) and NC2 (*right*) domains of type VII Col. IgG antibodies in our patient's serum (*lanes 2*) showed clear reactivity with NC1 domain, but not with NC2 domain. **C**, Immunoblotting using pepsin-treated pro-Col VII (7% sodium dodecyl sulfate [SDS]). Control polyclonal antibody (NC2-10) (*left*), which recognizes C-terminus of type VII Col, reacted with recombinant protein of full-length type VII Col (*arrowhead*). Also, control antibody mainly recognized full triple helix (*TH*) (*arrow*) of pepsin-digested Col VII and peptide 1 (P1)-fragment of TH.[13] Patient's serum (*right*) mainly recognized full-length type VII Col, TH, and shorter peptide 2 (P2)-fragment, although intensities of bands of full-length type VII Col and TH were relatively weak. For technical reasons, bands do not exactly correspond to one another.

Brunsting-Perry pemphigoid. In addition, this case reacted not only with type VII collagen but also with laminin 332.

Immunoblotting using bacterial recombinant proteins and cell-derived fragments of type VII collagen revealed that the patient's IgG antibodies reacted with the NC1 domain and the triple-helical collagenous domain of type VII collagen. The former reaction is common in typical cases of epidermolysis bullosa acquisita. Whether this set of antigenic sites is specific for the clinical features of Brunsting-Perry pemphigoid remains to be determined in more patients in the future.

In the Japanese literature, there are 3 cases of Brunsting-Perry pemphigoid showing reactivity with a recombinant protein of BP180 NC16a domain by immunoblot analyses.[7,8] These results, in conjunction with the results in our study, suggest that Brunsting-Perry pemphigoid is a heterogeneous disease in regard to antigenic features.

Historically, autoimmune bullous diseases, including epidermolysis bullosa acquisita and

Brunsting-Perry pemphigoid, were diagnosed by their clinical manifestations.[21] However, current molecular biological techniques have changed the diagnostic approach and, as a result, some confusion exists concerning definitive diagnosis of some cases. Several reports suggest that Brunsting-Perry pemphigoid may be a clinical variant of epidermolysis bullosa acquisita.[2-6] Generally, the localization of lesions varies in patients with bullous dermatoses and might also be affected by subclass switching and intermolecular epitope spreading during long-term disease.[22] The current case showed typical clinical features of Brunsting-Perry pemphigoid. However, we ultimately diagnosed this case as epidermolysis bullosa acquisita with a Brunsting-Perry pemphigoid-like presentation because of the results of the molecular analyses.

It might then be asked whether application of current molecular biological techniques in the diagnoses of autoimmune bullous disease makes Brunsting-Perry pemphigoid an illusion? We do not think so. Rather, molecular dermatology has never fully revealed the basis for the localized skin manifestations of this disease, which was determined originally by traditional descriptive dermatology. Our careful observation and scientific exploration based on our predecessors' description have elucidated the pathogenesis of this unique disease at the molecular level.

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Ichthyosiform eruptions in association with primary cutaneous T-cell lymphomas

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None declared

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Summary

Background Malignant lymphoma is occasionally complicated by ichthyosiform eruptions.

Objectives To analyse histopathologically the ichthyosiform eruptions associated with cutaneous lymphomas.

Methods We reviewed the files of patients with malignant lymphoma seen in our dermatology department between January 2001 and May 2006 to search for patients with ichthyosiform eruptions.

Results In our series, nine of 106 patients with malignant lymphomas had ichthyosiform eruptions during their clinical courses, including three (30%) of 10 patients with anaplastic large cell lymphoma (ALCL) and six (14%) of 44 patients with mycosis fungoides (MF). None of the 18 patients with cutaneous B-cell lymphoma had ichthyosiform eruptions. The three patients with ALCL had ichthyosiform eruptions histopathologically consistent with acquired ichthyosis (AI) in which packed horny layers and thin granular layers were present without lymphocytic infiltration. In contrast, four of the six patients with MF (stages Ib and IIb) had ichthyosiform eruptions with epidermotropic infiltration of atypical lymphocytes, as observed in ichthyosiform MF (IMF). Of the remaining two patients, one showed histopathological features overlapping AI and IMF, and the other had AI alone. These two patients (stages IVa and IIb) had tumours composed of CD30+ cells. Filaggrin expression was markedly diminished in both AI and IMF-like eruptions, similar to that of inherited ichthyosis vulgaris

Conclusions Ichthyosiform eruptions are often associated with ALCL and MF and can be classified into three groups: AI associated with ALCL and MF expressing CD30, IMF, and their overlap.

Acquired ichthyosis (AI) is a reactive cutaneous manifestation associated with malignant and nonmalignant diseases that occur in adulthood [1–3] Patients with AI usually present with pityroid and rhomboid scales on the trunk and extremities. The histopathological findings show compact or laminated orthohyperkeratosis and epidermal atrophy with thinning or loss of granular layers, while no cell infiltration is observed in the dermis or epidermis. AI is a frequent complication of Hodgkin lymphoma, characterized by the appearance of CD30+ atypical cells.[3–5] CD30+ lymphoproliferative disorders, such as anaplastic large cell lymphoma (ALCL) and lymphomatoid papulosis (LyP), are also associated with AI [6–8]

In contrast, ichthyosiform mycosis fungoides (IMF) is a variant of mycosis fungoides (MF), arising in 1·8–3·5% of MF patients.[9,10] Although the clinical features of IMF are indistinguishable from those of AI, the histopathological findings reveal epidermotropic infiltrates composed of cerebriform lymphocytes typical for MF.[9–14] Although ichthyosiform eruptions with epidermotropic infiltrates often coexist with typical MF lesions (designated as IMF-like lesions in the present study), the diagnosis of IMF should be considered when it is the sole manifestation suggestive of MF. There has been controversy as to whether AI also occurs in MF.[1,2] Furthermore, a close association of AI with CD30+ lymphoma is another issue to be clarified. To explore these questions, we have studied ichthyosiform eruptions arising in patients with malignant lymphoma

Patients and methods

Patients

We reviewed the files of patients with malignant lymphoma seen in our dermatology department between January 2001 and May 2006 to search for patients with ichthyosiform

eruptions. All patients with ichthyosiform eruptions were diagnosed with MF or ALCL based on clinical and histological findings. Extensive staging evaluation was performed by cervicothoracoabdominal computed tomography, gallium scintigraphy and bone marrow aspiration. In addition to routine laboratory tests (full blood cell count and biochemical analyses), we examined serum-soluble interleukin 2 receptor and antihuman T-cell leukaemia virus type 1 antibodies to exclude adult T-cell leukaemia/lymphoma. Staging was determined by classification for MF[15] and by the Ann Arbor Cotswolds classification for ALCL.[16] The presence of T-cell neoplastic clones was confirmed by rearrangement analysis of T-cell receptor genes.

Histopathology

Biopsy specimens were obtained from all patients after we received their informed consent. Formalin-fixed, paraffin-embedded blocks were cut into 4-μm sections and processed for routine haematoxylin and eosin staining and immunohistochemistry

Clinicopathological criteria for AI and IMF were as follows. In addition to ichthyosiform eruptions, (i) AI demonstrated packed orthohyperkeratosis and thinning or absent granular layers mimicking ichthyosis vulgaris, without lymphocytic infiltrates; (ii) IMF showed epidermotropic infiltration of atypical lymphocytes without ichthyosis vulgaris-like packed hyperkeratosis, and (iii) the overlap of AI and IMF was defined as packed hyperkeratosis mimicking ichthyosis vulgaris, associated with epidermotropic infiltration of atypical lymphocytes.

Immunohistochemistry and *in situ* hybridization

Biopsy specimens were immunohistochemically examined using monoclonal antibodies to CD3, CD4, CD8, CD20, CD30, CD56 and anaplastic lymphoma kinase (ALK). To evaluate the expression of filaggrin, we reacted all specimens with monoclonal antifilaggrin antibody (Lab Vision, Fremont, CA, U.S.A.) and compared the results with those of normal skin (two patients), X-linked ichthyosis (three patients) and ichthyosis vulgaris (three patients). Histochemical visualization was carried out with an LSAB 2 kit (Dako, Carpinteria, CA, U.S.A.), according to the manufacturer's instructions. Epstein–Barr virus-encoded small nuclear RNA (EBER) was examined by in situ hybridization as previously reported.[17]

Results

Patient diagnoses

Between January 2001 and May 2006, 106 patients with malignant lymphoma were seen in our dermatology department. These patients included 44 with MF, 10 with ALCL and 18 with B-cell lymphoma. In our series, nine patients with cutaneous T-cell lymphomas had ichthyosiform eruptions, whereas none of the 18 patients with cutaneous B-cell lymphoma did. Of the nine patients with ichthyosiform eruptions, three, patients 1 and 2 (male, aged 57 and 30 years) and patient 3 (female, aged 64 years), were diagnosed as having ALK−, primary cutaneous ALCL based on histological findings and their clinical courses (Fig 1a) Although the primary lesions were localized on the skin, lymph node involvement occurred within a few months after the initial diagnosis in the three patients The remaining six patients with ichthyosiform eruptions (patients 4–9) presented with patch or plaque lesions consistent with MF, which was histologically proven (Fig 1b–d). This group included four male and two female patients with a mean age of 57·0 (range 34–82) years. Of the six patients with MF, two (patients 5 and 9) had skin tumours without lymph node involvement (stage IIb), while one (patient 8) had tumours on the skin and regional lymph nodes (stage IVa) The remaining three patients had widespread patches and plaques without tumour formation or lymph node involvement, indicating stage Ib (Table 1)

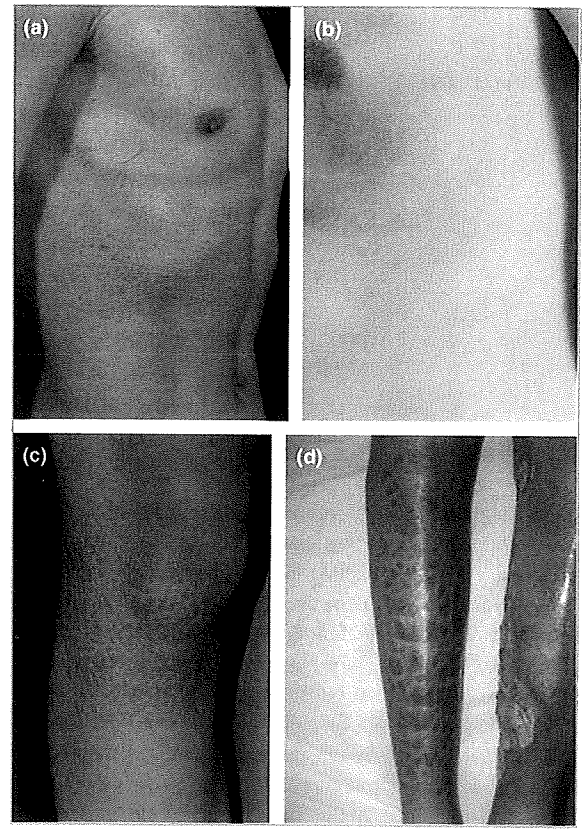

Fig 1. Clinical findings of ichthyosiform eruption (a) The trunk in patient 1 with AI and anaplastic large cell lymphoma (b) The trunk in patient 4 with IMF and conventional MF (c) The knee and the lower leg in patient 8 with both AI and IMF (d) The lower leg in patient 9 with AI and MF AI, acquired ichthyosis; MF, mycosis fungoides, IMF, ichthyosiform MF

Table 1 Clinical data on our nine patients

Patient no.	Age (years)/sex	Medical history	Onset of ichthyosiform eruption (years)	Onset of lymphoma (years)	Site of ichthyosiform eruption	Additional eruptions	Type of ichthyosiform eruption	Type of lymphoma	TCR rearrangement	sIL-2R	Clinical stage of lymphoma	CD30
1	58/M	–	57	57	Trunk	Tumour (nose)	AI	ALCL	Cβ1+ (SB)	1088	II_1	++
2	30/M	–	28	28	Trunk and ext.	Tumour (chest)	AI	ALCL	Cβ1+ (SB)	1434	III	++
3	64/F	–	64	58	Lower ext.	Tumour (L thigh)	AI	ALCL	γ+ (PCR)	991	II_3	++
4	43/M	–	43	43	Trunk and ext.	Plaques (trunk and ext.)	IMF-like eruptions	MF	Negative	2492	Ib	–
5	67/F	Prednisone	64	64	Trunk and ext.	Tumour and subcutaneous nodules (trunk and ext.)	IMF-like eruptions	MF	Cβ1+ (SB)	5172	IIb	++
6	82/M	Ca-blocker	70	70	Trunk and ext.	Plaques (trunk and ext.)	IMF-like eruptions	MF	ND	325	Ib	–
7	55/F	–	20s	30s	Trunk and ext.	Plaques (ext.)	IMF-like eruptions	MF	ND	291	Ib	–
8	34/M	–	28	30	Trunk and ext.	Tumour and plaques (thigh)	Overlap of IMF-like eruptions + AI	MF	Cβ1+ (SB)	776	IVa	++
9	61/M	–	61	56	Trunk and ext.	Tumour and plaques (trunk and ext.)	AI	MF	Cβ1+ (SB)	2029	IIb	+

TCR, T-cell receptor; sIL-2R, serum-soluble interleukin 2 receptor; ALCL, anaplastic large cell lymphoma; MF, mycosis fungoides; Cβ1, T-cell receptor Cβ1 chain; ext., extremities; CD30+, < 25% positive in tumour lesions; CD30++, > 25% positive in tumour lesions; ND, not done; PCR, polymerase chain reaction; SB, Southern blotting. AI, demonstrates packed orthohyperkeratosis and thinning or absent granular layers mimicking ichthyosis vulgaris, without lymphocytic infiltrates; IMF, shows epidermotropic infiltration of atypical lymphocytes without ichthyosis vulgaris-like packed hyperkeratosis; the overlap of AI and IMF is defined as packed hyperkeratosis mimicking ichthyosis vulgaris, associated with epidermotropic infiltration of atypical lymphocytes.

Fig 2. Histopathological findings of ichthyosiform eruption (a) In patient 4 with IMF, orthokeratosis, thinning of the granular layer, mild acanthosis and infiltration of atypical lymphocytes into the epidermis and the superficial dermis were seen (b) In patient 8 with both AI and IMF, compact hyperkeratosis, thinning of the granular layer, acanthosis and infiltration of atypical lymphocytes to the epidermis and the superficial dermis were seen (c) In patient 9 with AI, orthohyperkeratosis, thinning of the granular layer and atrophy of epidermis were observed No infiltrate was present AI, acquired ichthyosis; IMF, ichthyosiform mycosis fungoides

Histopathological and immunohistochemical findings

Ichthyosiform eruptions associated with ALCL (patients 1–3) had packed orthokeratotic horny layers with thinning or

absent granular layers. No lymphoma cell infiltration was observed. These histological features were consistent with AI, excluding IMF. The biopsy specimens from ichthyosiform eruptions of four patients with MF (patients 4–7) showed disappearance or thinning of the granular layer, and the infiltration of atypical lymphocytes in both the epidermis and superficial dermis (Fig. 2a). The ichthyosiform lesion of one patient with MF (patient 8) showed compact orthohyperkeratosis with thinning of granular layers, and epidermotropic infiltrates of atypical lymphocytes, which are characteristic of AI and IMF, respectively (Fig. 2b). The ichthyosiform eruption of another patient with MF (patient 9) was histologically consistent with AI, without epidermotropic infiltrates suggestive of MF (Fig. 2c).

In our series, 20 patients, including 10 patients with ALCL, seven patients with LyP, and three patients with MF, had CD30+ cells. Of the 20 patients, three with ALCL and three with MF had ichthyosiform eruptions (Table 1). The phenotypes of all three patients with ALCL associated with AI (patients 1–3) were CD3+, CD4+, CD8−, CD20−, CD30+, CD56− and ALK−. Tumour lesions of MF (patients 5 and 8) included large atypical cells exceeding 25% of the dermal infiltrate, which fulfilled the criteria of large cell transformation (Table 1), whereas in the tumour lesions of patient 9, CD30+ cells made up 3–10% of the infiltrating lymphoid cells. The phenotypes of atypical epidermotropic lymphocytes in all IMF-like lesions (patients 4–7) were CD3+, CD4+ and CD8−, and negative for CD30. No EBER+ cells were observed in all specimens from the nine patients with ichthyosiform eruptions.

Clinical course of ichthyosiform eruptions

The ALCL and ichthyosiform eruptions of patients 1 and 2 were temporarily improved by cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) chemotherapy and electron beam therapy (Fig. 1a). The ichthyosiform eruptions of patient 3 disappeared after six courses of CHOP chemotherapy, although the tumours later recurred. On the other hand, IMF-like eruptions in patients 4–7 also improved or disappeared after the skin-directed treatment for MF (Fig. 1b). Patients 4, 6 and 7 have remained in good condition with ongoing psoralen plus ultraviolet A treatment. A 67-year-old woman with stage IIb (patient 5) who developed large cell transformation was treated with three courses of CHOP chemotherapy with temporary improvement, but she died of complications of an infection of unclear origin.

A 34-year-old man (patient 8) first had MF lesions at the age of 28 years, and later developed tumorous lesions on the thigh associated with widespread ichthyosis (Fig. 1c). The tumour cells of a CD30+ phenotype rapidly progressed to lymph nodes in the inguinal and pelvic areas.

A 61-year-old man with stage IIb (patient 9) had progressive disease, in which neither electron beam nor CHOP therapy improved the tumours and ichthyosiform eruptions (Fig. 1d, Table 2).

Filaggrin expression in ichthyosiform eruptions

In normal skin and X-linked ichthyosis lesions, filaggrin was clearly stained in the granular layer (Fig. 3a, b). On the other hand, in common with findings in ichthyosis vulgaris, AI and IMF, filaggrin expression was markedly diminished in the thin granular layers, which was observed in all specimens of the nine patients (Fig. 3c–f).

Discussion

In our series of patients with cutaneous lymphoma, nine of 106 patients had ichthyosiform eruptions during the clinical

Table 2 Treatments and clinical courses of our nine patients

Patient no.	Therapy	Response of ichthyosiform eruption	Response of tumour/ plaque	Outcome
1	CHOP + EBT + salvage therapy	PR	PR	Dead (62 years)
2	CHOP + EBT + salvage therapy	PR	PR	Dead (32 years)
3	CHOP	CR	CR	Alive
4	RT + PUVA	PR	PR	Alive
5	CHOP	PR	PR	Dead (67 years)
6	PUVA	PR	PR	Alive
7	PUVA	CR	CR	Alive
8	CHOP + EBT + salvage therapy	NC	NC	Dead (35 years)
9	CHOP + EBT	NC	NC	Alive

CHOP, cyclophosphamide, adriamycin, vincristine and prednisone; EBT, electron beam therapy; salvage therapy, dexamethasone, cytarabine, etoposide, ifosfamide and cisplatin were used; PR, partial response; CR, complete response; RT, radiotherapy; PUVA, psoralen plus ultraviolet A; NC, no change.

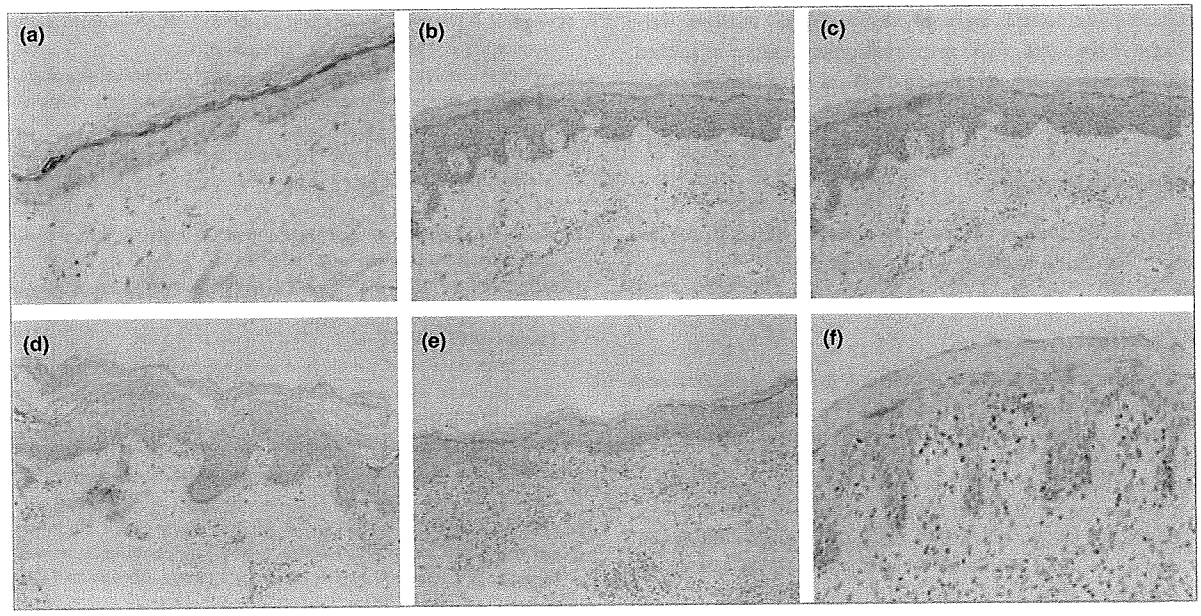

Fig 3. Immunostaining with filaggrin on normal skin and ichthyosiform eruptions. In normal skin (a) and an X-linked ichthyosis lesion (b), filaggrin was stained clearly in the granular layer On the other hand, in ichthyosis vulgaris (c), patient 1 with AI (d), patient 4 with IMF (e), and patient 8 with both AI and IMF (f), filaggrin was observed only slightly in the thin granular layers (c–f) AI, acquired ichthyosis, IMF, ichthyosiform mycosis fungoides

course, including three of 10 patients (30%) with ALCL and six of 44 patients (14%) with MF None of the 18 patients with cutaneous B-cell lymphoma had ichthyosiform eruptions or CD30 cells. The complication of ichthyosiform eruptions in B-cell lymphoma has not thus far been reported in the English literature.

Based on clinicopathological findings, we diagnosed all ichthyosiform eruptions associated with ALCL as being AI It is well known that AI is a frequent complication in patients with Hodgkin lymphoma In addition, some reports have described the coexistence of AI associated with ALCL or LyP.[6–8] In our case series, three patients with ALCL were in the advanced stages with involvement of internal lymph nodes. The expression of CD30 antigens is a hallmark of atypical lymphocytes composing Hodgkin lymphoma, ALCL and LyP lesions The CD30 antigen, or Ki-1 antigen, is a transmembrane glycoprotein with a molecular weight of 105 kDa and is expressed by not only Hodgkin cells and ALCL/LyP cells but also activated T cells and B cells [18] The CD30 molecule is a member of the tumour necrosis factor receptor superfamily and has a CD15 molecule as a ligand [18] The binding of the ligand transmits multifunctional signalling, which induces proliferation, activation, differentiation and cell death, depending on the situation These pleiotropic functions, mediated by CD30 signalling, might be associated with the development of AI

In most cases reported as IMF, the ichthyosiform eruption was the sole manifestation suggestive of MF, whereas Hodak *et al.*[10] have described three patients with typical MF associated with ichthyosiform eruptions under a diagnosis of IMF In the present study, we observed ichthyosiform eruptions in six of 44 patients with MF. The ichthyosiform eruptions were consistent with histopathological findings of IMF in four (patients 4–7), the overlap of AI and IMF in one (patient 8), and AI alone in one (patient 9) These observations indicate that patients with MF may develop ichthyosiform eruptions consistent with AI, IMF or their overlap during their clinical courses IMF in a strict sense usually occurs in patients with early MF [9] However, similar lesions may develop in patients with advanced stages, such as patients 5 and 8, whose tumours had large cell transformations and who died of MF-related complications. AI associated with MF was observed in two patients with more advanced MF (patients 8 and 9) As seen in patient 8, ichthyosiform eruptions having overlapping histological features of IMF and AI may occur in the same individual. The two patients with AI and MF had CD30+ atypical lymphocytes in tumours to various degrees Therefore, the development of AI might be associated with CD30 expression in MF as well as in Hodgkin lymphoma and ALCL

Filaggrin is essential for the formation of stratum corneum and is a key protein in epidermal differentiation and the maintenance of barrier function.[19] Recently it has been demonstrated that two functional mutations in the gene encoding filaggrin cause ichthyosis vulgaris, the most common disorder in inherited ichthyoses [20] In our series, the expression of filaggrin was markedly diminished in the thin granular layers in all our patients who had either AI, IMF-like eruptions, or both, as is usually observed in ichthyosis vulgaris

AI is considered a cutaneous sign of other diseases, whereas IMF represents a specific cutaneous manifestation of MF The present observations indicate that ichthyosiform eruptions

associated with ALCL are consistent with AI, whereas those associated with MF often reveal essentially the same histological findings as IMF, and may have AI in the advanced stages, with CD30 expression by tumour cells.

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c-*kit*解析を行った小児肥満細胞症の2例

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症例1：3カ月，女児。生直後から背部，右大腿部に拇指頭大までの瘙痒を伴う褐色斑および水疱が出現し，顔面，四肢にも同様の皮疹が拡大した。Darier徴候は陽性であった。抗アレルギー薬の内服とmediumクラスのステロイド外用剤で加療。その後9カ月を経た現在，褐色斑の新生はなく，個疹は消退傾向を示す。症例2：1歳9カ月，男児。生後7カ月頃より腹部に瘙痒を伴う小指頭大までの褐色斑が出現した。体幹および四肢に拇指頭大までの褐色斑が孤立性に散在しており，Darier徴候は陽性であった。Mediumクラスの外用剤のみで治療を行い，個疹は徐々に消退傾向を示す。病理組織学的に，2例ともに真皮乳頭層を中心に明るい胞体を有した類円形の細胞が帯状に浸潤し，リンパ球や少数の好酸球を混じていた。Toluidine blue染色にて，豊富な細胞質を有した浸潤細胞は細胞質内顆粒の異染性を示したことから，肥満細胞症と診断した。皮疹部組織を検体としたc-*kit*遺伝子変異の検索では，症例2にのみ，816番目のアミノ酸がアスパラギン酸(GAC)からバリン(GTC)への点突然変異を認めた。816番目の点突然変異は成人例での報告が多く，小児例の本邦報告例は自験例を含め13例と比較的少なかった。

はじめに

肥満細胞症は，肥満細胞が皮膚を含めて1つの器官，あるいは他の臓器にも異常増殖する比較的まれな疾患である。本症の分類は諸説あるが，基本的には病変が皮膚に限局する皮膚肥満細胞症と他臓器に病変の及ぶ全身性肥満細胞症，肥満細胞白血病やその他の血液疾患を合併する肥満細胞症などに大別されている[1]。色素性蕁麻疹は皮膚肥満細胞症の1亜型であるが，一方で全身性肥満細胞症の皮膚症状としても現れることがある。

肥満細胞症の病態形成には，現在2つの機序が考えられている[2]。1つは，肥満細胞表面に存在するc-*kit* receptorチロシンキナーゼの遺伝子突然変異によるものと，他の1つは局所における表皮由来のc-*kit* receptorチロシンキナーゼのリガンドであるstem cell factor(以下，SCF)の過剰産生によるものである。

今回，われわれはc-*kit*変異の検索をし得た幼児発症の肥満細胞症の2例を経験したので若干の文献的考察を加えて報告する。

症　例

症例1：3カ月，女児
初診：2007年10月中旬
主訴：体幹，四肢の褐色皮疹
家族歴：特記すべきことなし
既往歴：特記すべきことなし
現病歴：生直後から背部，右大腿部に小指頭大までの瘙痒を伴う褐色斑が出現した。同部位に水疱を生じることもあった。生後1カ月頃より背部全体と顔面，四肢にも同様の皮疹が出現，拡大したため，2007年10月中旬に近医より当科紹介受診となった。
現症：顔面，体幹および四肢に拇指頭大までの褐色斑が孤立性に散在し，一部は褐色斑上に水疱を伴っていた。Darier徴候は陽性であった(**図1a**)。初診時までに，発熱，下痢，嘔吐，ショック等は認められなかった。
臨床検査所見：初診時血液検査所見は特に異常を認めなかった。その他，胸部X線検査および心電図は正常範囲内であった。腹部エコー検査上，肝脾腫などの所見は認めなかった。
病理組織学的所見：体幹の褐色斑より皮膚生検を施行した。HE染色では，表皮は一部菲薄化を呈していた。真皮乳頭層を中心に明るい胞体を有した類円形の細胞が帯状に浸潤し，リンパ球や少数の好酸球も混在していた。膠原線維の増生もみられた(**図1b**)。Toluidine blue染色では，豊富な細胞質を有する浸潤細胞は細胞質内顆粒の異染性を示した(**図1c**)。以上より，浸潤細胞を肥満細胞と同定した。
治療および経過：皮膚肥満細胞症の一亜型である色素性蕁麻疹と診断し，体幹，四肢の皮疹に対し，抗アレルギー薬(ペリアクチンシロップ®)0.05 mg/kg/日の内服を開始した。外用はmediumクラスのステロイド外用剤(ロコイド®軟膏)を使用した。加療開始後しばらくは入浴後と衣類の着脱時において体幹，四肢に水疱を伴う褐色斑が生じていたが，その後9カ月現在で褐色斑の新生はなく，消退傾向を示している。また抗アレルギー薬投与に伴うけいれん発作は生じていない。
症例2：1歳9カ月，男児
初診：2007年11月下旬
主訴：体幹，四肢の褐色皮疹
家族歴：特記すべきことなし
既往歴：生後11カ月頃入浴後に突然倒れ，数秒間呼吸が停止したことがあった。
現病歴：生後7カ月頃から腹部に小指頭大までの瘙痒を伴う褐色斑が出現した。同様の皮疹が四肢にも拡大してき

たため，2007年11月下旬，近医より当科紹介受診となった。

現症：体幹および四肢に拇指頭大までの褐色斑が孤立性に散在し，一部は膨疹となっていた。Darier徴候は陽性であった(**図2a**)。他部位に病変はなく，発熱，下痢，嘔吐等は認めず，ショック症状もなかった。

臨床検査所見：初診時血液検査所見は特に異常を認めなかった。その他，胸部X線検査および心電図所見は正常範囲内であった。腹部エコー検査上，肝脾腫などの所見は認められなかった。

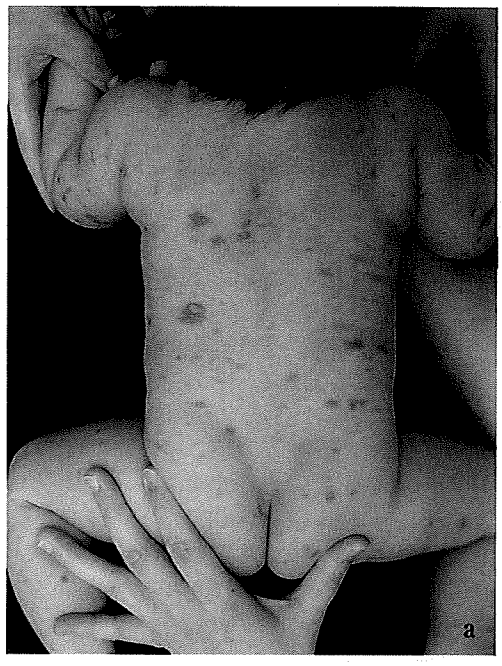
病理組織学的所見：真皮上層から中層にかけて類円形の細胞が帯状に浸潤していた(**図2b**)。Toluidine blue染色では，浸潤した細胞は紫色を呈し，異染性を示した(**図2c**)。

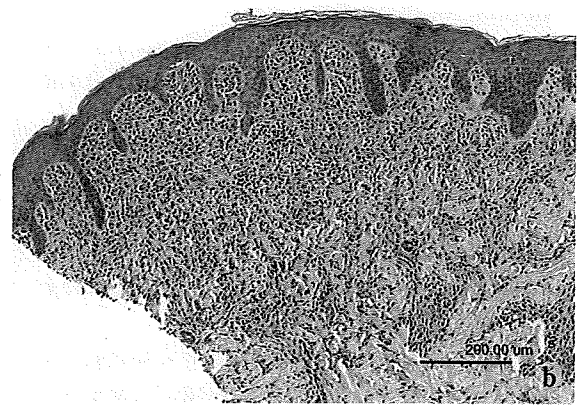
治療および経過：本症も症例1と同様に，色素性蕁麻疹の診断のもと，mediumクラスのステロイド外用剤(ロコイド®軟膏)のみで加療した。現在，皮疹の新生はなく，個疹は扁平化し消退化傾向にある。

c-*kit*の点突然遺伝子の検索：PCR-direct sequence法を用い，Yanagihoriら[3]の示した方法で遺伝子変異検索を行った。2症例の病変部皮膚組織のパラフィン切片を用い，過去に報告のあったc-*kit*変異の全てを同定出来るように設計し，DNAシークエンサーで解析した。その結果，症例1では変異を認めなかったが，症例2では，816番目のアミノ酸において，アスパラギン酸(GAC)からバリン(GTC)へ置換される点突然変異を認めた(**図3**)。なお，両症例の末梢より採取した血液を検体として同様の遺伝子変異検索を行ったところ，症例2にのみ病変部組織と同一の遺伝子変異がみられた。

かんがえ

肥満細胞症の分類方法にはいくつかあるが，病型が疾患の予後と良く相関するMetcalfeの分類[4]が一般に用いられている。この分類によると，本症は2例ともに血液学的異常を合併していない無症候性肥満細胞症のうち，皮膚に限局したものであり，もっとも予後が良い群に相当する。肥満細胞症の発症頻度は，約65%が幼児型，残りの35%が成人型で，発症年齢は病態や予後とも密接に相関するとの報告がある[5]。自験例は2例ともに小児期の発症で，皮膚外症状を認めなかったことから皮膚限局型の肥満細胞症と診断した。発症要因としては，近年その解明がすすんでおり，代表的な2つの説として，①c-*kit*の変異と，②SCF(c-*kit*リガンド)の代謝異常が考えられている[2]。肥満細胞表面に存在するc-*kit* receptorチロシンキナーゼの遺伝子が突然変異をきたし，肥満細胞の自己活性化を促し，腫瘍性に細胞増殖を引き起こすと考えられている。この異常はチロシンキナーゼ領域特定のアスパラギン酸がバリンやグリシンに変わる点突然変異である。c-*kit*の変異は成





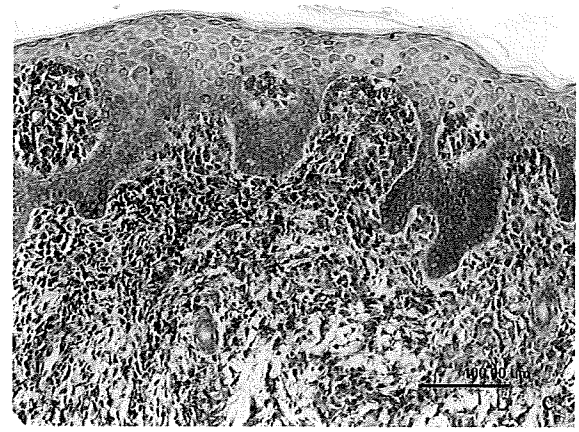


図1 症例1
a：初診時臨床像；顔面，体幹および四肢に拇指頭大までの褐色斑と水疱が孤立性に散在している。Darier徴候は陽性
b：病理組織像(H-E染色)；真皮乳頭層を中心に，明るい胞体を有した類円形の細胞が帯状に浸潤している。リンパ球や少数の好酸球も混在しており，膠原線維の増生もみられる
c：Toluidine blue染色；豊富な細胞質を有した浸潤細胞は，細胞質内顆粒の異染性を示す

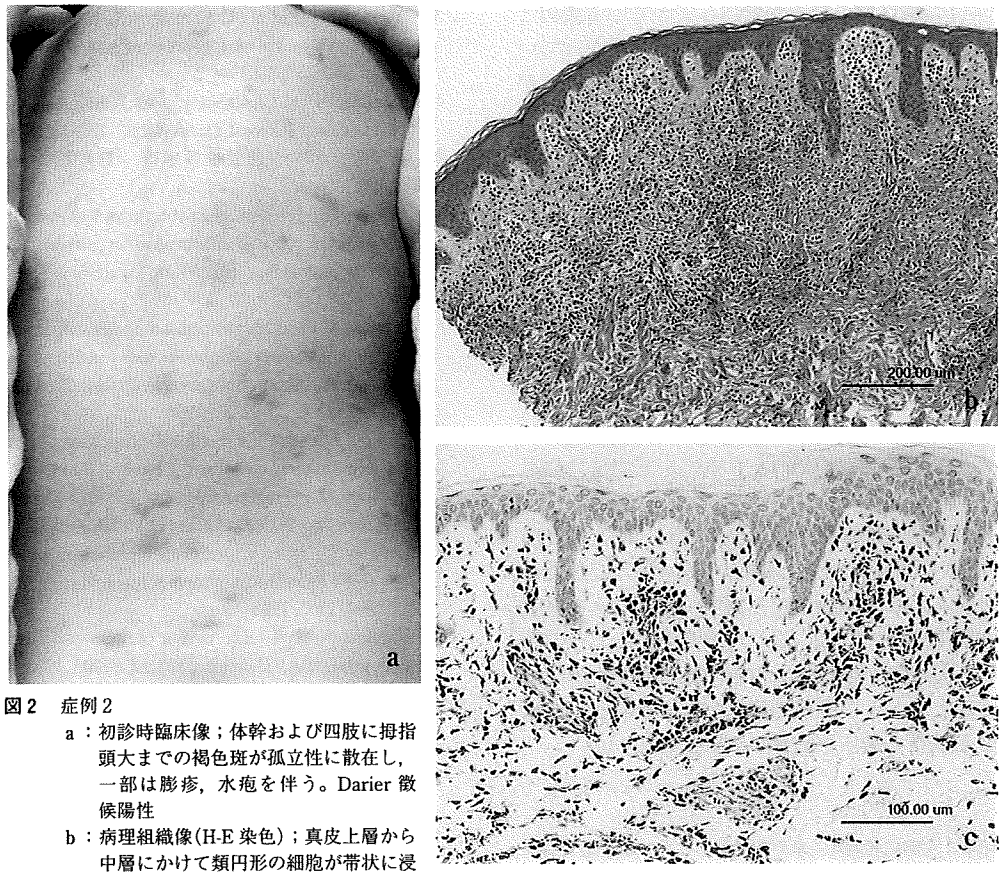


図2　症例2
- a：初診時臨床像；体幹および四肢に拇指頭大までの褐色斑が孤立性に散在し，一部は膨疹，水疱を伴う。Darier 徴候陽性
- b：病理組織像(H-E 染色)；真皮上層から中層にかけて類円形の細胞が帯状に浸潤している
- c：Toluidine blue 染色；有棘層は肥厚し，真皮上層から中層にかけて異染性を示した肥満細胞の集団が島嶼状にみられる

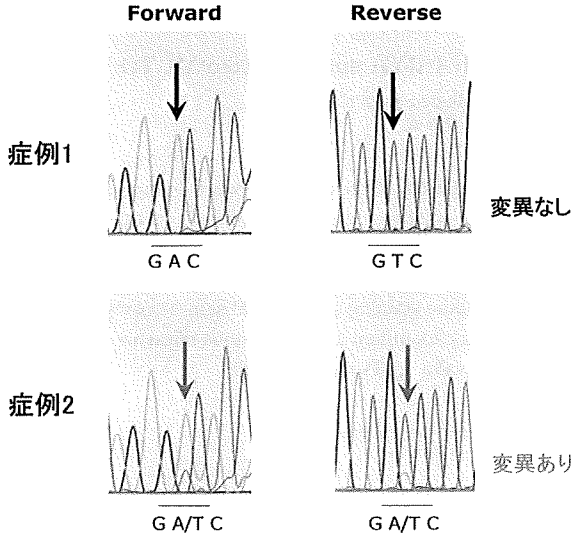


図3　c-*kit* 変異の同定
症例1は変異を認めず(上段)，症例2において816番目のアスパラギン酸がバリンへ置換される点突然変異を検出した(下段の矢印)。その他の codon-560，-820 および-839 には変異は認めなかった

人発症の肥満細胞症で造血系の異常(白血病，悪性リンパ腫など)を伴う症例に多くみられ，小児皮膚肥満細胞症や家族性肥満細胞症においてはほとんどみられないとされていたが，文献により差がある[3)6)~9)]。一方，SCF は膜結合型と分泌型の形態で存在し，肥満細胞の分化，増殖，遊走，活性化および生存などに関与している。表皮ケラチノサイトは線維芽細胞や血管内皮細胞と同じく，SCF を産生することが知られており，本症の SCF 過剰産生の原因となって肥満細胞の分化，増殖に関与しているものとして重要視されている。Longley ら[10)]は，健常皮膚と肥満細胞症患者の皮膚における免疫染色の結果と SCF mRNA の発現の差から，表皮ケラチノサイト由来の分泌型 SCF が過剰に産生されることにより，皮膚肥満細胞の分化，増殖を促していることを推察しているが，一方，Hamann ら[11)]は肥満細胞腫の患者と色素性蕁麻疹の患者における SCF の免疫染色の結果が各々異なるパターンを示したことから，これを否定する見解をとっており，未だ見解の統一には至っていない。

これまで報告されている小児期発症の肥満細胞症における c-*kit* の変異例は成人例に比較して少なく，Buttner ら[7)]は小児と成人の肥満細胞症各11例，6例の c-*kit* 点突然変異の有無を解析したが，Asp816Val，Val560Gly の変異がみられたのは6例とも全て成人例であった。しかし近年，Boissan ら[8)]が小児の肥満細胞症において，7例中5例に変異があったと報告しており，また Yanagihori ら[3)]も小児発症の肥満細胞症12例中，10例に変異があったとして

いる。このように陽性例の報告が増加してきている要因として，変異の解析方法が各施設間，研究者間で異なっていたものが統一されつつあり，解析の精度が向上したことが挙げられる。さらには対象とする患者群の個々の臨床像の相違も少なからず結果に影響を及ぼしていることも考えられる。また，自験例2においては血液からも遺伝子変異が認められた。同様に小児例での変異を報告したAkinら[12]によると，成人の皮膚肥満細胞症では全例にAsp816Valの変異を認めたが，小児例では血液疾患を合併していない例にのみ変異を認めたことから，小児では末梢血での変異の有無と病型については関連がはっきりしないとしている。今回自験例では2例ともに色素性蕁麻疹と診断しており，経過も現在の時点では良好であるが，今後変異を認めた例で血液疾患などの発症が認められるのかを慎重に経過観察する必要がある。

近年，小児期発症の肥満細胞症においても，成人例と同様にc-*kit*突然変異が陽性であった報告例が増えてきており，小児例と成人例との病態の差を遺伝子変異のみで説明することは困難となってきている。自然消退することの多い小児例では，陽性例と陰性例との間で臨床経過や予後にいかなる差が生じるのか，今後の慎重な経過観察と，同様な症例の更なる蓄積と遺伝子解析が必要とされる。

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Two Pediatric Cases of Cutaneous Mastocytosis：Searching for a Mutation in the c-*kit* Gene

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We here describe 2 pediatric cases of cutaneous mastocytosis in which mutations of the c-*kit* gene were analyzed. Case 1 is a 3-month-old Japanese girl with brownish spots and bullae that emerged beginning a few days after birth on the back and the right leg. Case 2 is a 21-month-old Japanese boy who presented 2 months previously with small, thumb-sized, brownish spots arising on his abdomen. The number of eruptions has gradually increased in this patient. In both cases, mastocytosis was diagnosed by the clinical presentation and plane histology and toluidine blue staining of a lesional skin biopsy specimen. In Case 2, c-*kit* analysis using polymerase chain reaction and direct sequencing identified a heterozygous missense mutation located in exon 17 (A>T substitution that changed an aspartate (GAC) to a valine (GTC), Asp816Val).

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LETTER TO THE EDITOR

Atypical fibroxanthoma presenting immunoreactivity against CD10 and CD99

Dear Editor,

Atypical fibroxanthoma (AFX) is a relatively uncommon low-grade skin neoplasm.[1] AFX usually has a benign clinical course and complete tumor resection is generally curative. AFX presents clinically as a rapidly enlarging, solitary nodule or ulcer ranging 1.5–2 cm in diameter on damaged actinic skin in the head and neck of elderly patients. A less common form, accounting for 25% of cases, occurs on the trunk and limbs of young individuals.[2] Histologically, AFX needs to be differentiated from pleomorphic malignant fibrous histiocytoma (MFH), squamous cell carcinoma (SCC), malignant melanoma (MM), leiomyosarcoma and metastatic carcinoma.[3] The use of immunohistostaining is a helpful tool to rule out these other tumors, as AFX has historically been a tumor of exclusion. Recently, however, CD10 and CD99 have been reported as useful markers for the diagnosis of AFX.[4–8] Herein, we report a case of AFX exhibiting immunoreactivity against CD10 and CD99.

An 83-year-old Japanese woman was referred to our department, complaining of an asymptomatic reddish tumor on her left cheek, which had enlarged rapidly over a period of approximately 1 month. On physical examination, the tumor was a solitary, dark red, dome-shaped mass with ulceration that was 2 cm in diameter (Fig. 1). Computed tomography showed no evidence of infiltration into subcutaneous tissue, and both lymph nodes and distant metastases were not observed. The histopathological findings of incisional biopsy showed the tumor was well circumscribed with an epithelial collarette and was centered in the dermis (Fig. 2a). The tumor was formed of pleomorphic spindle cells arranged in a storiform pattern (Fig. 2b). Scattered mitosis, including atypical forms, was also observed, and multinucleated giant cells were seen frequently. No subcutaneous/vascular invasion or necrosis was observed.

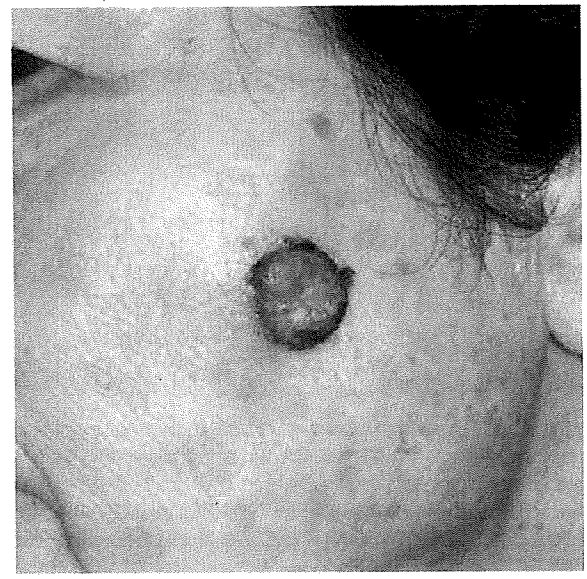

Figure 1. Solitary, dark red, dome-shaped nodule with ulceration was observed on the left cheek.

Immunohistochemical findings confirmed that tumor cells were positive for vimentin, and were focally positive for CD68. Tumor cells did not stain for cytokeratins, desmin, α-smooth muscle actin (α-SMA), CD34, S100, HMB-45 or Melan-A. Based on these findings, we ruled out SCC, MM, leiomyosarcoma and metastatic carcinoma. However, we could not differentiate AFX from pleomorphic MFH with certainty, as two previous case reports have described lesions that were initially diagnosed as AFX, but subsequently recurred as deeper invasive lesions more typical of superficial MFH.[9] Therefore, we performed immunohistochemical staining for CD10 (Ventana Medical System, Tuscan, AZ, USA) and CD99 (Cell Marque Corporation, Hot Springs, AR, USA), and the tumor cells showed diffuse, strong cytoplasmic staining for CD10 and CD99

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